RESEARCH ARTICLE

REVISED Cross-sectional assessment of cardiovascular risk factors in patients with knee osteoarthritis [version 3; peer review: 2 approved]

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Abstract

Background: Osteoarthritis (OA) and cardiovascular disease (CVD) are prevalent in India. However, there is dearth of literature among Indians studying the relationship between the two. This study was carried out to assess various cardiovascular (CV) risk factors in patients with knee OA with an objective to investigate their association, screening and management.

Methods: In total, 225 patients were included in this cross-sectional study. Participants were diagnosed with knee OA on the basis of the Kellgren and Lawrence (K-L) classification of their radiograph. Participants were also assessed for CV risk factors; age, body mass index, systolic blood pressure, diabetes mellitus, total cholesterol, high-density lipoprotein, smoking. Joint British Society QRisk3 calculator (JBS3) a comprehensive risk score calculator as well as a screening tool, which produces three more variables, namely 10-years risk of developing CVD, physiological heart age and life expectancy, was used. Chi Square, Fishers exact test and one-way ANOVA tests were used to compare the categorical and quantitative variables, respectively.. Multiple regression analysis was done to adjust the multiple con-founders and determine their significance.

Results: Patients with severe knee OA had a statistically significantly higher prevalence of CV risk factors ($p < 0.05$). Grade 4 knee OA patients were found to have a mean JBS3 risk of 38%, heart age of 82 years and life expectancy of 77 years as compared to grade 2 patients who had a mean JBS3 risk of 11%, heart age of 63 years and life expectancy of 82 years.

Conclusions: Our study concluded that there is a strong relation

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between knee OA and CVD, with CV risk score being positively correlated to the severity of OA.

Keywords

Osteoarthritis, Cardiovascular disease, Cardiovascular risk factors, JBS3 risk, Hypertension, Diabetes Mellitus, Smoking, Age, Sex, SES, Heart Age, Life Expectancy, Kellgren Lawrence,

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REVISED Amendments from Version 2

In this version of article, the author has tried to further concise the material especially in discussion part. Concept of systemic inflammation underlying OA and CVD is added in introduction and discussion. Figure 5 and text related to Pearson's coefficient has been removed as it was found to be wrongly used in earlier version. In order to further concise the tables in results section, inference column is removed. Conclusion and implication are rephrased in order to suit the aims and objectives of the article as mentioned in the introduction.

Any further responses from the reviewers can be found at the end of the article

Introduction

Osteoarthritis (OA), a degenerative joint disease, is the sixth most predominant cause of disability around the world and a well-established cause of restricted activity, disability, and low quality of life.¹ Its prevalence, currently at 3.5% of the world's total population and about 35% in adults older than 60 years,² is on the rise. OA has become an important public health issue and is burdensome for both personal health and social well-being.² Both developed and developing nations see it as a major liability on their health care sector with it having severe social and economic impacts.¹

OA is associated with joint pain, functional limitation and deformity and it incurs articular cartilage degeneration, osteophyte formation in joints, reduced joint space and subchondral sclerosis.³ The etiology of OA is idiopathic, yet age, genetics, obesity, menopause, hypertension, and diabetes mellitus have been found to be major contributors.⁴ Some of these risk factors that are directly involved and others indirectly involved in the etiopathogenesis of OA are also seen to increase the risk of cardiovascular diseases (CVDs), namely congestive heart failure (CHF), ischemic heart disease (IHD), transient ischemic attacks (TIA) and stroke.⁴ This group of cardiovascular diseases are also the leading cause of mortality and morbidity worldwide.⁵ Therefore, it becomes important to identify the various cardiovascular risk factors like age, gender, obesity, hypertension, cholesterol, sedentary lifestyle, smoking and nutrition at the earliest opportunity through various screening methods, especially in patients with OA.³

A possible association between OA and cardiovascular risk factors is evident by a study done at Leigh where above average levels of serum cholesterol were observed, especially in women with osteoarthritis of hands.³ Another study found a high prevalence of cardiovascular risk factors in adults with knee OA.⁵ Recently, a new classification for phenotyping of OA, which includes metabolic syndrome, aging, and posttraumatic arthritis, has been developed. Obesity is a well-known contributor for metabolic syndrome.⁶ Observational studies have shown that hypertension is an independent risk factor for knee OA.^{6,7} Indirectly, physical inactivity, due to debilitating joint pain, also makes patients more prone to CVD.⁷ Recently, in a systemic review and meta-analysis, it was questioned whether aerobic exercise is being used adequately in patients with knee OA as under-prescription of it could be a potential source of increased risk of CVD.⁸ The concept of systemic inflammation as potential pathogenesis, underlying both OA and CVD has been under scanner for some time now; as opposed to the traditional view of wear and tear.^{2,3} There are studies showing positive correlation of knee OA with metabolic syndrome, hypercholesteremia and DM.^{6,12,25}

Given that OA and CVD are common conditions in the elderly, a thorough knowledge of the relationship between OA and CVD could help further our understanding of potential biological and behavioral mechanisms, which could in turn help in making informed decisions regarding further management of OA. There is a dearth of literature relating knee OA and cardiovascular risk factors in the Indian population, hence we wanted to study this association among Indian participants. The objectives of the study were (i) to screen patients diagnosed with knee OA for cardiovascular risk factors who don't have a history of cardiovascular diseases; (ii) to find out the risk of developing a cardiovascular disease in next 10 years in patients suffering from knee OA using a simple standardized risk score calculator; and (iii) to correlate CVD risk with severity of knee OA.

Methodology**Ethics statement**

The research protocol with the informed consent form was approved in October 2018 by the Institutional Ethics Committee of Kasturba Medical College, Mangaluru (reference number IEC KMC MLR 10-18/363). Participants provided written informed consent to participate. In addition, case records of patients diagnosed with knee OA between January 2017 to September 2018 were studied. Permission to access the previous records was obtained from the medical superintendent of the hospitals associated with Kasturba Medical College, Mangalore through the proper channel including head of department of orthopedics and Institutional Ethics committee. Confidentiality of the participants was maintained by concealing their name and identity. Each participant was given a unique serial number. The patients were not charged extra for any test or investigation other than their routine healthcare charges.

Study design

This cross-sectional study was done in the tertiary care centres associated with Kasturba Medical College, Mangalore, India. The study was carried out between October 2018 and September 2020.

Study participants

Patients diagnosed with knee osteoarthritis (Kellgren and Lawrence (KL) grade ≥ 2 on knee X-ray⁹) and ≥ 50 years old¹⁰ were invited to take part. The KL grading system is as follows:

1. Grade 0 (none): the definite absence of x-ray changes of osteoarthritis
2. Grade 1 (doubtful): doubtful joint space narrowing and possible osteophyte lipping
3. Grade 2 (minimal): definite osteophyte and possible joint space narrowing
4. Grade 3 (moderate): moderate multiple osteophytes, definite narrowing of joint space, and some sclerosis and possible deformity of bone ends.
5. Grade 4 (severe): large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone ends.

Exclusion criteria were patients who refused to give consent, patients who were suffering from secondary knee OA, and patients who were known cases of coronary artery disease. We did not exclude patients based on their comorbidities such as diabetes, hypertension, RA.

The sample size was calculated to be 187 using the Cochran's formula¹¹:

$$n = \frac{p*q*Z\alpha^2}{d^2}$$

where, $Z\alpha = 1.96$ at 95% confidence level

p (estimated proportion of an attribute that is present in the population) = 34% with respect to study by Kim HS *et al.*¹² This is comparable to the prevalence of knee OA found in Indian population. In a community based cross sectional study overall prevalence of knee OA was found to be 28.7%.¹³ Along similar lines, another community based cross sectional study found prevalence of knee OA to be 27.1%.¹⁴

q = 66% (q = 100-p)

d (desired precision) = 20% of p at 80% power

With 95% confidence level and 80% power. Though the sample size was calculated to be 187, we collected data from 225 patients due to additional time and resources.

Sampling

This study employed convenience sampling. Patients aged more than 50 years presenting to the orthopaedics out-patient department with complains of knee pain between October 2018 and September 2019 were recruited for the study. Also, case records of patients diagnosed with knee OA between January 2017 to September 2018 were studied. No prior randomization was done.

Variables

Patient demographics such as age, gender, weight, height, body mass index (BMI), socioeconomic status and their smoking habits were recorded. Weight bearing knee radiographs in anterior, posterior and lateral views were done. Those with knee OA of K-L grade of 2 or more were included in the study. Serum total cholesterol and high-density lipoprotein (HDL) was determined. History of ongoing treatment for hypertension, diabetes, rheumatoid arthritis and CVD in relatives before age of 60 years was gathered. All these variables were added in the JBS3 risk score calculator which then produced three more variables; physiological heart age, life expectancy, and JBS3 risk of developing CVD in the next 10 years.

JBS3 risk score calculator was devised by joint British society for general practitioners to help guide their work with patients, in preventing CVD. A major role of the JBS3 risk score calculator is the idea of estimating CVD risk over a lifetime. Patients can also be screened for cardiovascular risk factors that they are unaware of.

Procedure

Case records of patients aged 50 years and above, diagnosed with knee osteoarthritis, between January 2017 and September 2018, and patients coming to the Out Patient Department (OPD) from October 2018 to September 2019 were studied. Patients were briefed about the aims and implications of the study, and consenting patients were recruited into the study.

Each patient was given a unique serial number and a detailed history and examination were done by the principle investigator of the study. History of presenting illness along with past, treatment and family history were gathered. Examination included general physical examination along with cardiovascular systemic examination and local knee examination. Orthopaedic evaluation was done using K-L grading¹⁰ and CV risk was determined using the JBS3 CV risk score calculator.¹⁵ Fasting blood sample was collected to know the levels of their serum total cholesterol and serum high density lipoprotein. The standard procedure of phlebotomy was followed. 3ml of blood was drawn from the patient and collected in plain vacutainer for serum analysis of total cholesterol and serum high density lipoprotein. The sample was sent to Biochemistry laboratory where they analysed using enzymatic colorimetric method using enzyme cholesterol esterase and peroxidase for total cholesterol and polymer polyanion method for HDL. Patient details and blood test results were uploaded to the unique profile created for each one of them in the mobile application based JBS3 CV risk score calculator¹⁵ which then predicted physiological heart age, life expectancy, and JBS3 risk of developing CVD in the next 10 years.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) version 20 was used to do the statistical analysis. The categorical variables like age, gender, smoking habits, ongoing treatment for hypertension, diabetes, history of CVD in relatives before age of 60 years and history of rheumatoid arthritis (RA) were compared with K-L grade of knee OA using chi square test. Socioeconomic status and history of RA were compared with K-L grades using Fishers exact test. The quantitative variables like BMI, total cholesterol, HDL, physiological heart age, life expectancy and 10 years risk of developing CVD were compared with K-L grades using analysis of variance (one-way ANOVA) test. A p value of <.05 was considered significant and less than 0.01 was considered highly significant.

Post hoc analysis was done to compare multiple groups means. The mean heart age and mean physiological heart age among the three K-L grades of knee OA were compared using paired t test. A p value <.05 was considered significant. Receiver operating characteristic (ROC) curve was used to show in a graphical way the connection/trade-off between clinical sensitivity and specificity for 10 years risk of developing CVD in the study population.

Results

A total of 225 patients visiting the orthopaedics OPD with complaints of knee pain took part in the study.³² All participants were over 50 years of age with more than half (53%) of them between the age of 50-60 years (Figure 1). The majority of these patients were females (59%) (Figure 1). As per the BG Prasad socioeconomic scale (SES),¹⁶ the majority of them belonged to either the middle or lower socio-economic group (Figure 1).

Grade 2 K-L classification of knee OA was found to be the most common (45%) among the study population. Higher grades of knee OA, i.e. 3 and 4, were found to be 42% and 13%, respectively (Figure 1). Overall, 57% of the patients belonging to the lower socio-economic class as per the BG Prasad SES had knee OA grade 2, 33% of them had grade 3 and only 10% had grade 4 OA. Among the lower middle and middle-class groups, a decrease in the percentage of patients with grade 2 and increase in percentage of patients with grade 3 and 4 was found as socioeconomic status increased. The same trend was observed, not strictly though, as we go further up the SES. Upper middle and upper-class patients had either grade 3 or 4 knee OA (Figure 2).

The Fishers exact test was used to find out the statistical significance of the relationship between socioeconomic status and knee OA grade, which was found to be highly significant (p value<.01). Chi square test, when applied to compare knee OA grade with age { $X^2(4, 225) = 3.801, p = .434$ } or gender { $X^2(2, 225) = 1.016, p = .602$ }, was not found to be statistically significant. A one-way ANOVA test was applied to K-L grade of knee OA with BMI and found to be highly statistically significant { $F(4,225) = 60.652, p < .01$ }. An increasing trend in the BMI of patients was noted with a higher grade of knee OA, e.g. 60% of grade 2 knee OA patients had a BMI of less than 25 as compared to 40% in grade 3 and only 7% in grade 4. In addition, 57% of patients with grade 4 knee OA had a BMI of more than 30 as compared to 13% in grade 3 and only 4% in grade 2 (Table 1).

Figure 1. Age, Gender, BG Prasad socioeconomic scale, KL grade, BMI and history of smoking distribution of the study population.

Figure 2. Distribution of knee osteoarthritis (OA) severity by socioeconomic group. Higher socioeconomic groups had a higher proportion of patients with severe grade knee OA.

The mean BMI of patients with grade 2 knee OA was 24.82, grade 3 was 26.39 and grade 4 was 30.96, with each knee OA grade showing statistically significant data when compared with the BMI of patients (Table 2). In post hoc analysis using the Bonferroni test with BMI as the dependent variable, it was found that multiple comparisons of each of grade of knee OA with the other were found to be statistically significant, as depicted in Table 3.

Of the 225 participants, 18.2% (n = 41) were smokers. All the smokers were male, and 39% of them had grade 2 knee OA, 44% of them had grade 3 and 17% of them had grade 4. However, this data was not statistically significant on chi square test $\{X^2(2, 225) = 0.964, p = .617\}$ (Table 1).

The mean systolic blood pressure (SBP) of participants was 128mmhg, 139mmhg and 150mmhg for grade 2, grade 3 and grade 4 knee OA, respectively. Table 2 shows the representation of mean SBP for each K-L grade. On comparing each grade with each other using post hoc analysis with SBP as the Bonferroni dependent variable, the comparisons came out to be highly significant (Table 3).

Of the 225 participants, 88 had a SBP reading of 140 or more, out of which 28 (33%) were not taking any antihypertensive medication. In total, 25.8% of the entire sample had a history of diabetes mellitus (DM), which is much lower than more than half (53%) of patients with grade 4 knee OA. Of grade 3 patients, 40% had DM, yet of grade 2, only 4% had DM. This was found to be statistically significant $\{X^2(2, 225) = 47.574, p < .01\}$ as per the chi square test (Table 1).

Table 1. Results of all of the qualitative variables against each of the grade of severity of knee OA (K-L Grade) and p value as measured by chi square/Fischer's exact test.
 Count = number of study samples in each K-L grade with respect to the corresponding variable; Total = number of study samples in each K-L grade; Column N% = Count/Total;
 Row N% = Count/number of study samples in a subgroup of a variable; p value < .05 is considered significant, p value of < .01 is considered highly significant.

		Severity of knee OA (K-L Grade)												Chi square/Fishers exact test p value
		Grade 2			Grade 3			Grade 4						
		Count	Column N %	Row N %	Count	Column N %	Row N %	Count	Column N %	Row N %	Count	Column N %	Row N %	
BMI	< 25	60	59%	60%	38	40%	38%	2	7%	2%				.000
	25-30	37	37%	40%	44	47%	48%	11	37%	12%				
	> 30	4	4%	12%	12	13%	36%	17	57%	52%				
	Total	101	100%	45%	94	100%	42%	30	100%	13%				
History of smoking	No	85	84%	46%	76	81%	41%	23	77%	13%				.617
	Yes	16	16%	39%	18	19%	44%	7	23%	17%				
	Total	101	100%	45%	94	100%	42%	30	100%	13%				
History of antihypertensive treatment	No	83	82%	70%	27	29%	23%	8	27%	7%				.000
	Yes	18	18%	17%	67	71%	63%	22	73%	21%				
	Total	101	100%	45%	94	100%	42%	30	100%	13%				
History of Diabetes Mellitus	No	97	96%	58%	56	60%	34%	14	47%	8%				.000
	Yes	4	4%	7%	38	40%	66%	16	53%	28%				
	Total	101	100%	45%	94	100%	42%	30	100%	13%				
H/O of CVD in near relative of <60 years of age	No	96	95%	51%	78	83%	41%	16	53%	8%				.000
	Yes	5	5%	14%	16	17%	46%	14	47%	40%				
	Total	101	100%	45%	94	100%	42%	30	100%	13%				
History of Rheumatoid arthritis	No	101	100%	47%	85	90%	40%	28	93%	13%				.007
	Yes	0	0%	0%	9	10%	82%	2	7%	18%				
	Total	101	100%	45%	94	100%	42%	30	100%	13%				
JBS3 (%)	0 - 10	56	55%	76%	15	16%	20%	3	10%	4%				.000
	11 - 25	41	41%	44%	45	48%	48%	8	27%	9%				
	> 25	4	4%	7%	34	36%	60%	19	63%	33%				
	Total	101	100%	45%	94	100%	42%	30	100%	13%				

Table 2. Total count, mean, standard deviation, ANOVA p value and significance of all of the quantitative variables against each of the grade of severity of knee OA (K-L Grade). p value <.05 is considered significant, p value <.01 is considered highly significant.

	Severity of knee OA (K-L Grade)	Count N	Mean	Standard deviation	95% Confidence interval for mean		ANOVA p value
					Lower bound	Upper bound	
BMI	2	101	24.8289	2.79067	24.2780	25.3798	.000
	3	94	26.3934	3.60523	25.6550	27.1318	
	4	30	30.9680	4.02460	29.4652	32.4708	
Mean systolic BP (mm Hg)	2	101	128.57	14.847	125.64	131.51	.000
	3	94	139.40	17.519	135.82	142.99	
	4	30	150.07	14.607	144.61	155.52	
Total cholesterol (mg/dl)	2	101	188.34	32.987	181.82	194.85	.000
	3	94	213.66	31.311	207.25	220.07	
	4	30	234.90	36.159	221.40	248.40	
High density lipoprotein (mg/dl)	2	101	53.74	7.152	52.33	55.15	.013
	3	94	51.99	7.444	50.46	53.51	
	4	30	49.30	8.014	46.31	52.29	
Mean age	2	101	59.72	6.763	58.39	61.06	.035
	3	94	61.71	6.558	60.37	63.06	
	4	30	62.80	7.194	60.11	65.49	
Mean physiological age	2	101	63.06	9.330	61.22	64.90	.000
	3	94	74.77	11.671	72.38	77.16	
	4	30	82.80	12.007	78.32	87.28	
Life expectancy	2	101	82.27	4.032	81.47	83.06	.000
	3	94	79.71	4.357	78.82	80.61	
	4	30	77.33	5.536	75.27	79.40	
JBS3 risk score (%)	2	101	11.18	6.560	9.88	12.47	.000
	3	94	23.19	14.433	20.24	26.15	
	4	30	37.86	22.043	29.63	46.09	

Table 3. Post hoc analysis of each of the variables using Bonferroni method and p value. p value <.05 is considered significant, p value <.01 is considered highly significant.

Bonferroni dependent variable	Comparisons between each grade of severity of knee OA		Bonferroni test p value
BMI	2	3	.004
		4	.000
	3	4	.000
Mean systolic BP	2	3	.000
		4	.000
	3	4	.005
Total cholesterol	2	3	.000
		4	.000
	3	4	.007
High density lipoprotein	2	3	.299
		4	.013
	3	4	.252
Mean age	2	3	.121
		4	.039
	3	4	1.00
Mean physiological age	2	3	.000
		4	.000
	3	4	.001
Life expectancy	2	3	.000
		4	.000
	3	4	.031
JBS3 risk score	2	3	.000
		4	.000
	3	4	.000

Similar trends were seen in the history of CVD among the relatives of the study population. A total of 35 (15.5%) patients gave a history of their relatives suffering from CVD in the past. Compared by grade, 46.7% of the patients with grade 4 knee OA gave a positive relative CVD history as compared to only 17% and 5% of the patients with grade 3 and 2 knee OA, respectively (Table 1). The chi square test for this difference was statistically significant { $X^2(2, 225) = 30.907$, $p < .01$ }.

None of the patients in the study population suffered atrial fibrillation (AF) or gave a history of chronic kidney disease in the past. Only 11 patients gave a history of rheumatoid arthritis which was found to be statistically significant by Fisher exact test ($p < .01$) (Table 1).

Serum total cholesterol (TC) and high-density lipoprotein (HDL) were tested for all the patients. Table 2 shows the mean levels of TC and HDL with respect to each of the KL grades of knee OA. An increase in mean value of TC and decrease in mean value of HDL were noted as K-L grades of knee OA increase. Patients with grade 2 knee OA had a mean TC value of 188.34 and mean HDL value of 53.74. Similarly, patients with grade 3 knee OA had a mean TC and HDL value of 213.66 and 51.99, respectively. Patients with grade 4 knee OA had a mean TC and HDL value of 234.90 and 49.30, respectively (Table 2).

In post hoc analysis using the Bonferroni test with TC as the dependent variable, it was found that multiple comparisons of each of grade of knee OA with the other were found to be highly statistically significant (Table 3). The same was not true,

however, with HDL, which showed statistically significant data only when K-L grade 2 was compared to grade 4 knee OA (Table 3).

This JBS3 risk score calculator gave us three parameters about the cardiovascular condition of the heart, i.e. physiological heart age, 10-year risk in percentage of developing a CVD and life expectancy provided any other cause of death is ruled out. Statistically significant results were obtained when studying the severity of knee OA with heart age and life expectancy. Physiological heart age came out lesser but life expectancy higher for patients with a lower grade of knee OA. As we go up the K-L grade of knee OA, the physiological heart age went up and the life expectancy came down (Figure 3).

The mean physiological heart age was found to be 70 years; 10 years older than the mean chronological age (60) of the study population.

Figure 3. As we go up the K-L grade of knee OA, the physiological heart age went up and the life expectancy came down.

Figure 4. ROC analysis for the JBS 3 risk score showed that a patient with K-L grade 4 of knee OA is more likely to be running a 10 years risk of developing CVD at minimum 14% with sensitivity of 72.3% and specificity of 66%.

Table 4. Multiple regression analysis with K-L Grade of knee OA as dependent variable.

Variable	Standardized coefficients (Beta value)	p value
History of antihypertensive treatment	.262	.000
History of Diabetes Mellitus	.115	.043
H/O of CVD in near relative of <60 years of age	.094	.079
History of Rheumatoid arthritis	.084	.095
BMI	.283	.000
Total cholesterol	.283	.000
High density lipoprotein	-.067	.168
Mean systolic BP	.051	.381

The JBS3 risk score also increased with the increase in the K-L grade of knee OA. Patients with grade 2 knee OA had a mean risk of around 11% of developing a CVD in the next 10 years and this increased with K-L grades, i.e. there was a 23% risk among the patients with grade 3 knee OA and 38% risk among those with grade 4 knee OA (Table 2). Chi square test found this to be statistically significant $\{X^2(4,225) = 70.776, p < .01\}$.

The Bonferroni post hoc analysis of K-L grade with the JBS3 risk score as the dependent variable showed multiple comparisons of each K-L grade with the others as statistically significant (Table 3). The ROC curve showing area under the curve of sensitivity vs specificity of grade 4 vs 2 and 3 for risk score is depicted in Figure 4. According to ROC analysis for the JBS3 risk score, it was determined that patients with K-L grade 4 knee OA were more likely to run a 10-year risk of developing CVD at minimum 14% with sensitivity of 72.3% and specificity of 66%. On analyzing the data using multiple regression with dependent variable as K-L Grade of knee OA (Table 4), we found that variables like history of hypertension treatment, diabetes mellitus, serum levels of total cholesterol and body mass index were found to be significant, rest all variables were found to be not significant.

Discussion

Osteoarthritis is a common disease in the elderly population, with its higher prevalence in the 50+ year age group well documented in the literature.^{1,3,12} The current study's entire sample of 225 patients were above the age of 50 years. Higher prevalence of knee OA in the 50-60-year age group was seen but with no statistical significance when compared with groups of higher ages. This could be attributed to the fact that this study did not include the entire population of the given area but rather only the patients coming to orthopaedic OPD with pain in the knee joint. Women are more likely to have knee pain above the age of 50 years¹⁰ and with no surprise our study also had women forming almost two thirds (60%) of the sample size. The estimated global prevalence of OA is around 10% in men and 20% in women.^{3,5,12,13,17} One study on epidemiology of knee OA in India showed a prevalence of 28.7%.¹²

American and European studies have found OA to be a disease of the upper class.¹⁷ The COPCORD study from Bangladesh also showed the same.¹⁸ On the contrary, a study conducted in south Delhi found the prevalence of OA was higher in perimenopausal women of lower classes than upper classes.¹⁹ Our study participants of lower socioeconomic status mostly had grade 2 knee OA but upper classes had the more severe grades of 3 or 4 as per K-L grading. BMI was found to be higher in groups with severe grades of knee OA as compared to milder grades, and there was a statistically significant association found between BMI and K-L grade of knee OA. Upper class people tend to have more modifiable risk factors,¹⁹ which is quite evident in the current study, showing increased prevalence of these modifiable risk factors (BMI, TC, HDL, SBP, DM) in these groups.

Atherosclerosis, hypertension, diabetes and hypercholesterolemia cause systemic inflammation in the body, which can lead to CVD.²⁴ Association between knee OA and CVD has been studied and linked to underlying systemic inflammation, however, it is unsure if this relationship is direct or indirect. For example; A meta-analysis of 299 publications found a high prevalence of OA in patients with DM.⁶ They also emphasized that metabolic OA phenotypes needs to be studied further. Another meta-analysis to explore the correlation between metabolic syndrome and knee OA, found a significant odds ratio (OR) even after adjusting for many risk factors.²⁵ The aforementioned Korean study displayed a significantly higher knee OA prevalence in patients with hypertension and impaired glucose tolerance.¹² Veronese *et al.* while studying elderly participants without CVD found that OA at baseline was associated with subsequent incident CVD.^{24,26} In the current study, the mean SBP was significantly higher in patients with K-L grade 3 and 4 of knee OA. Similar trends

were seen while studying the prevalence of DM in these patients. In the total sample, 25.8% patients had DM, yet the largest percentage (53%) was seen in patients with K-L grade 4 knee OA, showing the risk of DM increases with severity of knee OA, as found by Louati K *et al.*⁶ Hypercholesterolemia was also studied here, being another systemic inflammatory marker. It showed a statistically significant relationship with K-L grades of knee OA; mean serum TC was found to be higher in patients with severe grades of knee OA, whilst mean serum HDL was found to be lower in patients with severe grades of OA.

Systolic BP, DM and hypercholesterolemia are three of the major contributors to CVD.¹² As per the results of this study it would be safe to say that patients with severe knee OA have a higher risk of developing a CVD in the future. On the contrary, Hoeven *et al.*²⁷ believe that OA-related disability and not OA predicts CVD. This is along the lines of belief of many other researchers who postulate that OA doesn't directly lead to a CVD, rather it renders a patient physically more inactive and disabled than those without OA, which ultimately increases the CV risk factors. Recently, in a systemic review and meta-analysis, it was questioned whether aerobic exercise is being used adequately in patients with knee OA as under-prescription of it could be a potential source of increased risk of CVD.⁸ Whether OA causes CVD directly or indirectly, it is hard to ignore the fact that they often exist co-dependently in a patient's body. Assessment of a patient with knee OA for CV risk factors would be of no harm and rather provide the doctor a systemic approach to the patient's morbid condition and also make the patient aware about their unknown CV risk factors and risk of developing a CVD. Korean National Health Survey and Nutrition Examination Survey (KNHANES) found a higher prevalence of hypertension, DM, dyslipidaemia, angina and myocardial infarction in patients with OA compared with healthy individuals.²⁸

Contrary to traditional belief, smoking was not found to have any statistically significant effect on the K-L grade of knee OA.²⁹ Other variables such as atrial fibrillation, chronic kidney disease and rheumatoid arthritis were not found to be prevalent in our study population, preventing us from analysing any relationship between them and knee OA.

This study has attempted to collaborate the basic mechanical, causal and shared risk factors (age, obesity, gender) between knee OA and CVD. It has also tried to study various other CV risk factors (hypertension, DM, dyslipidaemia, smoking, family history) in patients with OA. Ho Sun Kim *et al.*¹² used the Framingham risk score (FRS) in south Koreans to study the association between OA and CV risk factors; however, it was found that the JBS3 risk score calculator is a better tool than FRS when applied to the Indian population.³⁰ We used the JBS3 risk score to calculate 10-year risk of developing CVD, physiological heart age and life expectancy. Statistically significant data revealed the mean physiological heart age of the patients to be as much as 10 years higher than their actual mean age and their life expectancy shortened with more CV risk factors. The mean JBS3 risk was 11% for patients with grade 2 OA, 23% for patients with grade 3 OA and 38% with grade 4 OA. This was along the same lines as studied in Korea.¹²

Our study had 225 patients with a prevalence of grade 4 knee OA of 13%. With the help of the ROC curve, the cut-off value of JBS3 was calculated to be 14%, which implies the amount of risk patients with grade 4 knee OA had of developing a CVD in the next 10 years, with a sensitivity of 72.3% and specificity of 66%. It would not be an overstatement to say that a patient with grade 4 knee OA undergoing total knee replacement could have a CV risk of as much as 14%.

India, although one of the countries where both OA and CVD is most prevalent, has very little literature stating the relationship between the two. The strength of this study lies in the different variables (demographic and CV risk factors) that were studied. With the genetic and phenotypic variations in the population in this part of the world, BMI plays a major role in understanding various pathologies in human body. The BG Prasad scale has helped us to divide the study population into various socio-economic strata and study its relation to both OA and CV risk factors. In addition, the diagnosis of knee OA has been made with the help of standard radiographs using K-L classification. The potential confounding factors (CV risk factors) are clubbed together with the help of a standardized risk score calculator devised by the Joint British Society. JBS3 also tells us about the physiological heart age and life expectancy. Although these factors have an individual effect on the patho-mechanisms of knee OA, when they are used as a part of this scale, various limitations are eliminated, and they are studied as a whole as well. The risk factors thus are studied both individually as well as co-dependently. However, this study has its limitations too. It is a cross-sectional study, which comes with its own inherent limitations. The study population only has patients with K-L grade of ≥ 2 , so the risk assessment of patients with K-L grade 1 was not done here. The JBS3 risk score calculator used here could only come close to being ideal for the study population of our country. A risk score calculator developed in our country for Indian genotypes and phenotypes would be ideal. Also, it doesn't include stress³¹ and activity level as variables, which has a known effect on cardiovascular status. The SBP values entered here are of single reading, which can be affected by the hemodynamic status of the patient at one particular moment. The readings of TC and HDL values may have differed depending on the investigator and equipment available from place to place. The JBS3 risk score calculator is not a tool to initiate treatment for a patient, rather a tool that

gives a fair idea of the patient's general condition and CV status. Some variables of this tool depend upon the history given by the patient, which has its own limitations.

Conclusion

Our study concluded that there is a strong relation between knee OA and CVD with CV risk score being positively correlated to the severity of OA.

Implication

Understanding the association between CV risk factors and knee OA could help the Orthopaedist and physician to approach the patient's condition in a more wholesome way and plan the necessary intervention accordingly. Also, routine screening and assessment of CV risk factors in knee OA patients would not only alert the unaware patient but also help them to comprehensively understand their comorbid condition and its prognosis.

Data availability

Underlying data

Dryad: Assessment of cardiovascular risk factors in patients with Knee Osteoarthritis. <https://doi.org/10.5061/dryad.79cnp5htv>.³¹

Data are available under the terms of the [Creative Commons Zero "No rights reserved" data waiver](#) (CC0 1.0 Public domain dedication).

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Version 3

Reviewer Report 23 February 2022

<https://doi.org/10.5256/f1000research.121262.r124117>

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Hayden F Atkinson

University of Prince Edward Island, Charlottetown, C1A 4P3, Canada

Jenna Schulz

Western University, London, ON, Canada

We have reviewed the authors' responses to our suggestions, as well as the changes made to the manuscript. We are satisfied with the responses and the newest version of the manuscript. We are happy to approve the manuscript for indexing with no reservations.

Competing Interests: No competing interests were disclosed.

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 2

Reviewer Report 08 February 2022

<https://doi.org/10.5256/f1000research.79143.r119851>

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Hayden F Atkinson

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Jenna Schulz

Western University, London, ON, Canada

Thank you for the invitation to review this manuscript. The authors examined cardiovascular (CV) risk factors in patients with knee osteoarthritis (OA), and concluded that there is a strong correlation between OA and CV disease, with the severity of OA and CV risk score being directly proportional.

Overall, this paper is well written, but there is some room for improvement. Specifically, the discussion would benefit from being more concise, and an improved overall flow to help tell the story the authors are trying to get across.

Abstract

- The second methods sentence is quite long. Suggestion to break it up into two smaller sentences.
- Please correct all instances in the abstract and text stating that CV risk score is directly proportional to the severity of knee OA and replace with “positively correlated”. ‘Directly proportional’ infers that the correlation is perfect.

Introduction

- Second paragraph: “OA is associated with knee pain”. Suggested to revise to “joint” pain as OA can occur in any synovial joint. Other option is to introduce the focus specifically as knee OA in the first paragraph.
- Third paragraph: If the authors could avoid namedropping as they have done in the following example and cite the source as they have done in the remainder of the text it would make for easier reading: “Dr. J.S. Lawrence [and his] work at Leigh where he...”. Same with the paragraph in the methods section with many names mentioned after the sample size calculation, and several other instances throughout the text.
- Third paragraph: It is recommended the authors cite the systematic review by Schulz *et al.*, 2020¹ at the end of this paragraph as a very relevant potential source of increased risk for CV disease in OA patients is the under-prescription of aerobic exercise for patients with knee OA. Health care providers often under-prescribe exercise, especially aerobic exercise for patients with osteoarthritis. Exercise physiologists agree that 150 minutes of moderate-to-vigorous physical activity on weekly basis contributes to reducing chronic disease risk and severity, especially for cardiovascular disease. Patients with OA should be instructed to meet these guidelines, however, research suggests that health care providers are prescribing exercise volumes below this 150-minute threshold, which can contribute to increased risk for CV disease onset or progression in patients with OA.
- Suggestion to add the concept of “systemic inflammation” as potential pathogenesis underlying both OA and CVD. Although not a primarily inflammatory disease, there is now evidence of a systemic component to OA, as opposed to the traditional view of a “wear and tear” disease.

Study Participants

- State that you did not exclude based on other comorbidities/systemic diseases (i.e. diabetes, hypertension, RA, etc). Including these patients could potentially confound results and therefore cannot draw causative conclusions (i.e. knee OA causes CVD or vice versa), and should make sure to keep results purely correlative in discussion/conclusion.

- Please provide an explanation as to why patients with secondary knee OA were not eligible to participate.

Statistical analysis

- Pearson correlation between JBS3 score and KL Grade is inappropriate as KL Grade is a categorical variable and not a quantitative variable (no direct, linear relationship between Grade 1-2-3-4). Pearson correlations are conducted between two continuous variables. All mentions of a Pearson correlation between KL Grade and JBS3 score will have to be removed. Please choose an appropriate analysis that permits correlation between a categorical variable and a continuous variable. Results will likely be similar but please ensure the test chosen is appropriate. The article by Gupta, 1960² may be helpful.
- Rheumatoid arthritis was mentioned in abbreviated form earlier (under variables).

Results

- Suggestion to remove the “inference” column to clean up the results table and just state in results that a p-value of <0.05 was deemed significant.
- Figure 5: Suggest removing the figure and replacing it with a table or just words in discussion.

Discussion

- Suggestion to begin the discussion and each paragraph by summarizing key findings from results, then using evidence from recent papers to support results.
- The paragraphs relating to age can likely be condensed into one.
- The paragraph relating to OA and socioeconomic status should also be clarified and condensed. Suggestion to remove the sentence and citation of the study in Japan and a higher prevalence of OA in mountainous regions as there is no mention in this current study about where participants were from or their current activity status. Additionally, OA is multifactorial (as listed in the sentence below), and attributing the cause of OA to activity (when we know inactivity is a large risk factor) is a bit of an over-conclusion.
- Suggestion to remove “many doctors and researchers who believe that...” and condense to the “association between knee OA and CVD has been studied and linked to underlying systemic inflammation, however, it is unsure if the relationship is either direct or indirect. For example...” and cite studies. The details of these studies (i.e. number of participants, exact results) could be removed and this would help condense the paragraph down.
- Suggestion to remove the sentence regarding the conclusion that patients with severe knee OA have a higher risk of developing CVD in the future as this is an over-drawn conclusion. Instead, rephrase to discuss the correlation between knee OA and risk factors for CVD found in this study.
- Suggestion to flip the order of the last two sentences in this paragraph.
- Suggestion to replace assumption with hypothesis.
- Suggestion to remove the information about the FRS to make it more concise and condense this paragraph with the following.

- Are the risk factors in the JBS3 score made to be studied individually or meant to be kept together as a whole? Please expand on this and add it as a limitation to the study. Also, suggest adding a limitation surrounding that there was no information regarding activity levels in the study participants.

Conclusion/implication

- There was no mention in the introduction of this study being used to determine the feasibility of implementing the JBS3 score. Refer back to objectives, and reflect on those here. Suggestion to keep the conclusion/implication section around the correlation between knee OA and CVD, and how these findings may impact health care practitioners, patients, and the field as a whole.

References

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Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

Author Response 18 Feb 2022

Sagar Goel, Kasturba Medical College, MAHE Manipal, Manipal, India

Thank you for your valuable feedback which has helped us to improve this paper. We have attempted to address all your suggestions and queries as follows:

Abstract

- The second methods sentence is quite long. Suggestion to break it up into two smaller sentences.

Author response: Done.

- Please correct all instances in the abstract and text stating that CV risk score is directly proportional to the severity of knee OA and replace with “positively correlated”. ‘Directly proportional’ infers that the correlation is perfect.

Author response: Done.

Introduction

- Second paragraph: “OA is associated with knee pain”. Suggested to revise to “joint” pain as OA can occur in any synovial joint. Other option is to introduce the focus specifically as knee OA in the first paragraph.

Author response: Done.

- Third paragraph: If the authors could avoid namedropping as they have done in the following example and cite the source as they have done in the remainder of the text it would make for easier reading: “Dr. J.S. Lawrence [and his] work at Leigh where he...”. Same with the paragraph in the methods section with many names mentioned after the sample size calculation, and several other instances throughout the text.

Author response: Done.

- Third paragraph: It is recommended the authors cite the systematic review by Schulz *et al.*, 2020¹ at the end of this paragraph as a very relevant potential source of increased risk for CV disease in OA patients is the under-prescription of aerobic exercise for patients with knee OA. Health care providers often under-prescribe exercise, especially aerobic exercise for patients with osteoarthritis. Exercise physiologists agree that 150 minutes of moderate-to-vigorous physical activity on weekly basis contributes to reducing chronic disease risk and severity, especially for cardiovascular disease. Patients with OA should be instructed to meet these guidelines, however, research suggests that health care providers are prescribing exercise volumes below this 150-minute threshold, which can contribute to increased risk for CV disease onset or progression in patients with OA.

Author response: Done.

- Suggestion to add the concept of “systemic inflammation” as potential pathogenesis

underlying both OA and CVD. Although not a primarily inflammatory disease, there is now evidence of a systemic component to OA, as opposed to the traditional view of a “wear and tear” disease.

Author response: Done.

Study Participants

- State that you did not exclude based on other comorbidities/systemic diseases (i.e. diabetes, hypertension, RA, etc). Including these patients could potentially confound results and therefore cannot draw causative conclusions (i.e. knee OA causes CVD or vice versa), and should make sure to keep results purely correlative in discussion/conclusion.

Author response: The exclusion criteria mention only patients with cardiovascular disease which we find is self-explanatory that all the other comorbid conditions were not excluded.

- Please provide an explanation as to why patients with secondary knee OA were not eligible to participate.
- **Author response:** Our goal was to find an association between primary OA and CV risk factors that's why secondary OA was excluded.

Statistical analysis

- Pearson correlation between JBS3 score and KL Grade is inappropriate as KL Grade is a categorical variable and not a quantitative variable (no direct, linear relationship between Grade 1-2-3-4). Pearson correlations are conducted between two continuous variables. All mentions of a Pearson correlation between KL Grade and JBS3 score will have to be removed. Please choose an appropriate analysis that permits correlation between a categorical variable and a continuous variable. Results will likely be similar but please ensure the test chosen is appropriate. The article by Gupta, 1960² may be helpful.

Author response: We have decided to remove Pearson's correlation as this was wrongly used by us. We have not tried to add any other method as it was not providing any additional information pertaining to the results.

- Rheumatoid arthritis was mentioned in abbreviated form earlier (under variables).

Author response: Done.

Results

- Suggestion to remove the “inference” column to clean up the results table and just state in results that a p-value of <0.05 was deemed significant.

Author response: The inference column has been removed.

- Figure 5: Suggest removing the figure and replacing it with a table or just words in discussion.

Author response: Done.

Discussion

- Suggestion to begin the discussion and each paragraph by summarizing key findings from results, then using evidence from recent papers to support results

Author response: Done.

- The paragraphs relating to age can likely be condensed into one.

Author response: Done.

- The paragraph relating to OA and socioeconomic status should also be clarified and condensed. Suggestion to remove the sentence and citation of the study in Japan and a higher prevalence of OA in mountainous regions as there is no mention in this current study about where participants were from or their current activity status. Additionally, OA is multifactorial (as listed in the sentence below), and attributing the cause of OA to activity (when we know inactivity is a large risk factor) is a bit of an over-conclusion.

Author response: Done.

- Suggestion to remove “many doctors and researchers who believe that...” and condense to the “association between knee OA and CVD has been studied and linked to underlying systemic inflammation, however, it is unsure if the relationship is either direct or indirect. For example...” and cite studies. The details of these studies (i.e. number of participants, exact results) could be removed and this would help condense the paragraph down.

Author response: Done.

- Suggestion to remove the sentence regarding the conclusion that patients with severe knee OA have a higher risk of developing CVD in the future as this is an over-drawn conclusion. Instead, rephrase to discuss the correlation between knee OA and risk factors for CVD found in this study.

Author response: Done.

- Suggestion to flip the order of the last two sentences in this paragraph.

Author response: Done.

- Suggestion to replace assumption with hypothesis.

Author response: Done.

- Suggestion to remove the information about the FRS to make it more concise and condense this paragraph with the following.

Author response: Done.

- Are the risk factors in the JBS3 score made to be studied individually or meant to be kept together as a whole? Please expand on this and add it as a limitation to the study.

Author response: The CV risk factors were analysed individually as well as whole using the JBS3 risk score calculator as evident in the results and discussion part.

- Also, suggest adding a limitation surrounding that there was no information regarding activity levels in the study participants.

Author response: Done.**Conclusion/implication**

- There was no mention in the introduction of this study being used to determine the feasibility of implementing the JBS3 score. Refer back to objectives, and reflect on those here. Suggestion to keep the conclusion/implication section around the correlation between knee OA and CVD, and how these findings may impact health care practitioners, patients, and the field as a whole.

Author response: Thank you for your suggestion and the conclusion and implications have been rephrased.

Competing Interests: No competing interests were disclosed.

Reviewer Report 07 December 2021

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Win Min Oo

Rheumatology Department, Royal North Shore Hospital, Institute of Bone and Joint Research, Kolling Institute, Faculty of Medicine and Health, The University of Sydney, Sydney, NSW, Australia

Htoo Dar Li

University of Medicine, Mandalay, Myanmar

We have reviewed the manuscript and found that the authors have already responded to most of our concerns satisfactorily.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Partly

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 09 September 2021

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Win Min Oo

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It's been a great pleasure reviewing this manuscript. The authors examined various cardiovascular (CV) risk factors in 225 patients with knee OA, concluding that a strong positive correlation between knee OA and CVD existed.

Generally, the manuscript is well written though there is still a large space for much improvement. I have several comments to improve it.

Abstract:

- In the conclusion section, we would suggest omitting some sentences as it is not appropriate to mention them here. Perhaps the best place would be in the methodology as the outcome measure: "JBS3 is a comprehensive risk score calculator as well as a screening tool, which...".

Introduction:

- Third paragraph: Generally, systemic inflammation is not part of the OA disease process nor florid as in rheumatoid arthritis which has an obvious association with CVD.
- References 3 and 4 you used for OA being associated with high cholesterol levels did not mention such - page 3, third paragraph: "recent studies have reported that OA is associated with high serum cholesterol levels in females".

Methodology:*Study design*

- Do you mean that a convenience sample was used? Any retrospective data? If so, please mention it.

Study participants

- Just wondering why the American College of Rheumatology criteria was not used for case definition. How are references 9 and 10 appropriate here, especially for case definition?
- For the sample size calculation, the estimated proportion was taken from a Korean study in which the prevalence of knee OA may be different from an Indian population, and it may be overestimated as the study was not conducted in the community setting.
- Are there any Indian studies for the record of community prevalence of knee OA? We think it would be more relevant if available.

Variables

- In knee X-rays, did you consider only patellofemoral or tibiofemoral OA or both eligible?
- Physical inactivity (sedentary lifestyle) and NSAID usage should be included and adjusted as the potential confounders.

Statistical analysis

- Just wondering why the multiple regression model for adjusting the confounders was not used.
- For post-hoc analysis, did you conduct any correction of the p-value for multiple comparisons? If so, please mention it here.

Results

- Instead of using many figures for each of the baseline characteristics, one table should work well for all variables. Strongly suggest doing so.
- Table 2 is difficult to understand without the inputs of blood pressure calculated. Suggested to modify it.

- Too many figures and interpretations for a research article. Please be concise.
- The current or previous medication used for OA should be reported as NSAID especially Cox-2 inhibitors may increase the CVD risk and morbidity. Therefore, such confounders should be adjusted in the statistical analysis to draw a valid interpretation.

Discussion

- Too long and involves the repetition of much of the results section instead of correlating with the findings of other papers.
- The redundancy of the language should be avoided, i.e. "This is the first study of its type to be conducted in this part of the world. India..."

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Osteoarthritis; Musculoskeletal imaging; Neurorehabilitation

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

Author Response 04 Nov 2021

Sagar Goel, Kasturba Medical College, MAHE Manipal, Manipal, India

Thank you for your feedback. We have tried our best to respond to some of your queries and made some modifications to the manuscript as per your suggestions.

Abstract:

- In the conclusion section, we would suggest omitting some sentences as it is not appropriate to mention them here. Perhaps the best place would be in the methodology as the outcome measure: "JBS3 is a comprehensive risk score calculator as well as a screening tool, which..."

Author response: Done.

Introduction:

- Third paragraph: Generally, systemic inflammation is not part of the OA disease process nor florid as in rheumatoid arthritis which has an obvious association with CVD.

Author response: Done.

- References 3 and 4 you used for OA being associated with high cholesterol levels did not mention such - page 3, third paragraph: "recent studies have reported that OA is associated with high serum cholesterol levels in females".

Author response: The text has been modified and the concerned reference is added.

Methodology:

Study design

- Do you mean that a convenience sample was used? Any retrospective data? If so, please mention it.

Author response: Yes, a convenience sample was used. Moreover, retrospective data was also collected as mentioned under the heading *Ethics Statement and Sampling*: "Also, case records of patients diagnosed with knee OA between January 2017 to September 2018 were studied..."

Study participants

- Just wondering why the American College of Rheumatology criteria was not used for case definition. How are references 9 and 10 appropriate here, especially for case definition?

Author response: We believed Kellgren and Lawrence grading of OA knee based on the X-ray was more suitable for case definition here. Using reference no 9, we decided to keep 50 years of age as a cutoff for patient selection.

- For the sample size calculation, the estimated proportion was taken from a Korean study in which the prevalence of knee OA may be different from an Indian population, and it may be overestimated as the study was not conducted in the community setting.
- Are there any Indian studies for the record of community prevalence of knee OA? We think it would be more relevant if available.

Author response: The Prevalence of knee OA among Indian and Korean Populations is comparable and has been mentioned with reference

Variables

- In knee X-rays, did you consider only patellofemoral or tibiofemoral OA or both eligible?

Author response: Both were considered.

- Physical inactivity (sedentary lifestyle) and NSAID usage should be included and adjusted as the potential confounders.

Author response: We used the JBS3 risk score calculator which did not include physical inactivity and NSAID usage as variables.

Statistical analysis

- Just wondering why the multiple regression model for adjusting the confounders was not used.

Author response: Done and added.

- For post-hoc analysis, did you conduct any correction of the p-value for multiple comparisons? If so, please mention it here.

Author response: Yes, it was done.

Results

- Instead of using many figures for each of the baseline characteristics, one table should work well for all variables. Strongly suggest doing so.

Author response: Done.

- Table 2 is difficult to understand without the inputs of blood pressure calculated. Suggested to modify it.

Author response: Done.

- Too many figures and interpretations for a research article. Please be concise.

Author response: Done.

- The current or previous medication used for OA should be reported as NSAID especially Cox-2 inhibitors may increase the CVD risk and morbidity. Therefore, such confounders should be adjusted in the statistical analysis to draw a valid interpretation.

Author response: We used the JBS3 risk score calculator which did not include physical inactivity and NSAID usage as variables.

Discussion

- Too long and involves the repetition of much of the results section instead of correlating with the findings of other papers.

Author response: Done.

- The redundancy of the language should be avoided, i.e. "This is the first study of its type to be conducted in this part of the world. India...".

Author response: Done.

Competing Interests: There are no competing interests

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