Does the prevalence of fabella vary in knee osteoarthritis and age-related degeneration? A meta-analysis of over 11,000 knees.

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Does the prevalence of fabella vary in knee osteoarthritis and age-related degeneration? A meta-analysis of over 11,000 knees.

Abstract

Introduction: Osteoarthritis (OA) and age-related degeneration (ARD) are stimulants for the development of the fabella in the knee joint. This meta-analysis updates previous studies and reviews on the prevalence of the fabella in OA or ARD knee joints. In addition, it provides a quantitative estimation of the fabellar prevalence in knees having OA and ARD.

Methodology: Twenty studies comprising of data from 11,056 knee joints were included in the analysis, consisting of 6,819 Knees of OA subjects (including those with age more than 40 years) and 4,237 knees of non-OA subjects (including less than 40years) knees, respectively. 2,434 knees had fabellae present in OA subjects (including more than 40years), and 844 fabellae were present in non-OA subjects (including less than 40years). The Odds and Risk Ratios were calculated. Sensitivity analysis and cumulative analysis were conducted to assess the robustness of the findings.

Results: Prevalence of fabella was found to be higher in OA knees, where the Risk Ratio of developing fabella was 2.50 (2.07-3.01). Compared with this, the Risk Ratio for the incidence of fabella in OA with ARD knee was 1.84 (1.66-2.03). The bilateral occurrence of fabella was more common than unilateral. The risk of developing fabella in individuals aged less than forty-year was 63% less than individuals aged more than forty years.

Conclusion: OA and ARD would increase the prevalence of fabella by 84%, thus acting as stimulants and risk factors for ossified fabella.

Keywords: Odds Ratio; Prevalence, Knee Joints, Osteoarthritis (OA), Age-related degeneration (ARD).

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Introduction

Fabella is a Latin word which means 'for the little bean.' This sesamoid bone is embedded in the lateral or medial head of the gastrocnemius in the posterior aspect of the femur (Heideman et al., 2011). It presents as a small fibrocartilaginous nodule developing after 8 to 12 years of age. The anatomical location of the fabella is at the intersection of tensile stress in the complex structure of the postero-lateral part of the knee, and it acts as a static stabilizer by reorienting various forces. Fabella increases the efficiency of the gastrocnemius muscle. It provides a biomechanical advantage in knee flexion (Minowa et al., 2004; Driessen et al., 2014). It makes fourth compartment of the knee joint and prevents friction-induced damage (Zipple et al., 2003).

The knee joint is most commonly affected by osteoarthritis (OA). In severe osteoarthritis, knee arthroplasty is a usual procedure these days. Fracture dislocation of fabella was uncommon before the era of knee arthroplasty (Segal et al., 2004). The implant of knee arthroplasty frequently causes impingement of fabella or fabellar syndrome, which is related to fabellar degeneration and OA changes and is a matter of concern in patients after total knee replacement (Alsharif et al., 2019). OA and degenerative changes in the knees generally begin in the fourth decade of life. However, the symptomatic presentation is commonly observed by the next decade. OA and aging or age-related degeneration (ARD) after forty years are considered as exposures for the formation of fabella (Heidari, 2011). OA or ARD may lead to degeneration of the articular cartilage or menisci and subsequent osteophyte formation. The pathogenesis of ossification and enlargement of fabella could be similar to the above mechanism (Heidari, 2011; Dominic et al., 2018). The prevalence of fabella varies from 3.1% to 86.9% and changes

with ethnicity and the methods of observation. Prevalence of fabella is higher in OA knees, as reported in preliminary findings of a few studies. A hypothesis was formulated for this study based on the above evidence that OA and ARD of knee joint have a positive association with the presence of fabella. A meta-analysis was conducted to assess the prevalence of fabella in OA and ARD knees of subjects with age greater than 40 years. The meta-analysis also tried to assess sex-linked prevalence and the laterality in prevalence of fabella.

Methods

Literature review

Available literature was explored from the electronic database of PubMed/ Medline, European PMC, CINAHL, Embase, EBSCO, Scielo, Clinical Key, Up To Date, OVID search, Google Scholar, AUSPORT and Cochrane library from June 2019 to November 2019. The search included MeSH terms such as prevalence, incidence, fabella, sesamoid bone, osteoarthritis, OA, arthritis, aging, ARD, knee pain, and knee degeneration in different strings of combinations. The string of terms were included in Boolean search with 'OR, AND, or NOT,' and speech marks such as 'Fabella or Knee Sesamoid or Popliteal sesamoid' and 'Fabella or Prevalence or Osteoarthritis' or 'Fabella or Prevalence or Knee pain,' to acquire maximum relevant articles. The delimiter 'NOT' was used to obtain appropriate studies. The strategy used for the PubMed database is mentioned at the end of manuscript. Appropriate published articles were collected from the journals of subjects like Anatomy, Anthropology, Orthopaedics, Sports Injuries, Biomechanics, Morphological Science, and Radiology from web sites or library archives. These search strategies yielded 119 works.

Literature Selection

These works were shortlisted based on titles and abstracts by Rayyan QCRI App (Ozzani et al., 2016) for systematic review. Case reports and case series were excluded because they did

not provide sample sizes, making risk estimation impossible. The publications without useable data, or where data did not exhibit 95% confidence intervals, were also excluded from the analysis. Studies providing risk estimates of OA or ARD were included. Further, to ensure an unbiased approach in selecting the studies, abstracts from conferences, unpublished articles with retrievable data, and published articles were also included. In addition, email correspondences were done to collect unpublished data of published articles and were included. Case reports accompanied with literature review were included for references, but their data was excluded from analysis. The average prevalence from text-books or published literature without sample references were omitted. No restriction was applied based on the year of publication, language, or ethnicity. Studies reporting fabella before 12 years of age in a population sample were not considered because the development of fabella in this age group could not be confirmed. In addition, if an author confused popliteal artery calcification with fabella in radiographic findings, results were excluded as they were not appropriate for analysis. The radiological studies included radiographs, CT, and MRI scans. USG and PET scan data were excluded from the analysis because of their low detection rates. Anatomical studies reporting the age of cadavers and OA changes were included in the analysis.

The prevalence of fabella was measured in knees of OA subjects, non-OA subjects, subjects aged less than 40 years, and subjects aged greater than 40 years. The Osteoarthritis Initiative (A project of National Institute of Health) recommended the lowest age of 45 years for the OA cohort study, with a baseline of 5 years of exposure. Consequently, 40 years of exposure was considered as a baseline for ARD in this analysis. The prevalence of fabella was measured separately in males and females. In addition, the incidences of unilateral or bilateral fabella, and right or left were noted. The data on the size of fabella was not used because of insufficient sample size and variable methods of measurement.

The primary outcome was to measure the risk estimates of fabella in ARD and OA knee based on radiological and anatomical assessment. The assessment of the prevalence of fabella based on sex, laterality, and ancestry were secondary outcomes.

Assessment of risk of bias

Evaluation and analysis for the risk of bias in all selected articles were performed by using the Anatomical Quality Assurance (AQUA) tool of the International Evidence-Based Anatomy (iEBA) working group. Two authors assessed the risk of bias independently. Any disagreement was resolved by a third author. The risk of bias was evaluated in all five domains - objective and subject characteristics, study design, methodology characteristics, descriptive anatomy, and reporting of results. Additionally, ROBINS I was utilized to assess the integrity or quality of these observational studies (Sterne et al., 2016) because the AQUA tool was inadequate to evaluate the exposure (intervention) in them.

Data extraction and statistical analysis

Authors independently extracted the data and information relevant for the study using a standard data extraction form. The form included the following details: the number of participants, age, sex, inclusion, and exclusion criteria. Also, the pieces of information recorded were the year of publication, country or geographical area or population, hospital or community-based population, mode of study (Anatomical or Radiological), the number of individual or knees examined, and number of fabellae observed (events). The contingency tables were prepared, and OR, as well as 95% confidence interval, were computed. Risk estimations for age, sex, and laterality were done separately. No previous data of meta-analysis was available to adjust for these confounding factors.

The unit of analysis was the prevalence of fabella in 100 knees examined. ProMeta v3 - Idostatistics and Revman 5.3 were used to analyze the pooled data. The OR and effect size were measured for each included study. The heterogeneity value was measured as i^2. If i^2 was less than 50%, then the fixed effect model was adopted; else, the random effect model was applied. The P-value of Cochrane Q statistics was reported. The OR, RR, and risk difference (RD) were measured with 95% confidence interval. Sensitivity and cumulative analysis were performed to test consistency of the findings. Publication bias was measured by the funnel plot. For the funnel plot, the logarithmically transformed OR against the standard error was utilized. Regression analysis was also performed to assess the relationship between outcome and moderators (age, sex, and ethnicity). The distribution of study risk estimates was visually examined in the funnel plot. Egger's linear regression test and Begg & Mazumdar's rank correlation test were used in addition for assessing publication bias. Rosenthal Fail-Safe Number (FSN) was measured to detect the file drawer effect by ProMeta 3. Subgroup analysis was done to measure the risk estimates related to intervention, if heterogeneity was above 50% because of the distribution of ethnicity or population and mode of study. The extracted data was as not suitable to study the dose-response and dose-time effects. Finally, the OR, RR, and RD were computed based on data in the random-effect model.

Results

Description of studies

The publications included were cross-sectional observational studies as case-controlled or cohort studies were unavailable despite extensive searches. One hundred seventeen relevant works were found as a result of cyber searches, and two studies were from conference proceedings. Five studies were excluded due to duplication of titles or abstracts. Another 37 studies were excluded because of non-human reports or case reports and series, review based

abstract, and title evaluation. Seventy-seven studies qualified after the title and abstract evaluation and three authors studied full texts of each work individually. A study was included based on the consensus of at least two authors. The interrater agreement was 0.87. For the meta-analysis, 22 studies from the years 1875 to 2019 were selected, which dealt with the prevalence of fabella associated with OA or ARD changes based on their abstract and full-text analysis. Of these, two studies (Chihlas et al., 1993; Corvalan et al., 2018) were excluded after evaluation of their risk of bias (ROBINS I) because of missing data. As a result, 20 observational studies were included (Figure 1) (Gruber W, 1875; Yano K, 1928; Sonntag, 1930; Chung L, 1934; Kitahara M, 1935; Sutro et al., 1935; Hessén, 1946; Hagihara et al., 1953; Lungmuss F, 1954; Pritchett, 1984; Sohn et al., 1985; Guermazi et al., 2012; Piyawinijwong et al., 2012; Tabira et al., 2013; Ehara, 2014; Hauser et al., 2015; Egerci et al., 2017; Ghimire et al., 2017; Pop et al., 2018; Berthaume and Bull, 2019; Hou et al., 2019) (Table 1). Studies which reported sex preference and laterality of fabella were also included (Ost W, 1877; Pfitzner W, and Schwalbe G., 1892; Parsons FG, and Keith A, 1896; Pancoast H, 1909; Sugiyama K., 1914; Rothe KR, 1927; Kojima, 1958; Falk, 1963; Kaneko K, 1966; Frey et al., 1987; Lencina, 2007; Silva et al., 2010; Phukubye and Oyedele, 2011; Ortega and Olave, 2018; Tatagari et al., 2018).

Risk of bias in the included studies

The AQUA tool probed for potential risk of bias in five study domains, as previously mentioned. The risk of bias within each domain was categorized in percentage (Table 2). A bias of less than 20% was considered low risk, 20-40% was categorized as moderate risk and >40% was high risk. Majority of the works included in this meta-analysis had low to moderate risk of bias in domain one (objectives and subject characteristics) and domain three (methodology characterization) because of missing baseline demographic data of the study population and lack of information regarding the experience of the researchers. Almost all studies revealed a low risk of bias in the remaining domains (study design, descriptive anatomy,

Table 1: Characteristics of included studies.

Author	Year	Method	Study	Country	Exposure##	ROB*
Berthuambe & Bull	2019	CT	RS	Korea	ARD	**L**
Chung	1934	D	CS	Korea	ARD	**M**
Egerci et al.	2016	D	CS	Japan	ARD	**L**
Ehara	2013	MRI	PS	Japan	ARD	**L**
Ghimire et al.#	2017	X-ray	CS	Nepal	ARD	**M**
Gruber	1875	D	CS	Russia	ARD	**M**
Haghihara et al.	1993	D	CS	Japan	ARD	**L**
Hauser et al.	2015	D	CS	Europe	ARD	**L**
Hessen	1946	X-ray	RS	Sweden	ARD	**L**
Kitahara	1935	X-ray	RS	Taiwan	ARD	**L**
Lungmass	1954	X-Ray	RS	Germany	ARD	**L**
Piyawinijwong et al.	2012	D	CS	China	ARD	**L**
Pop et al.	2018	MRI	CS	Romania	ARD	**L**
Sohn et al.	1985	X-ray	RS	Korea	ARD	**L**
Sonntag	1930	X-ray	CS	Germany	ARD	**M**
Sutro et al.	1935	X-ray	RS	USA	ARD	**L**
Tabira	2012	D	CS	Japan	ARD	**L**
Yano	1928	D	CS	Japan	ARD	**L**
Hou et al.	2019	X-ray	RS	China	OA	**L**
Pritchett	1984	X-ray	RS	Europe	OA	**L**

Foot note:Radiological method includes Radiographs, CT & MRI (X- ray-Radiograph, CT-Computerized Tomography, MRI-Magnetic Resonance Imaging). Anatomical method includes evaluation of dissected Knee. D-Dissected Specimen.

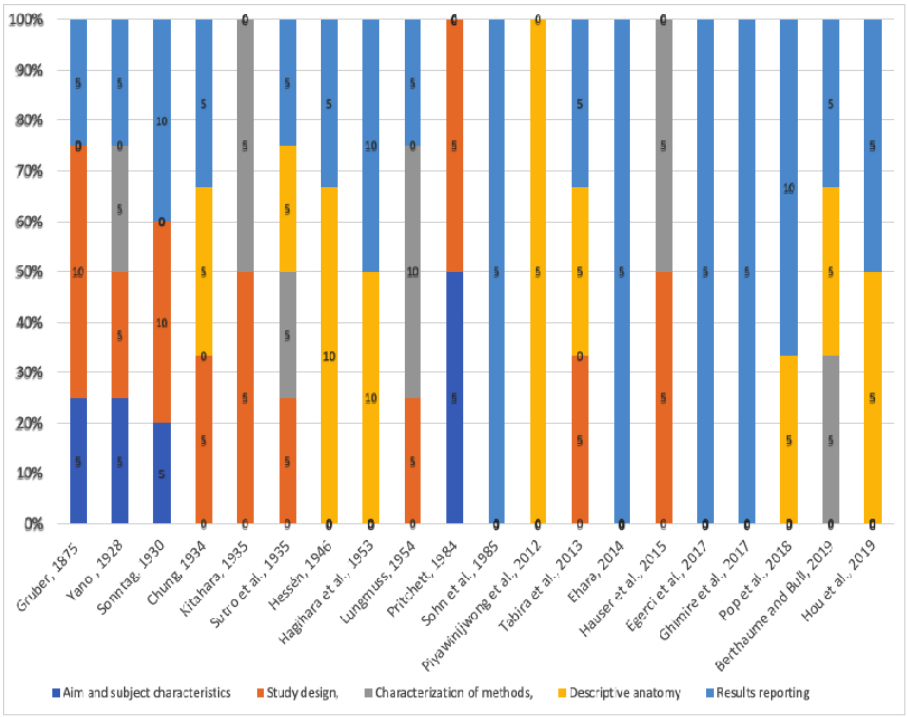
CS- Cross-sectional study, RS-Retrospective study, PS-Prospective study.

ARD: Age related degeneration(exposure of 40 years), OA-Osteoarthritis

Ghimire et al. was removed from analysis because of discrepancies in the data from published literature and graph.

Data of exposure (Intervention) were presented in forest plots.

*ROB: Risk of bias for intervention was evaluated by ROBINS I for all studies. L-Low and M-Moderate. Overall risk of bias was Low to Moderate.



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and reporting of results). The summary chart of the quality and risk of bias assessment, as evaluated by the AQUA tool, is displayed in Table 2. The inter-rater agreement between the two authors was 69.2 [53-78%]. The agreement varied from average to excellent. ROBINS I risk of bias was found as low to moderate in the twenty studies (Table 1). A reporting bias might be due to different methodologies. The cartilaginous fabella in the dissected knee may increase anatomical prevalence as only ossified fabellae were visible in radiographs.

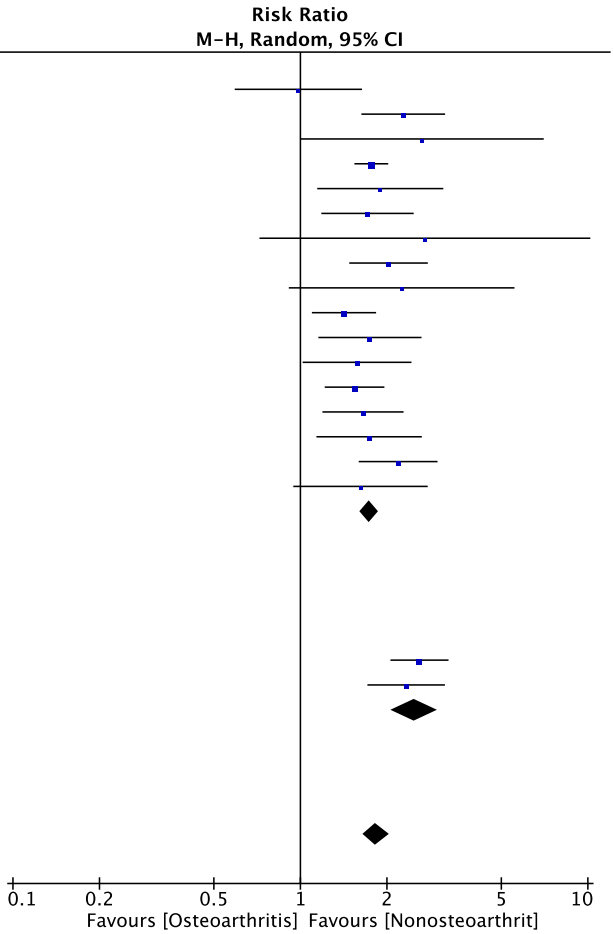
Effect of exposures

Eleven thousand fifty-six knees were evaluated for risk estimates in exposures of OA and the ARD processes. The risk estimate for the prevalence of fabella in combined exposure had OR of 2.16 (1.68, 2.76 95% CI), and a RR of 1.71 (1.40, 2.10 95% CI). The risk estimate of prevalence of fabella in persons <40 years of age had an OR of 0.54 (0.42, 0.71 95% CI) and RR of 0.63 (0.49, 0.81 95%CI). All studies revealed a serious heterogeneity, and the heterogeneity statistics (i^2) was 81%, while the Cochrane Q value was 96.38 for df = 19 (P=0.0001). It was unacceptable (i^2 acceptable up to < 50%) to combine the risk estimate, and needed subgroup analysis to deal with heterogeneity (Supplementary file).

Subgroup analysis

Considering that either OA or ARD was producing heterogeneity, subgroups were created, with OA studies being shifted into the 'OA only' subgroup and the remaining studies moved into the 'ARD only' subgroup. The 'ARD only' subgroup still exhibited heterogeneity, and this was dealt with using the eyeball test. It was observed that Ghimire et al., 2017 was producing heterogeneity. Upon further analysis, the data of Ghimire et al. was found faulty and was removed from the analysis, which reduced heterogeneity (i^2) to 37%. After removal of an outlier, heterogeneity was within the acceptable limit. The risk estimate for OA and ARD were measured again in 10,741 knees. OR and RR for co-exposure were 2.42 [2.03, 2.87 95%CI]

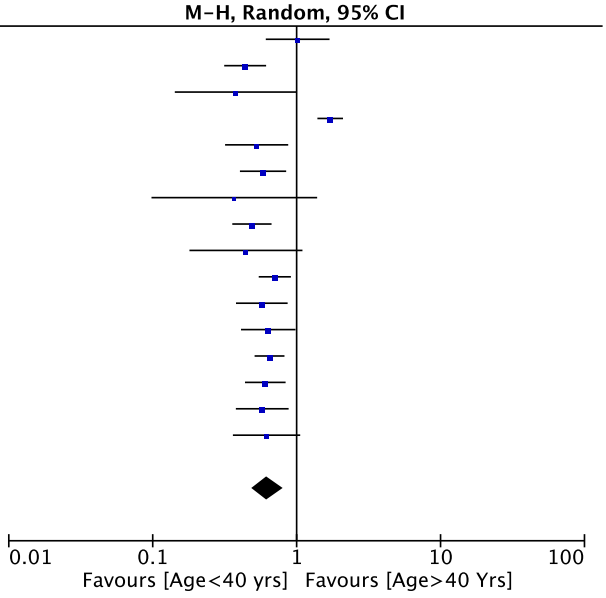
Study or Subgroup	OA+>40yrs Events	Total	Non-OA+<40 yrs Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 ARD only						
Berthuambe 2019	85	192	9	20	3.2%	0.98 [0.59, 1.64]
Chung 1934	65	147	39	201	5.9%	2.28 [1.63, 3.19]
Egerci 2016	110	912	4	88	1.0%	2.65 [1.00, 7.02]
Ehara 2013	353	653	200	653	12.7%	1.76 [1.54, 2.02]
Gruber 1875	46	141	16	93	3.3%	1.90 [1.14, 3.14]
Haghihara 1953	144	244	20	58	5.2%	1.71 [1.18, 2.48]
Hauser 2015	103	380	2	20	0.6%	2.71 [0.72, 10.20]
Hessen 1935	104	482	49	460	6.4%	2.03 [1.48, 2.77]
Kitahara 1935	5	14	10	63	1.2%	2.25 [0.91, 5.56]
Lungmass 1954	124	484	73	404	8.0%	1.42 [1.10, 1.83]
Piyawinijwong 2012	125	294	19	78	4.4%	1.75 [1.15, 2.64]
Pop 2018	46	224	27	207	4.1%	1.57 [1.02, 2.43]
Sohn 1985	115	300	79	318	8.6%	1.54 [1.21, 1.96]
Sonntag 1930	60	263	59	427	6.2%	1.65 [1.19, 2.28]
Sutro 1935	51	302	30	308	4.3%	1.73 [1.14, 2.64]
Tabira 2012	70	102	32	102	6.4%	2.19 [1.60, 3.00]
Yano 1928	21	62	18	86	2.9%	1.62 [0.94, 2.77]
Subtotal (95% CI)		**5196**		**3586**	**84.6%**	**1.74 [1.61, 1.88]**
Total events	1627		686			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 15.62$, df = 16 (P = 0.48); $I^2 = 0\%$						
Test for overall effect: Z = 13.83 (P < 0.00001)						
1.1.2 Osteoarthritis only						
Hou 2019	601	1083	59	276	8.9%	2.60 [2.06, 3.28]
Pritchett 1985	105	300	45	300	6.5%	2.33 [1.71, 3.18]
Subtotal (95% CI)		**1383**		**576**	**15.4%**	**2.50 [2.07, 3.01]**
Total events	706		104			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.29$, df = 1 (P = 0.59); $I^2 = 0\%$						
Test for overall effect: Z = 9.65 (P < 0.00001)						
Total (95% CI)		**6579**		**4162**	**100.0%**	**1.84 [1.66, 2.03]**
Total events	2333		790			
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 28.72$, df = 18 (P = 0.05); $I^2 = 37\%$						
Test for overall effect: Z = 11.68 (P < 0.00001)						
Test for subgroup differences: $Chi^2 = 12.52$, df = 1 (P = 0.0004), $I^2 = 92.0\%$						



Study or Subgroup	Age< 40 yrs Events	Total	Age >40 yrs Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Berthuambe 2019	9	20	85	192	6.1%	1.02 [0.61, 1.69]
Chung 1934	39	201	65	147	7.2%	0.44 [0.31, 0.61]
Egerci 2016	4	88	110	912	3.7%	0.38 [0.14, 1.00]
Ghimare 2017	54	75	101	240	7.8%	1.71 [1.39, 2.10]
Gruber 1875	16	93	46	141	6.2%	0.53 [0.32, 0.87]
Haghihara 1953	20	58	144	244	7.0%	0.58 [0.40, 0.85]
Hauser 2015	2	20	103	380	2.5%	0.37 [0.10, 1.39]
Hessen 1935	49	460	105	482	7.3%	0.49 [0.36, 0.67]
Kitahara 1935	10	63	5	14	4.0%	0.44 [0.18, 1.10]
Lungmass 1954	73	404	124	484	7.5%	0.71 [0.55, 0.91]
Piyawinijwong 2012	19	78	125	294	6.7%	0.57 [0.38, 0.87]
Pop 2018	27	207	46	224	6.6%	0.64 [0.41, 0.98]
Sohn 1985	79	318	115	300	7.6%	0.65 [0.51, 0.82]
Sonntag 1930	59	427	60	263	7.2%	0.61 [0.44, 0.84]
Sutro 1935	30	308	51	302	6.7%	0.58 [0.38, 0.88]
Yano 1928	18	86	21	62	6.0%	0.62 [0.36, 1.06]
Total (95% CI)		**2906**		**4681**	**100.0%**	**0.63 [0.49, 0.81]**
Total events	508		1306			

Heterogeneity: $Tau^2 = 0.21$; $Chi^2 = 102.00$, df = 15 ($P < 0.00001$); $I^2 = 85\%$

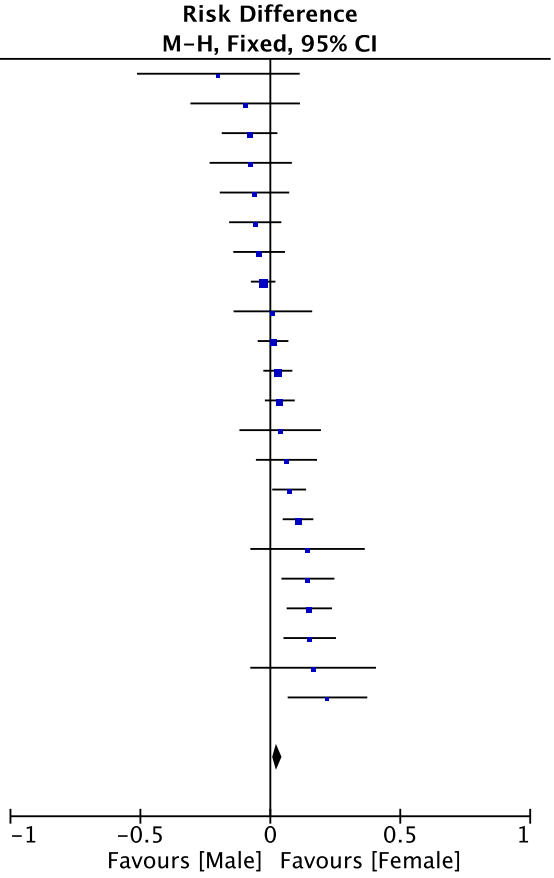
Test for overall effect: $Z = 3.61$ ($P = 0.0003$)



Study or Subgroup	Male Events	Male Total	Female Events	Female Total	Weight	Risk Difference M-H, Fixed, 95% CI
Ost 1877	2	20	3	10	0.4%	-0.20 [-0.51, 0.11]
Ghimare 2017	50	124	13	26	1.4%	-0.10 [-0.31, 0.11]
Ortega 2018	24	88	110	312	4.4%	-0.08 [-0.19, 0.03]
Kojima 1958	29	100	19	52	2.2%	-0.08 [-0.23, 0.08]
Berthuambe 2019	42	102	52	110	3.4%	-0.06 [-0.19, 0.07]
Lencina 2007	5	58	14	97	2.3%	-0.06 [-0.16, 0.04]
Piyawinijwong 2012	75	204	69	168	5.9%	-0.04 [-0.14, 0.06]
Hessen 1935	70	468	84	474	15.1%	-0.03 [-0.07, 0.02]
Kitahara 1935	9	50	8	47	1.6%	0.01 [-0.14, 0.16]
Rothe 1927	59	402	27	198	8.5%	0.01 [-0.05, 0.07]
Lungmass 1954	160	770	44	246	12.0%	0.03 [-0.03, 0.08]
Sonntag 1930	83	448	36	242	10.1%	0.04 [-0.02, 0.09]
Kaneko1966	50	124	19	52	2.4%	0.04 [-0.12, 0.19]
Parson 1897	49	157	21	84	3.5%	0.06 [-0.06, 0.18]
Pfizner 1892	25	198	5	93	4.1%	0.07 [0.01, 0.14]
Mikami 1932	61	315	17	195	7.7%	0.11 [0.05, 0.17]
Ooi 1930	11	27	14	53	1.1%	0.14 [-0.08, 0.36]
Frey 1913	14	80	1	33	1.5%	0.14 [0.04, 0.25]
Hanumaro 1927	72	200	42	200	6.4%	0.15 [0.06, 0.24]
Chung 1934	89	266	15	82	4.0%	0.15 [0.05, 0.25]
Sugiyama 1914	28	53	8	22	1.0%	0.16 [-0.08, 0.41]
Yano 1928	44	151	1	14	0.8%	0.22 [0.07, 0.37]
Total (95% CI)		**4405**		**2810**	**100.0%**	**0.03 [0.01, 0.05]**
Total events	1051		622			

Heterogeneity: $Chi^2 = 56.81$, df = 21 ($P < 0.0001$); $I^2 = 63\%$

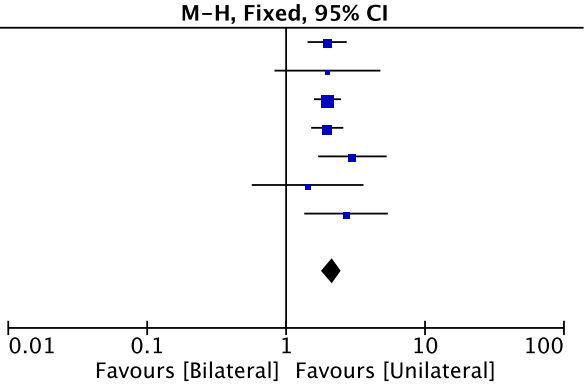
Test for overall effect: Z = 2.78 (P = 0.005)



Study or Subgroup	Bilateral Events	Bilateral Total	Unilateral Events	Unilateral Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Berthuambe 2019	38	38	18	36	16.1%	1.97 [1.43, 2.73]
Chung 1934	61	61	2	4	3.9%	1.98 [0.83, 4.77]
Egerci 2016	76	76	38	76	32.6%	1.99 [1.59, 2.49]
Gruber 1875	42	42	27	54	20.4%	1.98 [1.51, 2.58]
Hauser 2015	45	400	15	400	12.7%	3.00 [1.70, 5.29]
Kitahara 1935	10	100	7	100	5.9%	1.43 [0.57, 3.60]
Yano 1928	27	165	10	165	8.5%	2.70 [1.35, 5.40]
Total (95% CI)		**882**		**835**	**100.0%**	**2.14 [1.83, 2.50]**
Total events	299		117			

Heterogeneity: $Chi^2 = 3.54$, df = 6 (P = 0.74); $I^2 = 0\%$

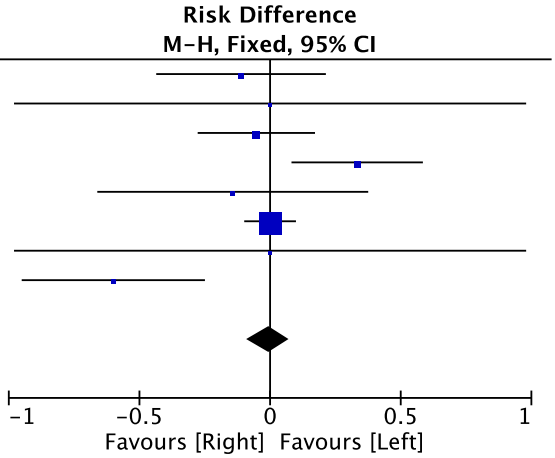
Test for overall effect: Z = 9.44 (P < 0.00001)



Study or Subgroup	Right Events	Right Total	Left Events	Left Total	Weight	Risk Difference M-H, Fixed, 95% CI
Berthuambe 2019	8	18	10	18	6.2%	-0.11 [-0.44, 0.21]
Chung 1934	1	2	1	2	0.7%	0.00 [-0.98, 0.98]
Egerci 2016	18	38	20	38	13.1%	-0.05 [-0.28, 0.17]
Gruber 1875	18	27	9	27	9.3%	0.33 [0.08, 0.58]
Kitahara 1935	3	7	4	7	2.4%	-0.14 [-0.66, 0.38]
Piyawinijwong 2012	72	186	72	186	64.1%	0.00 [-0.10, 0.10]
Sutro 1935	1	2	1	2	0.7%	0.00 [-0.98, 0.98]
Yano 1928	2	10	8	10	3.4%	-0.60 [-0.95, -0.25]
Total (95% CI)		**290**		**290**	**100.0%**	**-0.01 [-0.09, 0.07]**
Total events	123		125			

Heterogeneity: Chi^2 = 18.86, df = 7 (P = 0.009); I^2 = 63%

Test for overall effect: Z = 0.17 (P = 0.86)



and 1.84 [1.66, 2.03 95%CI] respectively, which meant that combined effect of ARD and OA increased the prevalence of fabella by 84%. The OR and RR for 'OA only' in 1,959 knees were 3.81 [2.56, 5.68 95% CI] and 2.50 [2.07, 3.01 95%CI] respectively. Thus, OA had increased the prevalence of fabella by 150%. OR and RR for 'ARD only' in 8,782 knees were 2.22 [1.91, 2.58 95%CI] and 1.74 [1.61, 1.88 95%CI] respectively, and ARD would increase the fabellar prevalence by 74% (Table 3). The RR for developing fabella 'under 40 years' was 0.63 [0.49, 0.81 95%CI], which meant ARD increased the prevalence of fabella by 63% (Table 4). The difference of 11% risk in age 'more than 40 years' might be due to the early development of OA, which was not recognized in radiographs.

The RR of fabella in the USA (North American) and Middle - East Asian were 2.65 and 2.18, but quite lower in European (1.79) and Asian Mongoloid ethnicity (1.65). The observed higher risk in North American or Middle-East Asians could be attributed to the smaller sample size. Female participants had a 3% higher risk (RD) of prevalence of fabella in comparison with males (P=0.007) (Table 5). Laterality analysis did not show any risk difference of fabellar prevalence, and fabella was distributed equally on both sides (the diamond of risk estimate located on 'no effect line'). The prevalence of bilateral fabella was higher than unilateral fabella, but estimation was done based on seven studies, and the estimated RR was 2.14 (1.83-2.50; 95% CI) in OA and ARD (Table 6). Thus, bilateral fabellar prevalence was 114% higher than the unilateral. The data pooled from Asian -Mongoloid ethnicity (Chinese, Japanese, Korean, and other nearby ethnicities) presented significant heterogeneity compared with European studies. Data from the USA and the Middle East could not be compared due to insufficient studies for comparison. There was no significant difference between the OR of studies from journal articles and conference presentations. The meta-regression of the effect size of fabellar prevalence with the year of publication had an insignificant association. Sensitivity and cumulative analysis were done to detect RR variation after adding and

removing each study, respectively. The variation in RR was constant with minimum variation (0-0.05) after 4,768 knees were included in the studies. The authors examined approximately 11,000 knees, and RR will not vary beyond this range. Hence it was determined that any further study would not impact the RR.

Publication bias

Some publication bias was presumed to be present, as presented in the funnel plot, but that could be due to sample variations (Figure 2). The same bias was further investigated by Egger's regression test (P = 0.517) and Begg & Mazumdar's rank correlation test (P = 0.846). These two findings indicated no publication bias. Rosenthal's fail-safe number was estimated and found to be higher than the Rosenthal rule of thumb 5k + 10 value, e.g., 110 (k = 20). Rosenthal Fail-safe number passed the File drawer test. Reporting bias was expected in the qualitative analysis, but the quantitative analysis refuted the assumption. Thus, the observed prevalence did not need adjustment. Dose-response meta-analysis was not performed due to lack of suitable data.

Discussion

This meta-analysis summarizes the finding of 20 observational studies, encompassing a total of 11,056 knees, investigating the association of prevalence of fabella and OA along with ARD. This analysis presented the increased risk of developing fabella in an OA knee. The ARD process has an additional impact on the prevalence of fabella. This analysis measured the risk estimates of the cumulative as well as individual effects of OA and ARD. Sufficient data was unavailable to find age-adjusted risk estimates of fabellar prevalence in OA. The fabellar prevalence was higher bilaterally, and on the right side in case of unilateral prevalence. A similar distribution was found in the literature for OA. OA has bilateral with asymmetrical

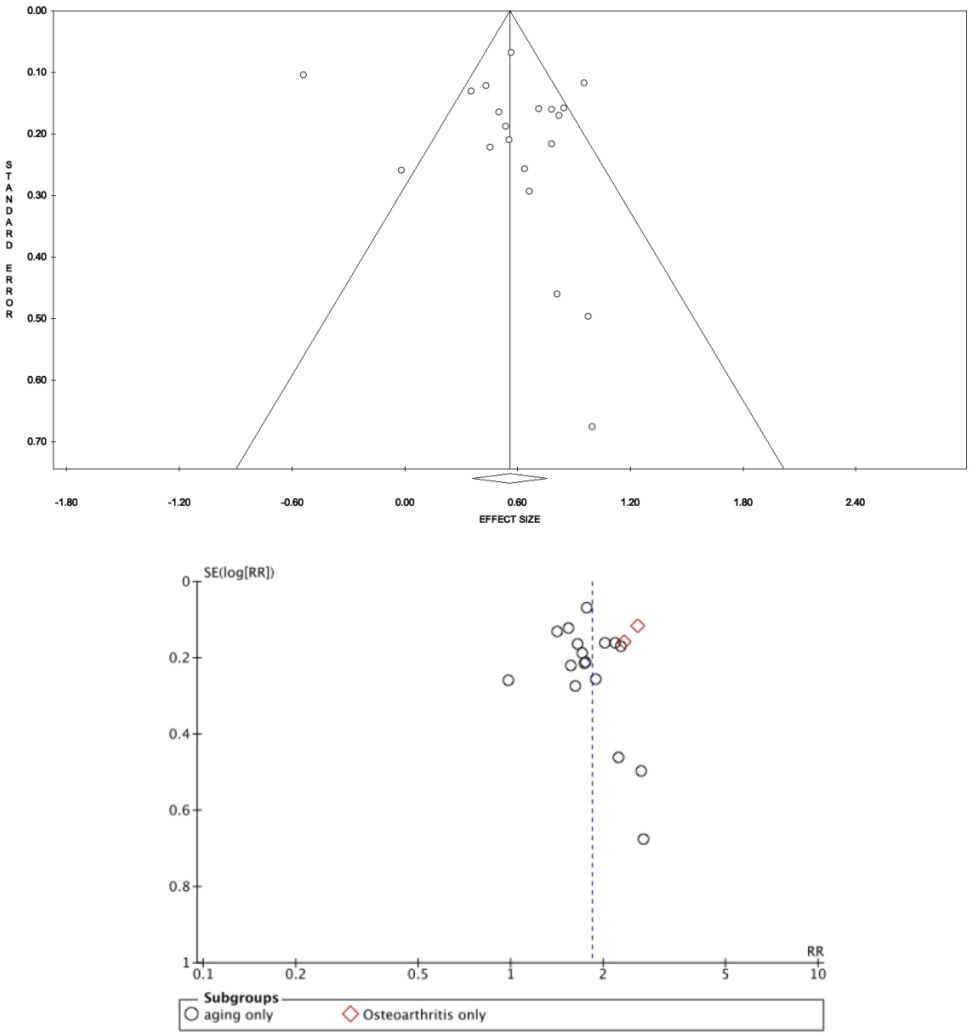


Figure 2: Publication bias of included studies.

508x557mm (72 x 72 DPI)

presentation and farther on the right side in terms of severity, which mimics the distribution of fabella in OA (Heidari, 2011; Guermazi et al., 2012). In this meta-analysis, publication bias may have a minor role due to the existence of some unpublished data. The publication bias and other biases were reduced to a minimum by excluding studies that did not meet the selection criteria and ROBINS I grading. As very few small sample sized studies were missing on examining the funnel plot, so it did not affect the risk estimates. Some degree of heterogeneity was due to the differences between the methodologies and the study populations.

Potential biases in the study

Because only 20 studies were included for the risk estimate without adjustment of age and sex, the analysis was not free of possible confounding factors. ARD and OA are inter-related to each other, and their relationship is a major hurdle to get the pooled estimates of effect size. The size of fabella and its degeneration could not be considered because of variable methods of measurement of dimensions (linear measurement or three-dimensional measurement). Apart from OA and ARD, traumatic injury, chondromalacia, bony stress, physical habits, or occupational need may affect the fabellar prevalence in these studies. But studies included in this meta-analysis did not have sufficient information to stratify for the above factors.

This meta-analysis confirms the role of biomechanical stimulus due to knee degeneration, and ARD in the prevalence of fabella. The sesamoid bone appears as a cartilaginous nodule, and it is under the regulation of genetic and environmental factors (Yammine, 2014, 2015; Berthaume and Bull, 2019). But, the ossification of fabella in a later stage needs a mechanical stimulus, especially in the form of traction (Eyal et al., 2019). Sesamoid bones form in the area of high mechanical stimuli like traction, friction, pressure, and stress. Without mechanical stimuli, genetics and ARD processes may have a key role in ossification. The genetic influence could not be measured, but the effects of ARD were measured in this meta-analysis. ARD was

another predisposing factor which may cause fabellar ossification even in less active individual (Laird, 1991; Ando et al., 2017). There was disagreement about the age of fabellar ossification, but Pancoast and Ehara demonstrated that an ossified fabella could be found in as early as 12 years of age (Pancoast H, 1909; Ehara, 2014). Chung did not find cartilaginous fabella in individuals aged more than 60 years. An increasing ratio of ossified fabella and cartilaginous fabella with age was documented by Chung (1934). The prevalence of fabella was rising with age and reaching a plateau phase near the age of sixty in normal adults (Scheuer and Black, 2004). Laird et al. (1991) showed the fabellar prevalence increased with age. A similar finding was also documented by Phukubye et al. (2011), but they did not find a correlation with age. Recently, Egerci et al. (2017) demonstrated the correlation between fabellar prevalence with age. Conversely, Tabira et al. (2013) did not get such association, which might be due to low sample size.

There were five case reports of fabella syndrome after total knee arthroplasty (Driessen et al., 2014; Dominic et al., 2018). The mean age of the subjects presenting with fabella syndrome (one male and five females) was 63 years. The case reports showed that ossified fabella often produces clinical symptoms in runners and soccer players (Dashefsky, 1977; Kuur, 1986; Chávez and Chaparro, 2010). These reports supported the idea of biomechanical stimulus or mechanical loading. The gastrocnemius acts as a protagonist at the late stance phase of gait kinematics and undergoes into rotational strain during the locking mechanism of knee extension. Popliteus also undergoes rotational strain during the unlocking of the knee. So, the tendons of both gastrocnemius and popliteus develop sesamoids named as fabella and cyamella, respectively. The presence of fabella is advantageous in Knee OA. The disability because of knee OA is less if fabello-fibular ligament existed (Terry and LaPrade 1996). The Fabello- fibular ligament connects the fabella with the fibula, which would help to redirect and redistribute mechanical load to the fibula.

Limitation of study

Although this analysis provides invaluable data about the prevalence of fabella in OA and ARD, there are some limitations. The studies included in the analysis were from different ethnicity and methodologies, and hence were not comparable. The pooled estimates were not free of possible confounding factors like age, sex, physical habitus or occupation, and severity of OA. The unequal samples of knees per study and variable knee and individual ratio may influence the outcome. The sample variation could have an impact on prevalence estimates. Relatively low numbers of studies (20 studies) may have skewed the results.

Conclusions

The prevalence of fabella is higher in OA than non-OA subjects and lesser prevalence of fabella in subjects under 40 years (Table 7: Summary of findings). It helps to understand the variation of fabellar prevalence in old and young subjects. Consistent with previous findings, the prevalence of fabella is higher in female subjects and on the right side of the knee. The prevalence of bilateral fabella is much higher than the unilateral fabella. These are related to the distribution of OA, which is bilateral, asymmetrical, and common on the right side. The further scope of the study is to evaluate the prevalence of fabella in players, security personnel, and population residing near the mountains, which will provide the impact of biomechanical stress or load on the prevalence of fabella. The stratification of the suggested study will provide the final estimate of the prevalence of fabella based on the biomechanical load on the knee and help in understandings the role of fabella in knee kinematics.

Conflicts of Interest: Nil

Funding supports: Nil

Prospero registration: CRD42020161834 (Dated 28-04-2020)

Author(s):
Question: [Osteoarthritis or ageing] compared to [Nonosteoarthritic or age <40yrs] for [Fabellar prevalence worldwide]
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[Osteoarthritis or ageing]	[Nonosteoarthritic or age <40yrs]	Relative (95% CI)	Absolute (95% CI)		
Fabellar prevalence (assessed with: Event rate)												
19	observational studies	not serious	not serious	not serious	not serious	none	2333/6579 (35.5%)	790/4160 (19.0%)	**RR 1.84** (1.66 to 2.03)	**160 more per 1,000** (from 125 more to 196 more)	⨁⨁⨁⨁ HIGH	IMPORTANT
								0.0%		**0 fewer per 1,000** (from 0 fewer to 0 fewer)		
Fabellar prevalence in ageing (assessed with: Event rate)												
17	observational studies	not serious	not serious	not serious	not serious	none	1627/5196 (31.3%)	686/3586 (19.1%)	**RR 1.74** (1.66 to 1.88)	**142 more per 1,000** (from 126 more to 168 more)	⨁⨁⨁⨁ HIGH	IMPORTANT
								0.0%		**0 fewer per 1,000** (from 0 fewer to 0 fewer)		
Fabellar Prevalence in Osteoarthritis (assessed with: Events rate)												
2	observational studies	not serious	not serious	not serious	not serious	none	706/1383 (51.0%)	104/576 (18.1%)	**RR 2.50** (2.07 to 3.01)	**271 more per 1,000** (from 193 more to 363 more)	⨁⨁⨁⨁ HIGH	CRITICAL
								0.0%		**0 fewer per 1,000** (from 0 fewer to 0 fewer)		

CI: Confidence interval; **RR:** Risk ratio

Author(s):
Question: [No ageing] age less than 40 years compared to Age more than 40 years for Fabellar Prevalence worldwide
Setting: Hospital Settings
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[No ageing] age less than 40 years	Age more than 40 years	Relative (95% CI)	Absolute (95% CI)		
Fabellar Prevalence in age group less than 40 years (assessed with: Events rate)												
17	observational studies	not serious	not serious	not serious	not serious	none	508/2906 (17.5%)	1306/4681 (27.9%)	**RR 0.63** (0.49 to 83.00)	**103 fewer per 1,000** (from 142 fewer to 1,000 more)	⨁⨁⨁⨁ HIGH	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Author contributions:

AA: Conceptualization, Generating Keywords, Search strategy, Analysis, Manuscript draft

SN: Search strategy, Shortlisting, Inclusion & exclusion criteria, Manuscript editing

RN: Literature search, Shortlisting, Collection of studies, Data extraction, Manuscript Drafting

AK: Literature search, Shortlisting, Collection of Studies, Data Extraction, Manuscript editing

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Search strategy (PubMed):

(((((((Fabella[Title/Abstract]) OR Knee sesamoid[Title/Abstract]) OR Popliteal Sesamoid[Title/Abstract]) OR Sesamoid[Title/Abstract])) AND ((((Prevalence[Title/Abstract]) OR Incidence[Title/Abstract]) OR event rate[Title/Abstract]) OR events[Title/Abstract])) AND (((((Osteoarthritis[Title/Abstract]) OR Knee Degeneration[Title/Abstract]) OR Knee Pain[Title/Abstract]) OR Knee aging[Title/Abstract]) OR Genu pain[Title/Abstract])) NOT Animal').

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Table1: The characteristics of included studies and risk bias based on ROBINS I (for intervention based observational studies)

Table 2: AQUA tool risk of bias for anatomical studies. The five domains have twenty items in toto. The score of 5 for each response and total score calculated from 100 in percentage.

Table 3: The forest plot of fabellar prevalence in osteoarthritis and ARD and along with subgroup analysis. The subgroup analysis was done to deal with existing heterogeneity among the studies.

Table 4: The forest plot of fabellar prevalence to assess in age under 40 years.

Table 5: The forest plot of fabellar prevalence in both sexes.

Table 6: (A) The forest plot of laterality distribution of fabella (Bilateral vs unilateral) (B) Right vs Left

Table 7: The summary of findings

Figure 1:PRISMA flow chart.

Figure 2: Publication bias of included studies.