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Serum YKL-40 Levels are Increased in Patients with Diabetes Mellitus and Coronary Artery Diseases: A Meta-analysis

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Authors' contributions

This work was carried out in collaboration among all authors. Authors SSP and WL conceived the meta-analysis. Authors SSP and JK developed the research strategy and provided statistical expertise. Author SSP drafted the manuscript. Authors SSP, JK, NO and UG contributed to the development of the selection criteria, the risk of bias assessment strategy and data extraction criteria. All Authors read, provided feedback and approved the final manuscript.

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ABSTRACT

Background: YKL-40 also named as chitinase-3-like protein 1 (CHI3L1) is a novel inflammatory biomarker found to be elevated in inflammatory and chronic diseases. This meta-analysis was done to estimate the pooled SMD of serum YKL-40 and evaluate its use as a diagnostic biomarker for Diabetes Mellitus (DM) and Coronary artery disease (CAD).
Methods: Through searching the following electronic databases: Google scholar, PubMed, Scopus among others, related articles were extracted in English language. Stata (Version 12.0) was used for statistical analysis. Newcastle–Ottawa Scale was used for quality assessment. Standard mean

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difference (SMD) and its corresponding 95% confidence interval (95% CI) were calculated. Heterogeneity was assessed by I^2 statistic.
Results: Fourteen CAD studies with 1400 patients, 1685 controls and Thirteen DM studies with 1103 patients, 982 controls were selected for statistical analysis. The results showed that serum YKL-40 level in both CAD and DM patients was significantly higher than that in control subjects (SMD = 1.76 (95% CI 0.96-2.57) and (SMD=1.89 (95% CI 0.79-3.00) respectively. In both studies, stratified analysis showed that, studies which did not control for smoking had higher SMD compared to those controlled. Besides, CAD patients from developed countries had higher serum YKL-40 levels compared to those from developing countries.
Conclusion: This meta-analysis suggests that an elevated serum YKL-40 level may be used as a promising diagnostic tool for early identification of CAD and DM. However patients' age, history of smoking, and comorbidities should be put into consideration.

Keywords: Coronary artery disease; diabetes mellitus; meta-analysis; YKL-40.

1. INTRODUCTION

YKL-40, also named BPR-39, human cartilage glycoprotein-39 or chitinase-3-like protein 1 (CHI3L1) is a chitin-binding and heparin-binding glycoprotein which was first identified in 1992 [1,2]. It is crystal in structure, encoded by the CHI3L1 gene in humans, located at chromosome 1q31-32, and is approximately 40 k Da in size [3]. It is a highly conserved protein produced at the site of inflammation and secreted by various cell-types including human macrophages, neutrophils, fibroblast-like synovial cells, arthritic chondrocytes, and differentiated vascular smooth muscle cells [4,5]. YKL-40 is an essential factor in extracellular tissue remodeling involving type 1 collagen fibril formation. It is also a growth factor for fibroblasts and chondrocytes, and controls mitogenesis by modulating MAP kinase and PI-3 K signaling cascades in fibroblasts [6,7].

YKL-40 levels are elevated in the serum or plasma in chronic and inflammatory diseases such as inflammatory bowel disease, rheumatoid arthritis, asthma, coronary artery diseases (CAD), diabetes mellitus (DM) and also in various cancer patients, among others [6,8,9,10]. The increased levels of serum YKL-40 is associated with poor prognosis and decreased survival rates of different cancer patients and hence, this can also serve as a possible biomarker in cancers and inflammatory diseases [11,12]. Some experimental investigations show serum levels of YKL-40 to be elevated in patients with cardiovascular diseases such as heart failure (HF), acute myocardial infarction (MI), and stable CAD [13,14]. Therefore, it is assumed that serum YKL-40 level may be closely linked to the development and poor prognosis of CAD, even though the exact physiological role of YKL-40 in CAD is still unclear. The elevated levels of YKL-40 are also reported to be proportional to the results of HOMA-IR in type 2 diabetes mellitus (T2DM) subjects. This reveals the correlation of YKL-40 with insulin resistance and dyslipidemia, thus YKL-40 may act as a potential biomarker in detection of DM [15,16]. Several studies have reported elevated levels of plasma YKL-40 in both type 1 and type 2 diabetes mellitus patients compared to non-diabetic patients [17,18,19].

Many studies have reported elevated YKL-40 with CAD and DM; however, some studies have reported a smaller difference of YKL-40 between the case and controls compared to other studies [20,21,22]. We therefore have done this meta-analysis to estimate the pooled SMD and evaluate the use of YKL-40 as a diagnostic biomarker for CAD and DM.

2. MATERIALS AND METHODS

2.1 Search Strategy and Selection Criteria

This study followed the recommended and up-to-date guidelines for conducting and reporting the meta-analysis (PRISMA and MOOSE guidelines) [23,24].

The articles included in the analysis were searched from the following electronic databases: Web of Science, PubMed, Scopus and Google Scholar. The keywords and Medical Subject Headings (MeSH) terms were searched according to the following combinations: "New Biomarkers in CAD and DM", "inflammatory biomarkers in CAD and DM", YKL-40 serum levels ("CHI3L1 protein, human" or "CHI3L1" or "cartilage gp-39" or "YKL40" or "YKL-40" or "HCGP39" or "human cartilage glycoprotein-39" or "human cartilage gp39" or "HC-gp39" or "38-kDa heparin-binding glycoprotein"),

("myocardial infarction" or "coronary artery disease" or "MI" or "CAD" or "myocardial infarct" or "myocardial infarction" or "myocardium infarction" or "cardiac infarction" or "coronary heart disease" or "CHD" or "heart infarction" or "acute myocardial infarction" or "AMI") and ("Diabetes Mellitus" or "DM" or "diabetes", "type 1 diabetes", "diabetes 1", "type 1 diabetes mellitus", "T1DM", "type 2 diabetes", "diabetes 2", "type 2 diabetes mellitus", "T2DM", and "T2D"). The papers considered were only in English language from 2000 to 2020 (June 13th). An additional manual search was done to acquire other potential articles on the basis of references provided by the included articles.

2.2 Inclusion and Exclusion Criteria

The articles were included if the value of serum YKL-40 for CAD patients and DM patients was recorded. CAD studies were included if patients had symptoms sufficient to warrant angiography or, a cardiac history and the indications included a history of CAD, suspected chest pain, and clinical evidence of angina pectoris. Studies with patients who had organic valvular heart disease, malignancy, chronic kidney and hepatic failure, collagen vascular disease, pulmonary embolism, and infectious diseases were excluded.

For eligible studies of DM, patients should have been confirmed by glycated hemoglobin test, 2-h plasma glucose (2hPG) oral glucose tolerance test, or islet function results. DM studies were excluded if patients had any liver, kidney, rheumatoid, endocrine, cardiovascular, and metabolic diseases; cancer; gestational diabetes; and a history of using antihypertensive or lipid-lowering medications. All the included studies must have enough information on serum and plasma YKL-40 level. Articles that did not meet the inclusion criteria were excluded. For studies for more than one publication, the most recent or the one with the largest sample size was considered.

2.3 Data Extraction and Methodological Assessment

We developed a standardized data collection form before data collection [25]. The following data was collected: first author, publication year, country, age, type of disease, sample size (total number of cases and controls), detection method, serum YKL-40 level, controlled for confounders, among others.

Two observers (SSP and NO) separately assessed methodological quality using Newcastle–Ottawa Scale (NOS) criteria [26] for case-control and cohort studies. The NOS assesses the following three aspects: (1) subject selection: 04; (2) comparability of subject: 02; (3) clinical outcome: 03. NOS scores ranged from 0 to 9; and a score ≥ 7 is considered good quality. All disagreements were solved through discussion and consensus.

2.4 Statistical Analysis

The statistical analysis was done using Stata software (Version 12.0, Stata Corporation, College Station, TX). Standard mean difference (SMD) and its corresponding 95% confidence interval (95% CI) were calculated from means and medians reported in the studies. Studies that reported median and interquartile ranges were converted to mean and standard deviation [27]. The heterogeneity between studies was assessed by I^2 tests in the meta-analysis. A random-effect model was implemented and p value < 0.05 was considered significant. To explore reasons for heterogeneity, subgroup analyses on the following study characteristics was done: (1) Country; (2) Sample size; (3) Age; (4) Controlled for confounders; (5) Quality score; (6) Type of disease for DM. For evaluating the influence of single study on the overall estimate, a sensitivity analysis was implemented. The presence of publication bias was visually examined by funnel plots and confirmed by Egger's linear regression test.

3. RESULTS

The study retrieval and selection strategy is illustrated in Fig. 1. A total of 213 articles were initially found according to the relevant search strategy. After reviewing the titles and abstracts of all the studies, 50 articles were retrieved; and after data integrity was reviewed, a total of 27 studies were included in this analysis. Of these, 14 studies were about CAD with 1400 CAD patients and 1685 controls. In addition, 13 studies about DM were included with 1103 DM patients and 982 controls for quantitative data analysis [14,16,18,19,21,27-49]. The publication years ranged from 2007 to 2020. Enzyme-linked immunosorbent assay (ELISA) was the most used method for the detection of serum YKL-40 in the analyzed paper except for one study adopted for the novel method of immuno-radiometric assay (IRMA). Main characteristics

and methodological quality of all eligible studies are listed in Table 1.

3.1 Results of CAD

A total of 14 studies were evaluated using the random-effects model. Their SMDs ranged from -0.43 to 8.31. The pooled effect size was found to be SMD= 1.75 (95% CI 0.95-2.55, p<0.001) and showed a significant relationship between the increased serum levels of YKL-40 and CAD disease than those of control subjects (Fig. 2). There was considerable heterogeneity noted among these studies (I^2= 98.7%, p<0.001) (Table 2)

3.2 Results of DM

The random-effects model was conducted on total of 13 studies. The 1^2 studies that evaluated the pooled SMD's were ranging from -1.46 to 9.26. DM was found to be significantly associated with increased serum levels of YKL-40 with the pooled effect size, SMD= 1.89 (95% CI 0.79-3.00, p<0.001) (Fig. 3). There was also significant heterogeneity noted among these studies (I^2= 98.8%, p<0.001) (Table 2).

3.3 Factors Influencing the Outcome

Meta-regression was conducted to examine potential sources of heterogeneity. As shown in Table 3 and Table 4, there is no significant factor found to modulate serum YKL-40 levels. All studies of CAD showed significant heterogeneity on sub-group analysis (Table 3). For studies of CAD, country-stratified analysis showed developed countries had 2 fold higher serum levels of YKL-40 than developing countries with pooled SMD= 2.28 (95%CI 1.10-3.47) and SMD= 1.38 (95% CI 0.23-2.53) respectively. Patients <60 years old showed a pooled SMD of 1.91 (95% CI 0.21-3.61) while patients ≥60 years had a pooled SMD= 1.49 (95%CI 0.88-2.10) and both had significant heterogeneity noted. Studies that controlled for smoking showed less serum YKL-40 values compared to studies that did not control for smoking with a pooled SMD= 2.78 (95% CI 1.10-4.46) and 0.83(95% CI 0.53-1.13) respectively. In the group of NOS <7, the pooled SMD was 2.16 (95%CI 1.17-3.16) and NOS ≥7 showed SMD= 1.42 (95% CI 0.19-2.64).

On sub-group analysis for DM, studies that controlled for gender showed no heterogeneity (I^2= 0.00%) and studies of age ≥60 years had minimal heterogeneity (I^2= 5.8%). All the other studies showed considerable heterogeneity on sub-group analysis (Table 4). Country-stratified analysis for studies of DM, developing countries had a pooled SMD= 2.18 (95% CI 0.68-3.68), while developed countries had a pooled SMD= 1.25 (95% CI -0.19-2.70) although not significant. Sub-group analysis for sample size below 200 showed SMD= 1.37 (95% CI 0.65-2.09) while sample size above 200 had SMD= 3.09 (95% CI 0.37-5.81). When controlled for confounders, studies that considered gender had a pooled SMD= 2.04 (95% CI 1.70-2.38) while studies that didn't consider gender had a pooled SMD = 1.87 (95%CI 0.58-3.15). For studies of NOS ≥7 showed a pooled SMD= 3.34 (95% CI 0.16-6.53) while studies of NOS<7 had a pooled SMD= 1.25 (95% CI 0.26-2.25). Sub-group analysis according to type of diabetes showed that T2DM had higher SMD= 2.36 (95% CI 0.77-3.95) compared to T1DM SMD= 1.15 (95% CI -0.07-2.36) however, the pooled SMD of T1DM was not significant (Table 4). Studies that obtained controls from the community showed a pooled SMD= 1.35 (95% CI 0.44- 2.27) while those with hospital-based controls showed a pooled SMD= 2.52 (95% CI 0.18-4.85).

To assess the influence of each individual study on the pooled SMDs, a sensitivity analysis was performed by omitting individual studies. The analysis indicated that no individual study significantly affected the overall pooled estimates.

3.4 Publication Bias

Publication bias was assessed using visual inspection of funnel plots which showed asymmetry in CAD and DM studies, indicating probable publication bias towards small studies (Fig. 3 (a) and (b)). On further evaluation using Egger's test, confirmed possible publication bias was in CAD studies (p=0.002), and it was also significant among DM studies (p= 0.008). As illustrated in Table 5, the trim-and-fill adjusted SMDs for CAD show a reduction from the unadjusted SMDs (SMD= 1.34 (95% CI 0.80-2.25)) while adjusted SMDs for DM showed a slight increase (SMD= 2.00 (95% CI 1.16-3.45).

Table 1. Study characteristics and quality assessment

			Sample Size		Controlled for confounders					Serum YKL-40 Mean+SD		
First author and Year	**Country**	**Disease**	**Case**	**Control**	**Age**	**Gender**	**Smoking**	**Method**	**SMD(95% CI)**	**Case**	**Controls**	**NOS score**
Sakamoto F et al, 2013 [28]	Japan	DM(Type1)	131	97	24.7±5.9	No	Yes	ELISA	-0.70(-0.97,-0.43)	62.45+33.62	100.02+72.97	6
Jafary F et al,2015 [29]	Iran	DM(Type1)	49	43	12.20±3.86	Yes	No	ELISA	2.15(1.53,2.66)	108.88±50.53	28.39±9.84	5
Jin Y et al, 2017 [30]	China	CAD	116	82	56.4 ± 12.71	No	No	ELISA	1.05(0.75,1.35)	244.8 ± 128.6	132.9 ± 63.9	4
Batinic K et al, 2012 [31]	Austria	DM(Type2)	85	39	60.9 ± 9.8	Yes	No	ELISA	1.97(1.51,2.42)	105+32.92	49+14.45	7
Røndbjerg AK et al, 2012 [18]	Denmark	DM(Type 2)	20	49	61.3 ± 12.0	No	No	ELISA	3.54(2.74,4.33)	91+23.68	42.5+6.35	4
Erdogan T et al, 2013 [32]	Turkey	CAD	30	30	61±10	Yes	Yes	ELISA	0.77(0.25,1.30)	180+117	110±53	8
Sui X & GaoC, 2013 [33]	China	CAD	134	112	56.65±8.12	No	No	ELISA	1.25(0.97,1.52)	134.15+14.41	115.23+16.08	6
Xie F et al, 2012 [34]	China	CAD	410	442	59.81±11.17	No	No	ELISA	5.00(4.73,5.27)	104.21± 21.07	26.34± 7.47	7
Kim HM et al, 2012 [35]	Korea	CAD	41	29	60 ± 5	Yes	Yes	IRMA	0.66(0.17,1.15)	148.6 ± 82.3	96.7 ± 73.0	7
VelaD et al,2017 [19]	Macedonia	DM (Type 2)	30	20	60.7±4.7	No	No	ELISA	-1.46 (-2.10,-0.83)	60.82+10.95	87.95+26.17	3
Han JY et al, 2015 [16]	China	DM (Type 2)	260	210	52.83 ± 4.30	No	No	ELISA	9.26(8.64,9.88)	44.77+2.23	27.25+1.36	7
Kulkarni NB et al, 2018 [36]	India	DM(Type 2)	28	30	52.1±10.4	No	No	ELISA	2.30(1.63,2.97)	3.13±1.14	0.82±0.86	3
ÇetinM et al, 2020 [37]	Turkey	CAD	28	107	58.7 ± 10.6	No	No	EIA	0.99(0.55,1.42)	141.5 ± 73.1	89.8 ± 45.7	7
Chen XL et al, 2017 [38]	China	CAD	85	141	61.33±10.13	Yes	Yes	ELISA	1.42(1.12,1.72)	95.5+14.43	77.25+9.53	8
Çetin M et al, 2013 [39]	Turkey	CAD	80	30	56±31	Yes	Yes	EIA	0.90(0.47,1.34)	194±104	110±53	7
Zheng JL et al,2011 [40]	China	CAD	213	248	64 ± 10	Yes	Yes	ELISA	0.50 (0.31,0.68)	87.69 ± 64.65	62.64 ± 34.04	6
Zheng JL et al,2010 [41]	China	CAD	103	210	67 ± 10	Yes	Yes	ELISA	0.85(0.61,1.10)	123.93 ± 74.01	71.05 ± 55.14	8
Rathcke CN et al, 2009 [21]	Denmark	DM(Type 1)	58	55	55.6 ± 10.8	No	No	ELISA	1.41 (1.00,1.83)	60.75+21.08	38.25+7.23	7
Rathcke CN et al,2010	Denmark	CAD	68	175	61.0±11.5	Yes	Yes	ELISA	0.56(0.27,0.84)	60.5+12.14	53+13.87	8

			Sample Size			Controlled for confounders				Serum YKL-40 Mean+SD		
First author and Year	**Country**	**Disease**	**Case**	**Control**	**Age**	**Gender**	**Smoking**	**Method**	**SMD(95% CI)**	**Case**	**Controls**	**NOS score**
[42]												
Kucur M et al, 2007 [43]	Turkey	CAD	48	53	61 ± 10.3	Yes	No	ELISA	8.31 (7.09, 9.53)	182 ± 10.7	84 ± 12.7	5
NøjgaardC et al, 2008 [44]	Finlnad	CAD	16	16	64.2 ±6	No	No	ELISA	-0.43 (-1.14,0.27)	141.5+71.03	189+137.43	4
Wang Y et al, 2008 [14]	Denmark	CAD	28	10	62±98	No	No	ELISA	3.66 (2.55,4.77)	70.75+15.31	20.75+6.67	4
El Dayem SM et al, 2015 [45]	Egypt	DM (Type 1)	62	30	16.32±1.52	No	No	ELISA	0.769 (0.318-1.219)	431.97±524.92	99.48±34.90	7
Rathcke, CN et al, 2006 [46]	Denmark	DM (Type 2)	87	158	54.6±8.66	No	No	ELISA	1.419 (1.128-1.709)	74.5±21.95	52.5±10.40	6
Sun L et al, 2015 [47]	China	DM (Type 2)	234	198	54.84 ± 10.23	No	No	ELISA	2.451(2.200-2.701)	207.22±36.53	137.22±14.24	5
Kumar PA et al, 2019 [48]	India	DM (Type 2)	10	10	44.50 ± 7.04.	No	No	ELISA	0.572 (-0.324-1.469)	8.07±6.12	4.74±5.50	4
Shiasi K et al, 2017 [49]	Iran	DM (Type 1)	49	43	12.20 ± 3.86	No	No	ELISA	2.146(1.630-2.662)	108.88 ± 50.53	28.39 ± 9.84	6

Table 2. Overall pooled SMD for CAD and DM

Outcome	Number of studies	SMD (95%CI)	P value	I^2 (%)	P value
CAD	14	1.75 (0.95-2.55)	p<0.001	98.7%	p<0.001
DM	11	1.87 (0.44-3.31)	p=0.011	99.0%	p<0.001

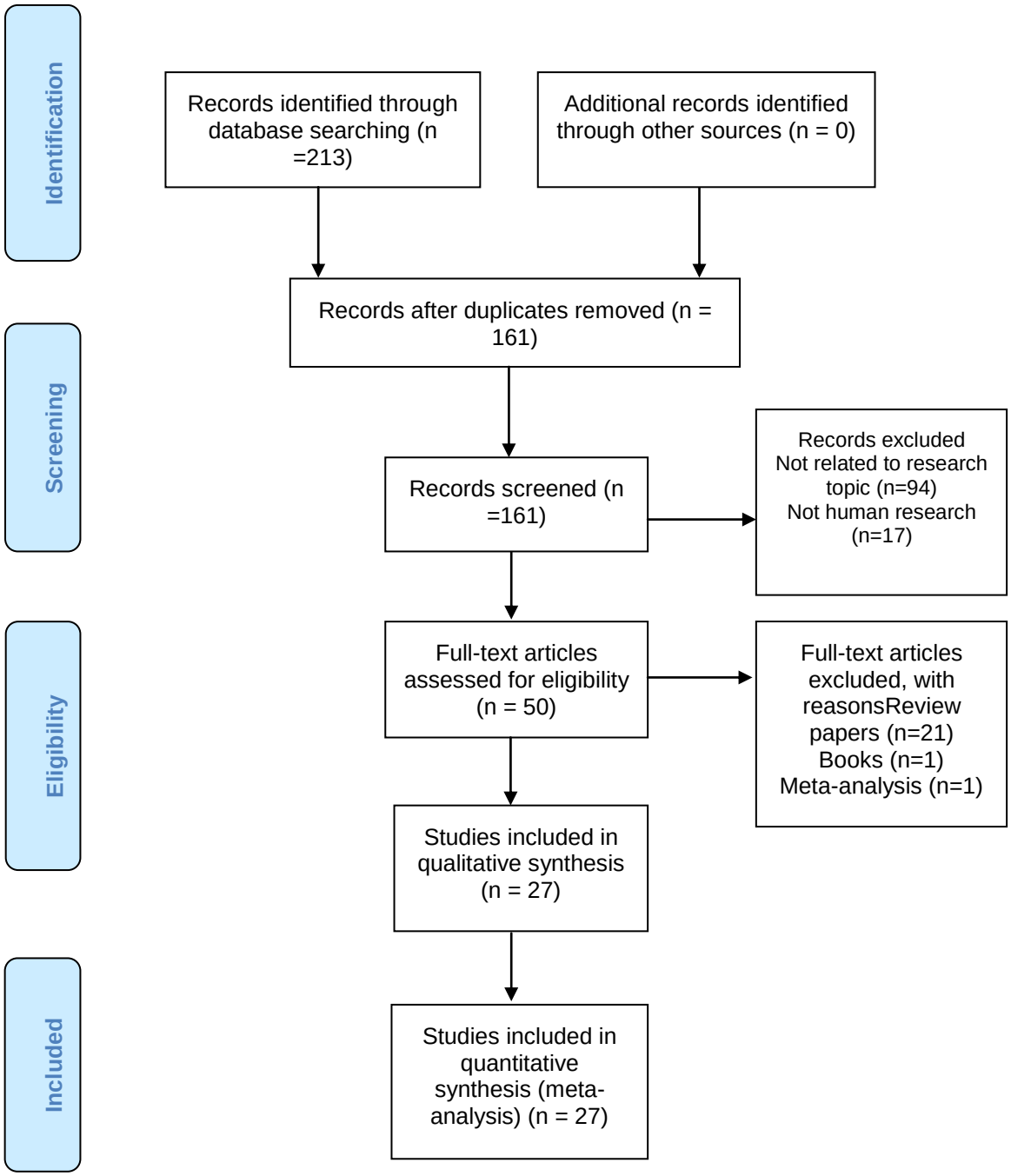


Fig. 1. Flow chart of literature search and study selection

Table 3. Moderators of the effect of CAD on Serum YKL-40 levels

				Heterogeneity		Effect of moderator	
Moderator	**No. of studies**	**SMD(95% CI)**	**P value**	**I^2 Within (%)**	**P value**	**I^2 between (%)**	**P Value**
Country						70.61%	0.41
Developing	8	1.38 (0.23-2.53)	0.02	99.1%	<0.001		
Developed	6	2.28 (1.10-3.47)	<0.001	97.3%	<0.001		
Sample Size						71.49%	0.79
Above 200	6	1.62 (0.29-2.95)	0.02	99.4%	<0.001		
Below 200	8	1.84 (0.91-2.77)	<0.001	96.1%	<0.001		
Age						99.82%	0.67
≥60	8	1.49 (0.88-2.10)	<0.001	96.2%	<0.001		
<60	6	1.91 (0.21-3.61)	0.03	99.2%	<0.001		
Controlled for confounders							
Gender						79.95%	0.92
Yes	8	1.49(0.88-2.10)	<0.001	96.2%	<0.001		
No	6	1.91(0.21-3.61)	0.03	99.2%	<0.001		
Smoking						71.21%	0.08
Yes	7	0.83(0.53-1.13)	<0.001	84.1%	<0.001		
No	7	2.78(1.10-4.46)	<0.001	99.1%	<0.001		
Quality Score						99.82%	0.26
≥7	8	1.42 (0.19-2.64)	0.02	99.0%	<0.001		
<7	6	2.16 (1.17-3.16)	<0.001	97.5%	<0.001		

Table 4. Moderators of the effect of DM on Serum YKL-40 levels

				Heterogeneity		Effect of moderator	
Moderator	**No. of studies**	**SMD(95% CI)**	**P value**	**I^2 Within (%)**	**P value**	**I^2 between (%)**	**P Value**
Country						99.90%	0.36
Developing	9	2.18 (0.68-3.68)	<0.001	98.8%	<0.001		
Developed	4	1.25 (-0.19-2.70)	0.09	98.3%	<0.001		
Sample Size						99.93%	0.12
Above 200	4	3.09 (0.37-5.81)	0.03	99.7%	<0.001		
Below 200	9	1.37 (0.65-2.09)	<0.001	93.6%	<0.001		
Age						99.94%	0.88
≥60	2	2.10 (1.72-2.49)	<0.001	5.8%	0.30		
<60	11	1.84 (0.58-3.11)	<0.001	99.0%	<0.001		
Controlled for confounders							
Gender						99.94%	0.76
Yes	2	2.04 (1.70-2.38)	<0.001	0.00%	0.61		
No	11	1.87 (0.58-3.15)	<0.001	99.0%	<0.001		
Smoking						99.94%	0.87
Yes	1	-0.69 (-0.97- -0.43)	<0.001	-	-		
No	12	2.11 (1.05-3.18)	<0.001	98.5%	<0.001		
Quality Score						99.82%	0.42
≥7	4	3.34 (0.16-6.53)	0.04	99.4%	<0.001		
<7	9	1.25 (0.26-2.25)	<0.001	98.0%	<0.001		
Type of disease							
DM1	5	1.15 (-0.07-2.36)	0.06	97.7%	<0.001	99.94%	0.35
DM2	8	2.36 (0.77-3.95)	<0.001	99.0%	<0.001		
Control Group							
Hospital-based	6	2.52 (0.18-4.85)	0.03	99.2%	<0.001	99.93%	0.35
Community-based	7	1.35 (0.44-2.27)	<0.001	97.2%	<0.001		

Table 5. Trim and fill analysis for CAD and DM studies

Moderators	No. of Studies	Unadjusted Pooled SMD (95% CI)	No. of Missing Studies	Trim-and-fill Adjusted Pooled SMD (95% CI)
CAD studies				
Overall	14	1.75 (0.95-2.55)	0	1.34 (0.80-2.25)
DM studies				
Overall	11	1.87 (0.44-3.31)	0	2.00 (1.16-3.45)

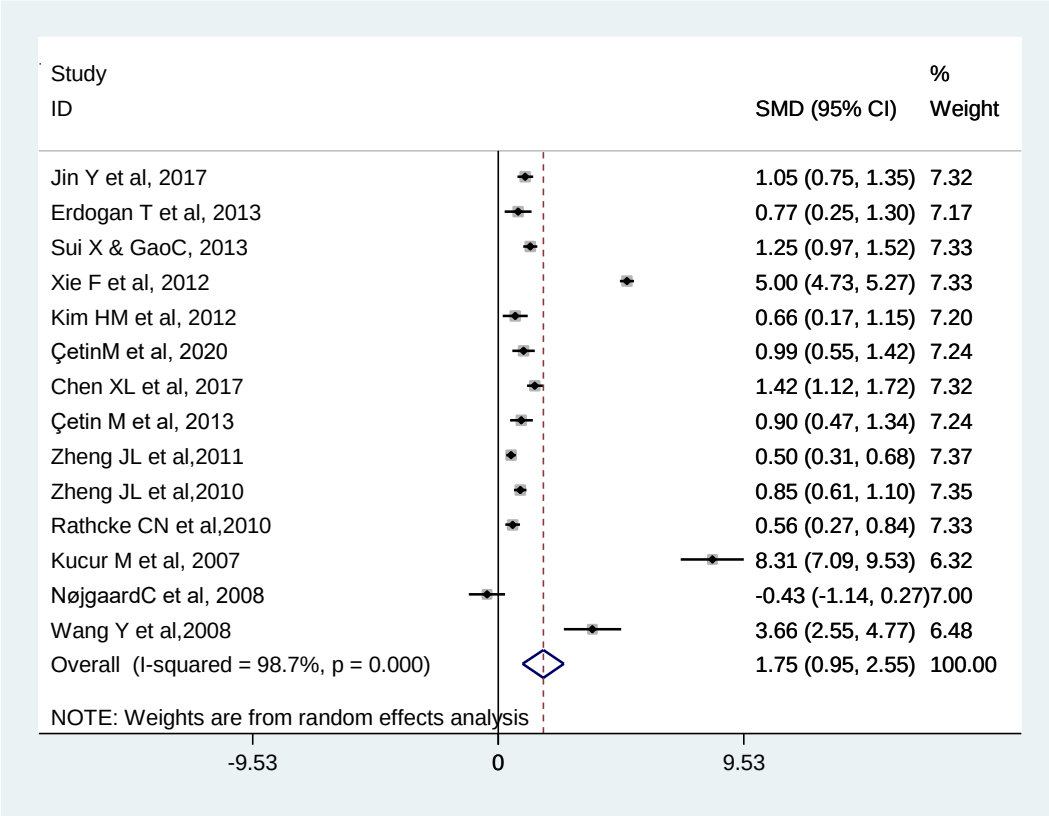


Fig. 2. Forest plots for the value of serum YKL-40 level for the diagnosis of coronary artery disease

4. DISCUSSION

This is the first meta-analysis done that concurrently investigated the value of serum YKL-40 for diagnosis of both CAD and DM. The results of this study showed that serum level in patients with CAD and DM was significantly higher than in the control participants. This indicates that, this relationship may represent a new opportunity for the possible utilization of serum levels of YKL-40 as a diagnostic biomarker for CAD and DM. Coincidently, Xie et al [34], Kucur and colleagues [43] also supported that serum YKL-40 levels were increased in CAD patients than controls indicating that YKL-40 may play an important role in prediction of atherosclerosis severity and inflammatory response, not only as a quantitative indicator of CAD, but also being a marker of CAD presence. In addition, the serum levels previously reported by Chun-Li et al showed a higher pooled SMD of YKL- 40 levels in CAD patients compared to our analysis. The possible reasons for this difference could be due to fewer numbers of papers (smaller sample size) in the previous study compared to this study. Other studies in our analysis have also reported that T1DM, T2DM patients displayed higher levels of serum YKL-40 than control subjects [50,18] indicating the importance of serum YKL-40 as a diagnostic biomarker for DM.

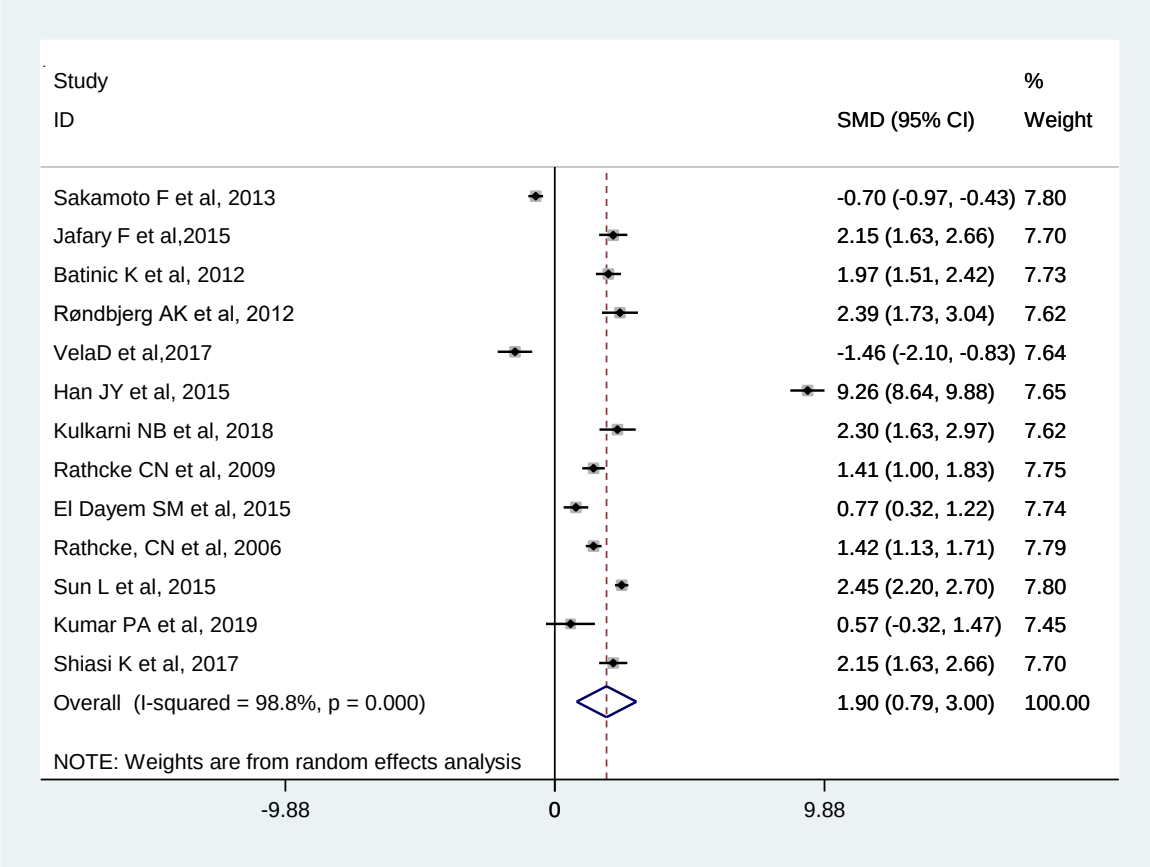
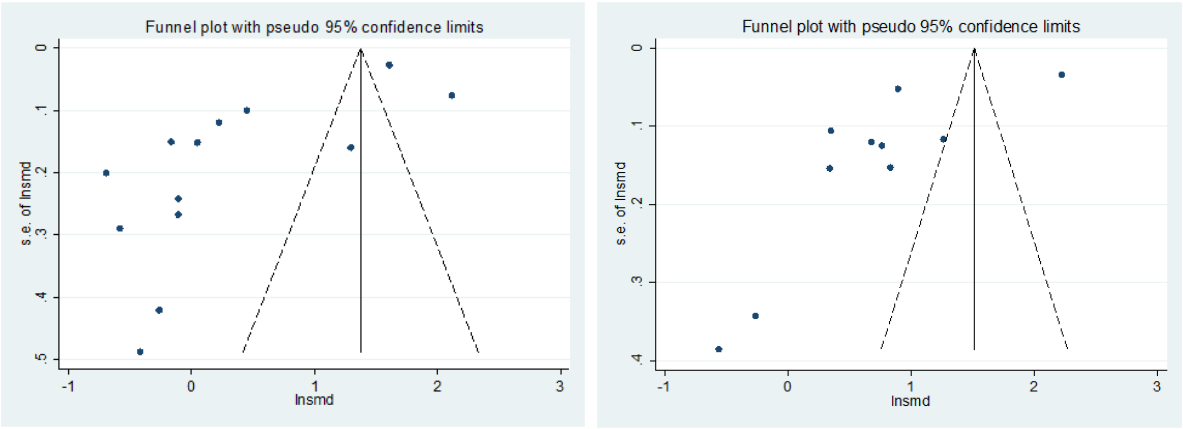


Fig. 3. Forest plots for the value of serum YKL-40 level for the diagnosis of Diabetes Mellitus



(a) (b)

Fig. 4. Funnel plots of Serum YKL-40 levels with (a) CAD risks and (b) DM risks

In patients with T2DM, YKL-40 is involved in endothelial dysfunction which is caused by an array of negative intracellular events when endothelium is exposed to hyperglycemia [36,51]. In both type 1 and type 2 diabetic patients, there are increased levels of YKL- 40, which is known to be a risk factor as well as an early marker of cardiovascular diseases [18,21,52]. Atherosclerosis is considered as a main cause of CAD [53] and it is noteworthy that macrophages exist in all phases of atherogenesis. Evidence has shown that the macrophages within atherosclerotic vascular plaques express YKL-40, predicting the impact on the presence and extent of CAD [54,55]. The functional role of YKL-40 in atherogenesis is

concentrated in the pathophysiological mechanisms, including inflammatory response, tissue destruction, ongoing fibrosis, smooth muscle proliferation, and migration of macrophages in the injured vessel wall [9,21]. In addition, laboratory and prospective clinical studies have proven the significant role of inflammation in the pathogenesis of atherosclerosis and highlights the critical effects of inflammatory parameters such as YKL-40 in the diagnosis and prediction of CAD [56,57].

Our stratified analysis based on country showed a significant difference of serum YKL-40 levels between developing and developed countries in both CAD and DM studies. Interestingly, developed countries showed higher levels of serum YKL-40 in CAD patients while in DM patients the serum YKL-40 was higher in developing countries. There is no definite explanation for this variant observation and it needs further investigation. However, some possible explanations could be due to the divergence in environments, genetic backgrounds, and risk factors relating to lifestyle like smoking, drinking, eating habits, physical inactivity among these populations.

We also found DM studies showed higher serum levels of the biomarker for people above the age of 60. This finding is also in line with other studies that have shown older patients to have higher YKL-40 levels [58,31]. However, studies of CAD showed slightly higher levels of YKL-40 among age group below 60 compared to older patients. This is in contrast with findings from other studies [37,38]. The possible reasons could be the formation of atherosclerosis and fatty streaks which begin in early life implying advanced atherosclerotic lesions may already appear in young adulthood. However, this needs further investigations [59,60].

In addition, studies that did not control for smoking showed a 2 fold higher levels of serum YKL-40 in detection of this biomarker compared to studies that controlled for smoking in CAD and DM studies. Many of the analyzed studies have adjusted for smoking, proving smoking may affect to a certain extent the changes in the levels of serum YKL-40. Furthermore, some studies reported that serum YKL-40 levels had a borderline change after adjusting for smoking [35,37] while others reported not to be a significant determinant after adjustment [28,61]. Thus the results should be interpreted with caution and assessing patient's history of smoking is critical if YKL-40 is to be based on as a diagnostic biomarker.

Our study also noted higher serum levels of YKL-40 in T2DM than T1DM. YKL-40 is found to be elevated in diabetic patients with complications like CAD and renal function [36]. This could be a possible explanation for this biomarker to be higher in T2DM patients. Also, T2DM usually presents at a later age than T1DM and usually serum YKL-40 levels are higher as age progresses [62,58].

5. STRENGTHS AND LIMITATIONS

This is the first meta-analysis evaluating serum YKL-40 levels in DM patients as well as CAD patients. The findings in this study can support the use of serum YKL-40 as a biomarker for CAD and DM. This study used a larger sample size compared to a previous meta-analysis. In addition, most studies included in this analysis, adjusted for one or more factors. We had a broad, accurate, precise and rigorous search strategy done for this meta-analysis.

However, the present study has certain limitations that warrant mentioning. There was persistent heterogeneity observed among studies that couldn't fully be explained. Furthermore, the study used a relatively small sample size that can affect the accuracy of the results. There was lack of access to some detailed information from few studies.

6. CONCLUSION

Biomarkers are essential for early diagnosis and assessment of prognosis of disease. The findings of this study have confirmed increased levels of serum YKL-40 in both CAD and DM patients compared to controls supporting serum YKL-40 as a promising biomarker for early identification of CAD and DM. Factors such as age, behavioral characteristic like smoking, and comorbidities were noted to affect the serum levels of YKL-40. Therefore, these factors should be considered when using YKL-40 as a biomarker for diagnosis for CAD and DM. In addition, more comprehensive studies with larger sample size are required to obtain a more profound statistical analysis with general applicability.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

DECLARATION

The present meta-analysis was conducted in accordance with the principles of the Declaration of Helsinki. Analyses were performed on data extracted from published papers.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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