Original Article

YKL-40 Levels in Rheumatoid Arthritis and Their Correlation with Disease Activity: A Meta-analysis

Young Ho Lee, Gwan Gyu Song

Department of Rheumatology, Korea University College of Medicine, Seoul, Korea

Objective. To examine the relationship of serum/plasma YKL-40 levels with rheumatoid arthritis (RA) and their correlation with RA activity and rheumatoid factor (RF) level. **Methods.** We performed a meta-analysis comparing the serum/plasma YKL-40 levels between patients with RA and controls and examined the correlation coefficients of the circulating YKL-40 level with the RF level and RA activity based on the 28-joint disease activity score (DAS28), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) level. **Results.** Nine studies (707 patients with RA and 1,041 controls) were included in the meta-analysis. The YKL-40 levels were significantly higher in the RA group than in the control group (standardized mean difference [SMD] = 1.071, 95% confidence interval [CI] = 0.726 ~ 1.417, p < 0.001). Stratification by ethnicity showed significantly elevated YKL-40 levels in the RA groups from European, Asian, North American, and Arab populations. The YKL-40 level was significantly higher in the RA group than in the control group in both age- and sex-matched and only age-matched populations (SMD = 0.937, 95% CI = 0.554 ~ 1.320, p < 0.001; SMD = 2.951, 95% CI = 1.389 ~ 4.512, p < 0.001, respectively). Subgroup analysis by sample size showed significantly increased YKL-40 levels in the RA group in both small (n < 100) and large (n > 100) populations. Meta-analysis of correlation coefficients showed a significant positive correlation between the YKL-40 levels and DAS28, ESR, CRP level, and RF level (DAS28: correlation coefficient = 0.381, 95% CI = 0.044 ~ 0.640, p = 0.028; RF level: correlation coefficient = 0.341, 95% CI = 0.176 ~ 0.487, p < 0.001). **Conclusion.** The circulating YKL-40 levels are high in patients with RA and positively correlate with RA activity and RF level. **(J Rheum Dis 2019;26:257-263)**

Key Words. YKL-40, Rheumatoid arthritis, Activity

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease that predominantly affects the synovial joints, causing significant morbidity and reduced life expectancy. RA is characterized by infiltration of neutrophils, macrophages, T cells, B cells, and dendritic cells in the synovium and by tissue damage. Although its cause and pathogenesis are not fully understood, it has been established that the inflammatory process plays a key role in RA [1].

YKL-40, a human cartilage glycoprotein-39 or chitinase-3-like-1 protein, is a 40-kDa glycoprotein produced in the arthritic joint by activated macrophages, neu-

trophils, synoviocytes, and chondrocytes [2]. It is suggested that YKL-40 plays a role in cell proliferation, differentiation, and protection against apoptotic signals and has an effect on extracellular tissue remodeling [3]. Increased serum YKL-40 levels are associated with diseases and inflammatory processes, such as RA, osteoarthritis, idiopathic pulmonary fibrosis, psoriasis, and type 2 diabetes, indicating that YKL-40 is related to inflammation, extracellular remodeling, and fibrosis [3-5]. Thus, YKL-40 has been considered as a useful potential biomarker of inflammatory diseases.

Studies on circulating YKL-40 levels between patients with RA and controls and on the relationship between plasma/serum levels and RA activity and rheumatoid fac-

tor (RF) levels have reported different results [6-14]. The reasons for such disparity might be their small sample size, low statistical power, and/or clinical heterogeneity. Therefore, to overcome the limitations of individual studies and improve precision, we performed this meta-analysis. The present study aimed to determine the plasma/serum YKL-40 levels between patients with RA and controls and to evaluate their correlation with RA activity and RF level via a meta-analysis.

MATERIALS AND METHODS

Eligible study identification and data extraction

We performed a literature search for studies that examined the YKL-40 levels in patients with RA and controls and their relationship with RA activity and RF levels. The MEDLINE, EMBASE, and Cochrane databases were searched to identify all available articles (published up to March 2019). The following keywords and subject terms were used in the search: "YKL-40," "level," and "rheumatoid arthritis." All references cited were also reviewed to identify additional studies not indexed by the electronic databases. Studies were considered eligible when they adhered to any of the following criteria: (1) case-control, cross-sectional, or longitudinal studies investigating patients with RA diagnosed in accordance with the American Rheumatism Association 1958, American College of Radiology (ACR) 1987, or ACR/European League Against Rheumatism classification criteria; (2) available data on plasma/serum YKL-40 levels of case and control groups; and (3) available data on the correlation coefficient between circulating YKL-40 levels and RF level or RA activity based on the 28-joint disease activity score (DAS28), erythrocyte sedimentation rate (ESR), or C-reactive protein (CRP) level. We excluded studies with any of the following characteristics: (1) overlapping or insufficient data and (2) reviews or case reports. The following information was extracted from each study: name of the first author, year of publication, country, ethnicity, number of participants, study design, sample type, means and standard deviations (SDs) of the YKL-40 levels, and correlation coefficients between the YKL-40 level and RF level, ESR, CRP level, or DAS28. When the data were presented as medians or ranges, we computed the means and SDs using previously described formulae [15,16]. Data from the methods and results were extracted from original studies by two independent reviewers. Discrepancies between the reviewers were re-

solved by a consensus. The meta-analysis was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses guidelines [17].

Evaluation of statistical associations

We performed meta-analyses examining the relationship between circulating YKL-40 levels and RA and the correlation coefficient between circulating YKL-40 levels and RF level, ESR, CRP level, or DAS28. For data continuity, results were presented as standardized mean differences (SMDs) and 95% confidence intervals (CIs). SMDs were calculated by dividing the mean difference between the two groups by pooled SD and were used when different scales were integrated to measure the same concept. This measure compares case and control arms in terms of standardized scores. The magnitude of the SMD was considered as follows: 0.2~0.5, small effect; 0.5~0.8, medium effect; and ≥0.8, large effect [18]. We assessed within- and between-study variations and heterogeneities using Cochran's Q-statistics [19]. When the significant Q-statistic ($p < 0.10$) indicated heterogeneity across studies, the random effects model was used for the meta-analysis [20]; otherwise, the fixed effects model was used. The fixed effects model assumes that all studies estimate the same underlying effect and considers only within-study variations [19]. We quantified the effect of heterogeneity using the I^2 value, where I^2 measures the degree of inconsistency between datasets [21]. Statistical manipulations were performed using the Comprehensive Meta-Analysis computer program (Biostat, Englewood, NJ, USA).

Evaluation of heterogeneity, sensitivity, and publication bias

To examine potential sources of heterogeneity in the meta-analysis, subgroup analysis was performed using the following variables: ethnicity, sample size, data type, adjustment for age and/or sex, and publication year. Sensitivity test was performed to assess the influence of each individual study on the pooled odds ratio (OR) by individually omitting each study and deleting studies with imputed data. Although funnel plots are often used to detect publication bias, they require diverse study types of varying sample sizes, and their interpretation involves subjective judgment. Therefore, we evaluated publication bias using Egger's linear regression test [22], which measures funnel plot asymmetry using a natural logarithm scale of ORs.

RESULTS

Studies included in the meta-analysis

We identified 94 studies using electronic and manual searching methods, and 11 of them were selected for full-text review based on the title and abstract. Two of these were excluded because they had no control group data [23,24]. Finally, nine articles met the inclusion criteria for this meta-analysis [6-14] (Table 1). One of the eligible studies included data on two different groups that were treated independently [14]. Therefore, 10 comparative studies were considered in the meta-analysis, which included 707 patients with RA and 1,041 controls (Table 1). Ten studies examined the circulating YKL-40

Table 1. Characteristics of individual studies included in the meta-analysis

Authors	Country	Ethnicity	Number of patients		YKL-40 level (mean)		YKL-40, unit	Matched for age and/ or sex	Data type
			RA	Control	RA	Control			
Jafari-Nakhjavani et al., 2019 [12]	Iran	Arab	60	30	951.63	444.92	pg/mL	Age, sex	Original
Basok et al., 2014 [13]	Turkey	European	27	27	66.95	48.70	ng/mL	Age, sex	Original
Turkyilmaz et al., 2013 [6]	Turkey	European	42	35	124.30	67.20	ng/mL	Age, sex	Original
Kozakova et al., 2013 [7]	Bulgaria	European	25	40	246.17	84.19	ng/mL	Age, sex	Original
Nielsen et al., 2011 [8]	Denmark	European	308	605	86.00	46.00	ng/mL	Age	Original
Janckila et al., 2008 [10]	USA	North American	50	26	710.00	67.15	μg/L	Sex	Original
Matsumoto et al.-1, 2001 [14]	Japan	Asian	56	26	197.00	68.75	pg/mL	Age, sex	Calculated*
Matsumoto et al.-2, 2001 [14]	Japan	Asian	16	14	220.00	77.25	pg/mL	Age, sex	Calculated*
Johansen et al., 2001 [9]	USA	North American	76	191	156.25	72.00	ug/L	Age	Calculated*
Vos et al., 2000 [11]	Netherlands	European	47	47	38.30	15.50	ng/mL	Age, sex	Original

RA: rheumatoid arthritis, USA: United States of America. *The means ± standard deviations were calculated from the medians and ranges.

Table 2. Meta-analysis of the YKL-40 levels between the patients with RA and controls

Groups	Population	Number of studies	Test of association			Test of heterogeneity		
			SMD*	95% CI	p-value	Model	p-value	I^2
All	Overall	10	1.071	0.726~1.417	<0.001	R	<0.001	86.6
Ethnicity	European	5	0.762	0.418~1.127	<0.001	R	<0.001	74.8
	Asian	2	1.353	0.921~1.785	<0.001	F	0.173	55.8
	North American	2	1.552	0.565~2.539	0.002	R	0.001	90.9
	Arab	1	0.954	0.494~1.414	<0.001	NA	NA	NA
Matched for age and/or sex	Both	7	0.937	0.554~1.320	<0.001	R	0.001	73.8
	Age or sex	3	2.951	1.389~4.512	<0.001	R	<0.001	98.4
Sample size	n<100	8	0.943	0.610~1.276	<0.001	R	<0.001	70.2
	n>100	2	1.463	0.358~2.568	0.029	R	<0.001	97.5
Data type	Original	7	0.824	0.572~1.075	<0.001	R	0.011	63.7
	Calculated	3	1.703	1.081~2.325	<0.001	R	<0.001	76.5

RA: rheumatoid arthritis, SMD: standardized mean difference, CI: confidence interval, F: fixed effects model, R: random effects model, NA: not applicable. *Magnitude of Cohen's d effect size (SMD): 0.2~0.5, small effect; 0.5~0.8, medium effect; ≥0.8, large effect.

levels in RA and control groups. Four, three, two, and four studies assessed the correlation coefficients between the YKL-40 levels and DAS28, ESR, CRP level, or RF level, respectively (Table 1). Table 1 shows the characteristic features of the studies included in this meta-analysis.

Meta-analysis of the circulating YKL-40 levels between the patients with RA and controls

The YKL-40 levels were significantly higher in the RA group than in the control group (SMD=1.071, 95% CI=0.726~1.417, p<0.001) (Table 2, Figure 1). In addition, stratification by ethnicity showed significantly ele-

vated YKL-40 levels in the RA groups from European, Asian, North American, and Arab populations (Table 2, Figure 2).

Meta-analysis of the circulating YKL-40 levels between the patients with RA and controls according to subgroups

The YKL-40 level was significantly higher in the RA group than in the control group in both age- and sex-matched and only age-matched populations (SMD= 0.937, 95% CI=0.554~1.320, p<0.001; SMD=2.951, 95% CI=1.389~4.512, p<0.001) (Table 2). Subgroup

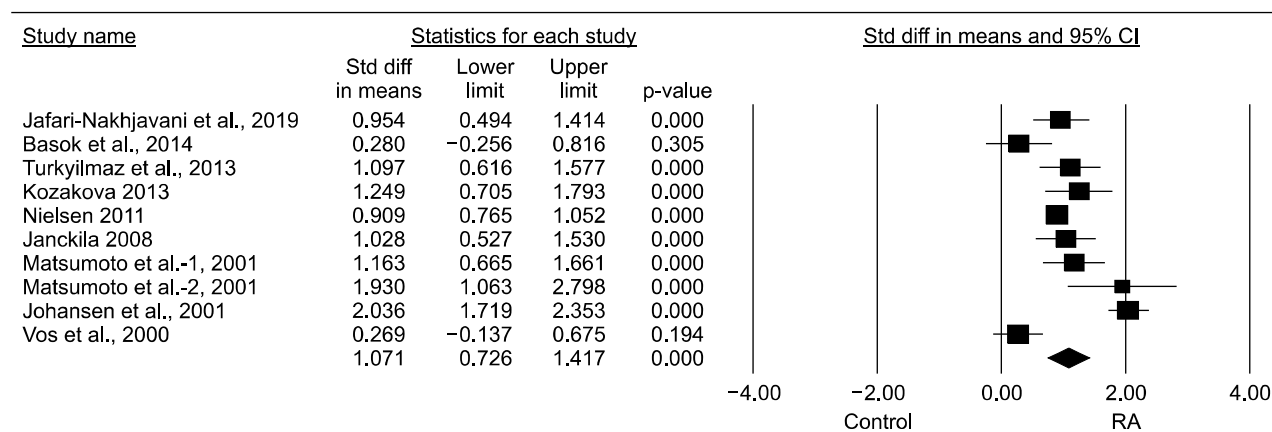| Study name	Std diff in means	Lower limit	Upper limit	p-value
Jafari-Nakhjavani et al., 2019	0.954	0.494	1.414	0.000
Basok et al., 2014	0.280	−0.256	0.816	0.305
Turkyilmaz et al., 2013	1.097	0.616	1.577	0.000
Kozakova 2013	1.249	0.705	1.793	0.000
Nielsen 2011	0.909	0.765	1.052	0.000
Janckila 2008	1.028	0.527	1.530	0.000
Matsumoto et al.-1, 2001	1.163	0.665	1.661	0.000
Matsumoto et al.-2, 2001	1.930	1.063	2.798	0.000
Johansen et al., 2001	2.036	1.719	2.353	0.000
Vos et al., 2000	0.269	−0.137	0.675	0.194
	1.071	0.726	1.417	0.000

Figure 1. Meta-analysis of the relationship between the plasma/serum YKL-40 levels and rheumatoid arthritis (RA) in all study subjects. Std diff: standardized difference, CI: confidence interval.
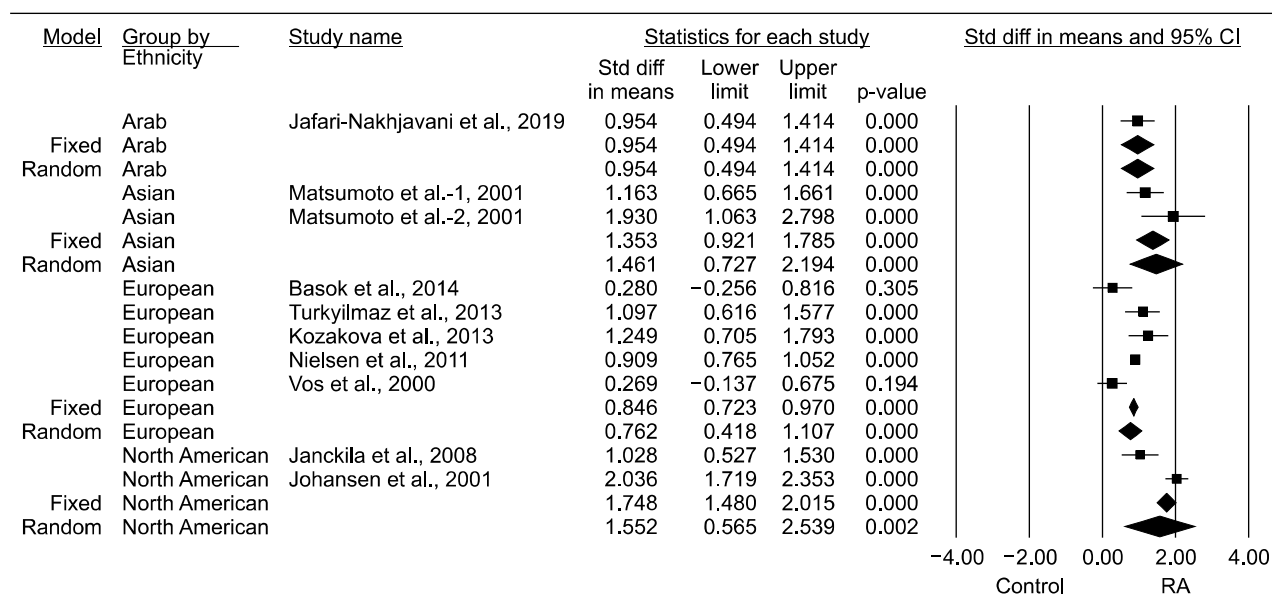
Model	Group by Ethnicity	Study name	Std diff in means	Lower limit	Upper limit	p-value
	Arab	Jafari-Nakhjavani et al., 2019	0.954	0.494	1.414	0.000
Fixed	Arab		0.954	0.494	1.414	0.000
Random	Arab		0.954	0.494	1.414	0.000
	Asian	Matsumoto et al.-1, 2001	1.163	0.665	1.661	0.000
	Asian	Matsumoto et al.-2, 2001	1.930	1.063	2.798	0.000
Fixed	Asian		1.353	0.921	1.785	0.000
Random	Asian		1.461	0.727	2.194	0.000
	European	Basok et al., 2014	0.280	−0.256	0.816	0.305
	European	Turkyilmaz et al., 2013	1.097	0.616	1.577	0.000
	European	Kozakova et al., 2013	1.249	0.705	1.793	0.000
	European	Nielsen et al., 2011	0.909	0.765	1.052	0.000
	European	Vos et al., 2000	0.269	−0.137	0.675	0.194
Fixed	European		0.846	0.723	0.970	0.000
Random	European		0.762	0.418	1.107	0.000
	North American	Janckila et al., 2008	1.028	0.527	1.530	0.000
	North American	Johansen et al., 2001	2.036	1.719	2.353	0.000
Fixed	North American		1.748	1.480	2.015	0.000
Random	North American		1.552	0.565	2.539	0.002

Figure 2. Meta-analysis of the relationship between the plasma/serum YKL-40 levels and rheumatoid arthritis (RA) in each ethnic group. Std diff: standardized difference, CI: confidence interval.

analysis by sample size showed significantly increased YKL-40 levels in the RA group in both small (n<100) and large (n>100) populations (Table 2). The YKL-40 level was significantly higher in the RA group than in the control group, regardless of data type (Table 2).

Meta-analysis of the correlation between the circulating YKL-40 levels and RA activity and RF level

Meta-analysis of the correlation coefficients showed a significant positive correlation between the YKL-40 levels and DAS28, ESR, or CRP level (correlation coefficient of the DAS28=0.381, 95% CI=0.044~0.640, p=0.028) (Table 3, Figure 3). Further, the YKL-40 levels were pos-

itively associated with the RF level (correlation coefficient=0.341, 95% CI=0.176~0.487, p<0.001) (Table 3).

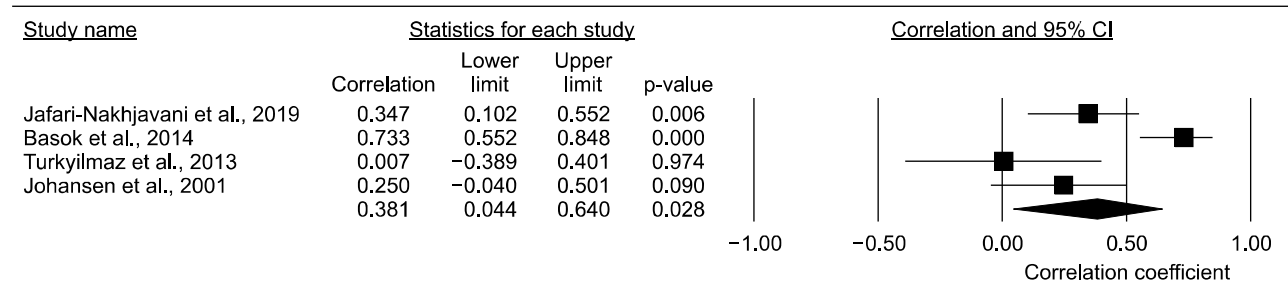## Heterogeneity, sensitivity, and publication bias

Between-study heterogeneity was identified in the meta-analyses of the YKL-40 levels in the patients with RA (Table 2). Meta-regression analysis showed that ethnicity, age or sex adjustment, publication year, sample size, and data type (p>0.05) had a significant impact on heterogeneity in the meta-analysis of the YKL-40 levels. Sensitivity analysis showed that no individual study signi ficantly affected the pooled OR, indicating that the results of this meta-analysis are robust. It was difficult to corre-

Table 3. Meta-analysis of the correlation coefficient between the YKL-40 level and RA activity (DAS28, ESR, and CRP level) and RF level

Comparison	Number of studies	Test of association			Test of heterogeneity		
		Correlation coefficient	95% CI	p-value	Model	p-value	I^2
DAS28	4	0.381	0.044~0.640	0.028	R	0.001	80.6
ESR	3	0.402	0.216~0.560	<0.001	F	0.981	0
CRP level	2	0.531	0.269~0.693	<0.001	F	0.513	0
RF level	3	0.341	0.176~0.487	<0.001	F	0.113	54.1

RA: rheumatoid arthritis, DAS28: 28-joint disease activity score, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, RF: rheumatoid factor, CI: confidence interval, R: random effects model, F: fixed effects model.

A

Study name	Statistics for each study				Correlation and 95% CI
	Correlation	Lower limit	Upper limit	p-value	
Jafari-Nakhjavani et al., 2019	0.347	0.102	0.552	0.006	
Basok et al., 2014	0.733	0.552	0.848	0.000	
Turkyilmaz et al., 2013	0.007	−0.389	0.401	0.974	
Johansen et al., 2001	0.250	−0.040	0.501	0.090	
	0.381	0.044	0.640	0.028	

B

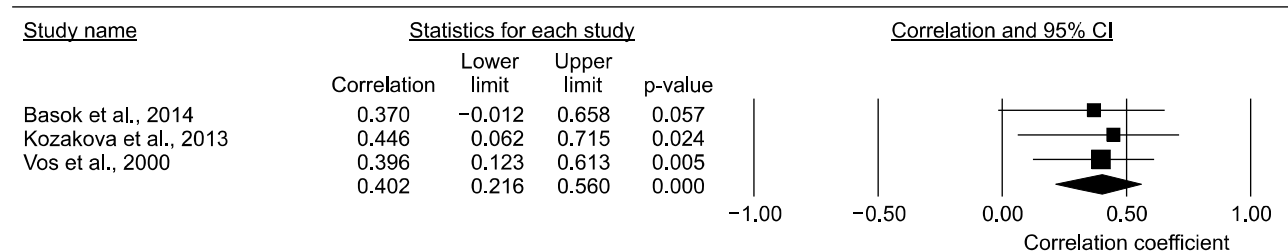| Study name	Statistics for each study				Correlation and 95% CI
	Correlation	Lower limit	Upper limit	p-value	
Basok et al., 2014	0.370	−0.012	0.658	0.057	
Kozakova et al., 2013	0.446	0.062	0.715	0.024	
Vos et al., 2000	0.396	0.123	0.613	0.005	
	0.402	0.216	0.560	0.000	

Figure 3. Meta-analysis of the correlation coefficient between the YKL-40 levels and DAS28 (A) and ESR (B). DAS28: 28-joint disease activity score, ESR: erythrocyte sedimentation rate, CI: confidence interval.

late the funnel plot, which is typically used to detect publication bias, because the number of studies included in the analysis was relatively less. The funnel plot showed no evidence of asymmetry, and Egger's regression test showed no evidence of publication bias in the meta-analysis of the plasma/serum YKL-40 levels in the patients with RA (Egger's regression test p-value=0.706).

DISCUSSION

In this meta-analysis, we combined the plasma/serum YKL-40 level in RA with the correlation between the YKL-40 levels and RA activity and RF levels. This meta-analysis of nine studies involving 707 patients with RA and 1,041 controls showed that the circulating YKL-40 levels were significantly higher in the former than in the latter. The YKL-40 level had a positive correlation with RA activity as measured using the DAS28, ESR, and CRP level. The YKL-40 levels were also significantly correlated with the RF level. The meta-analysis data suggest that the YKL-40 levels reflect significantly increased RA activity and that YKL-40 plays an important role in the proinflammatory process of RA.

YKL-40 is a heparin-human cartilage glycoprotein-39 without enzymatic activity, which is secreted by various cell types in the arthritic joint [2]. It is a major protein secreted by chondrocytes in vitro; conversely, it is identified in the chondrocytes from arthritic knee joints in vivo. YKL-40 regulates inflammation and immune response and is also related to cell migration and reorganization [3]. It is a transmembrane protein in which cleaved components bind to an unidentified receptor, and its expression is regulated by various inflammatory cytokines [25]. In vitro and in vivo studies showed that transforming growth factor-β, tumor necrosis factor-α, and other multifunctional cytokines can also stimulate YKL-40 secretion, and YKL-40 further promotes the expression of macrophage inflammatory protein-1α, monocyte chemoattractant protein-1, and metalloproteinase-9 [26]. YKL-40 secretion may regulate activation of the mitogen-activated protein kinase, nuclear factor-κB, protein kinase B, and other cytokine pathways; signaling pathways have been found to be related to the pathogenesis of RA [27]. YKL-40 was found to be a target of the immune response in RA, having several human leukocyte antigen-DR4 peptide-binding motifs that are recognized by T cells from patients with RA; this suggests that it plays a pathogenic role in inflammatory processes [28]. It

is assumed that YKL-40 is a candidate autoantigen in RA [28]. Our meta-analysis revealed higher serum YKL-40 levels in patients with RA than in healthy controls, which correlated positively with RA activity. Therefore, YKL-40 might be considered as a novel biomarker for disease activity estimation in RA.

The present study has some limitations that should be considered. First, most of the studies included in this meta-analysis had small sample sizes; thus, many of the individual studies that comprise this meta-analysis may be underpowered. Second, the studies included were heterogeneous in demographic characteristics and clinical features. This heterogeneity and the presence of confounding factors, such as drugs used, disease duration, and limited clinical information, may have affected the results. These limited data did not allow further analysis, although we performed a sensitivity test, subgroup analysis, and meta-regression analysis using available confounding factors. Nevertheless, this meta-analysis also has its strengths. Our meta-analysis is the first meta-analysis to provide combined evidence for YKL-40 levels in patients with RA. Individual studies included population sizes ranging from only 16 to 308 patients; however, our pooled analysis included 707 patients. Compared with individual studies, our study was able to provide data regarding the relationship between YKL-40 levels and RA with increased accuracy by increasing the statistical power and resolution through pooling of the results of independent analyses.

CONCLUSION

Our meta-analysis demonstrates that the circulating YKL-40 levels are significantly higher in patients with RA than in controls. In addition, the circulating YKL-40 levels positively correlated with RA activity and RF level. Thus, further studies are necessary to check the possibility that YKL-40 may play an important role in the pathogenesis of RA.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Y.H.L. was involved in conception and design of study,

acquisition of data, analysis and/or interpretation of data, drafting the manuscript, revising the manuscript critically for important intellectual content. G.G.S. was involved in conception and design of study, analysis and/or interpretation of data, drafting the manuscript.

REFERENCES

1. Lee YH, Bae SC, Choi SJ, Ji JD, Song GG. Genome-wide pathway analysis of genome-wide association studies on systemic lupus erythematosus and rheumatoid arthritis. Mol Biol Rep 2012;39:10627-35.

2. Hakala BE, White C, Recklies AD. Human cartilage gp-39, a major secretory product of articular chondrocytes and synovial cells, is a mammalian member of a chitinase protein family. J Biol Chem 1993;268:25803-10.

3. Johansen JS. Studies on serum YKL-40 as a biomarker in diseases with inflammation, tissue remodelling, fibroses and cancer. Dan Med Bull 2006;53:172-209.

4. Zivanović S, Rackov LP, Vojvodić D, Vucetić D. Human cartilage glycoprotein 39--biomarker of joint damage in knee osteoarthritis. Int Orthop 2009;33:1165-70.

5. Furuhashi K, Suda T, Nakamura Y, Inui N, Hashimoto D, Miwa S, et al. Increased expression of YKL-40, a chitinase-like protein, in serum and lung of patients with idiopathic pulmonary fibrosis. Respir Med 2010;104:1204-10.

6. Turkyilmaz AK, Devrimsel G, Kirbas A, Cicek Y, Karkucak M, Capkin E, et al. Relationship between pulse wave velocity and serum YKL-40 level in patients with early rheumatoid arthritis. Rheumatol Int 2013;33:2751-6.

7. Kazakova M, Batalov A, Deneva T, Mateva N, Kolarov Z, Sarafian V. Relationship between sonographic parameters and YKL-40 levels in rheumatoid arthritis. Rheumatol Int 2013;33:341-6.

8. Nielsen KR, Steffensen R, Boegsted M, Baech J, Lundbye-Christensen S, Hetland ML, et al. Promoter polymorphisms in the chitinase 3-like 1 gene influence the serum concentration of YKL-40 in Danish patients with rheumatoid arthritis and in healthy subjects. Arthritis Res Ther 2011;13:R109.

9. Johansen JS, Kirwan JR, Price PA, Sharif M. Serum YKL-40 concentrations in patients with early rheumatoid arthritis: relation to joint destruction. Scand J Rheumatol 2001;30: 297-304.

10. Janckila AJ, Neustadt DH, Yam LT. Significance of serum TRACP in rheumatoid arthritis. J Bone Miner Res 2008; 23:1287-95.

11. Vos K, Steenbakkers P, Miltenburg AM, Bos E, van Den Heuvel MW, van Hogezand RA, et al. Raised human cartilage glycoprotein-39 plasma levels in patients with rheumatoid arthritis and other inflammatory conditions. Ann Rheum Dis 2000;59:544-8.

12. Jafari-Nakhjavani MR, Ghorbanihaghjo A, Bagherzadeh-Nobari B, Malek-Mahdavi A, Rashtchizadeh N. Serum YKL-40 levels and disease characteristics in patients with

13. Basok BI, Kucur M, Kizilgul M, Yilmaz I, Ekmekci OB, Uzunlulu M, et al. Increased chitotriosidase activities in patients with rheumatoid arthritis: a possible novel marker? J Med Biochem 2014;33:245-51.

14. Matsumoto T, Tsurumoto T. Serum YKL-40 levels in rheumatoid arthritis: correlations between clinical and laborarory parameters. Clin Exp Rheumatol 2001;19:655-60.

15. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005;5:13.

16. Ridout KK, Ridout SJ, Price LH, Sen S, Tyrka AR. Depression and telomere length: a meta-analysis. J Affect Disord 2016;191:237-47.

17. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009; 6:e1000097.

18. McGough JJ, Faraone SV. Estimating the size of treatment effects: moving beyond p values. Psychiatry (Edgmont) 2009;6:21-9.

19. Egger M, Smith GD, Phillips AN. Meta-analysis: principles and procedures. BMJ 1997;315:1533-7.

20. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-88.

21. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539-58.

22. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-34.

23. Knudsen LS, Klarlund M, Skjødt H, Jensen T, Ostergaard M, Jensen KE, et al. Biomarkers of inflammation in patients with unclassified polyarthritis and early rheumatoid arthritis. Relationship to disease activity and radiographic outcome. J Rheumatol 2008;35:1277-87.

24. Peltomaa R, Paimela L, Harvey S, Helve T, Leirisalo-Repo M. Increased level of YKL-40 in sera from patients with early rheumatoid arthritis: a new marker for disease activity. Rheumatol Int 2001;20:192-6.

25. Ling H, Recklies AD. The chitinase 3-like protein human cartilage glycoprotein 39 inhibits cellular responses to the inflammatory cytokines interleukin-1 and tumour necrosis factor-alpha. Biochem J 2004;380:651-9.

26. Recklies AD, Ling H, White C, Bernier SM. Inflammatory cytokines induce production of CHI3L1 by articular chondrocytes. J Biol Chem 2005;280:41213-21.

27. Lee CG, Da Silva CA, Dela Cruz CS, Ahangari F, Ma B, Kang MJ, et al. Role of chitin and chitinase/chitinase-like proteins in inflammation, tissue remodeling, and injury. Annu Rev Physiol 2011;73:479-501.

28. Joosten LA, Coenen-de Roo CJ, Helsen MM, Lubberts E, Boots AM, van den Berg WB, et al. Induction of tolerance with intranasal administration of human cartilage gp-39 in DBA/1 mice: amelioration of clinical, histologic, and radiologic signs of type II collagen-induced arthritis. Arthritis Rheum 2000;43:645-55.