Clin. Lab. 2019;65:XXX-XXX

ORIGINAL ARTICLE

Serum Surfactant Protein D is a Potential Biomarker for Chronic Obstructive Pulmonary Disease: a Systematic Review and Meta-analysis

Hong Wang [*], Fangwei Li [*], Huirong Huang, Fanqi Wu, Lijun Chen, Degang Zhang, Tianming Zhang, Yixin Wan

[*] *These authors are co-first authors on this work*
Department of Respiratory Medicine, Lanzhou University Second Hospital, Lanzhou, China

SUMMARY

Background: **A number of studies have been conducted to investigate the association between serum surfactant protein D (SP-D) concentration and chronic obstructive pulmonary disease (COPD) risk. However, the results are inconsistent. This systematic review and meta-analysis aim to investigate whether serum SP-D concentration is a potential biomarker for COPD diagnosis.**
Methods: **We searched Web of Science, PubMed, China National Knowledge Infrastructure (CNKI), and Wanfang Database from inception through July 18, 2018. The standardized mean difference (SMD) with 95% confidence interval (CI) was used to investigate the effect sizes.**
Results: **Seventeen eligible studies from a total of 4,639 subjects were finally included in this systematic review and meta-analysis. The results indicated that serum SP-D levels in COPD patients were significantly higher than those in controls (SMD = 1.01, 95% CI = 0.62 - 1.41, p < 0.001). We also found that serum SP-D concentration in acute exacerbation of chronic obstructive pulmonary disease (AECOPD) patients was significantly higher than that in stable COPD patients (SMD = 1.50, 95% CI = 0.92 - 2.08, p < 0.001), and serum SP-D concentration was higher in smokers than in nonsmokers in healthy population (SMD = 1.50, 95% CI = 0.35 - 2.64, p = 0.025).**
Conclusions: **The current systematic review and meta-analysis indicates that serum SP-D levels may be a promising biomarker for COPD. In particular, increased serum SP-D levels appear to be associated with acute exacerbation of COPD and smoking in healthy population.**
(Clin. Lab. 2019;65:xx-xx. DOI: 10.7754/Clin.Lab.2019.190539)

Correspondence:
Yixin Wan
Department of Respiratory Medicine
Lanzhou University Second Hospital
Cuiying Men No. 82
730030 Lanzhou, Gansu
China
Phone: +86 0931-8942347
Email: wanyixinzr@163.com

Manuscript accepted June 16, 2019

KEY WORDS

SP-D, COPD, biomarker, meta-analysis

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by persistent respiratory symptoms and progressive airflow limitation that is due to chronic airway inflammation, carrying a significant and substantial socioeconomic burden on individuals and society [1]. Studies have found that COPD-related costs increase with disease severity, and prompt and accurate diagnosis enables early intervention [2]. Therefore, there is an increasing number of studies published on exploring

specific and novel biomarkers for early diagnosis of COPD, such as C-reactive protein, interleukin-8, eosinophil levels, and so on [3-5].

Surfactant protein D (SP-D) is a glycoprotein belonging to the collectin protein family and is encoded by a gene located on chromosome 10 [6,7]. It is synthesized mainly in type II pneumocytes in the lungs and has the largest and most flexible collagen domain among collectins, forming networks with various bound organisms [7]. Apart from defending against infectious agents and allergens, SP-D unusual expression is a biomarker for several chronic inflammatory diseases [8,9]. Many studies have reported the correlation between serum SP-D concentration and COPD risk [10-16]. However, the results were contradictory, and all relevant studies were performed in an individual medical center with small sample size. Therefore, it is necessary to clarify the relationship between SP-D concentration and COPD diagnosis based on all published studies, and the aim of the present study is to address this issue using meta-analysis.

MATERIALS AND METHODS

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) guidelines [17].

Identification of eligible studies

To identify all eligible studies that investigated the association between serum SP-D concentration and COPD risk, a systematic literature search of Web of Science, PubMed, China National Knowledge Infrastructure (CNKI), and Wanfang Database was performed until July 18, 2018. The key search terms were as follows: chronic obstructive pulmonary disease or COPD or chronic airway inflammatory disease and surfactant protein D or SP-D. Furthermore, the reference lists of reviews and retrieved articles were manually screened for additional studies. All analyses in the current meta-analysis were based on previously published studies and the language was restricted to English.

Inclusion and exclusion criteria

Studies identified from the above mentioned databases were screened by two independent authors according to the following predesigned inclusion criteria: (1) a cohort study or case-control study; (2) evaluating the relationship between serum SP-D concentration and COPD; (3) providing sufficient data to calculate the standardized mean difference (SMD) with a 95% confidence interval (CI); (4) not republished data.

Qualitative assessment

The qualities of the included studies were accessed by two investigators according to the Newcastle-Ottawa Scale (NOS). The NOS contains three main aspects: selection of subject (0 - 4), comparability of cases and controls (0 - 2), and exposure of subject (0 - 3). Studies were considered as high quality if their total scores were 7 - 9. Discrepancies were resolved by consensus and discussion.

Data extraction

Two independent reviewers extracted the detailed information and data from each primary study according to the predesigned data-collection form. The following information and data were extracted: first author, publication year, country of origin, number of both COPD cases and control subjects, serum SP-D concentration and method of SP-D measurement. Discrepancies occurring during the process of data extraction were resolved by discussion with a third reviewer, and consensus on each item was achieved eventually.

Data analysis

The statistical analysis was conducted using Stata 12.0. Pooled SMD with 95% CI was calculated and $p < 0.05$ was accepted as statistically significant. Heterogeneity among studies was examined with the χ^2-based Q testing and I^2 statistics. Meta-analysis was done using the fixed-effects model when there was no significant heterogeneity ($p < 0.10$). Otherwise, the random-effects model was used [18]. In addition, meta-regression analysis was used to investigate the sources of heterogeneity and subgroup analysis was operated to determine the role of disease status (exacerbation or stable) and smoking in serum SP-D concentration. The leave-one-out sensitivity analysis was performed by removing one study each time to check if an individual study influenced the pooled results. Publication bias was examined with Begg's test and Egger's test and $p < 0.05$ indicated significant publication bias.

RESULTS

Characteristics of eligible studies

A total of 922 papers were obtained after the initial search of databases. After screening, 17 case-control/cohort studies with a total of 4,639 participants (3,052 cases and 1,587 controls) were finally identified in the current meta-analysis. The flow chart for selection of studies and reasons of exclusion are presented in Figure 1. The 17 included studies were published between 2006 and 2017. A total of 3,052 COPD patients (2,114 males and 938 females) as well as 1,587 healthy controls (906 males and 681 females) were evaluated. The detail characteristics of these studies were shown in Table 1.

Overall meta-analysis

The forest plot for serum SP-D levels in COPD patients compared with controls is shown in Figure 2. The results indicated that serum SP-D concentration in COPD patients was significantly higher than that in controls (SMD = 1.01, 95% CI = 0.62 - 1.41, $p < 0.001$). A non-

Table 1. Characteristics of studies involving in the relationship between serum SP-D levels and COPD.

Study	Country	Group	N	Age	Gender (M/F)	Smoking (pack-years)	Sample	Assay method	SP-D (ng/mL)	NOS (Stars)
Fakih et al. (2017)	Lebanon	COPD	90	62.0 ± 5.3	52/38	NR	Serum	ELISA	1,510.0 ± 198.0	7
		Control	223	36.0 ± 6.5	89/134				1,122.0 ± 175.8	
Akiki et al. (2016)	Lebanon	COPD	90	62.0 ± 3.5	52/38	NR	Serum	ELISA	1,510.0 ± 198.0	7
		Control	180	55.0 ± 2.2	65/115				1,269.0 ± 203.0	
Alaabden et al. (2015)	Syria	COPD	56	61.6 ± 8.3	45/11	48.2 ± 28.0	Serum	ELISA	425.7 ± 126.3	9
		Control	28	58.7 ± 7.6	23/5	30.5 ± 27.6			177.3 ± 47.0	
Ou et al. (2015)	China	COPD	192	68.6 ± 11.4	100/92	44.8 ± 32.7	Serum	ELISA	63.7 ± 43.8	8
		Control	128	58.3 ± 12.8	100/28	37.3 ± 25.6			69.3 ± 52.2	
Wei et al. (2015)	China	COPD	8	70.0 ± 6.1	6/2	NR	Serum	ELISA	13.1 ± 2.2	8
		Control	8	67.0 ± 4.3	6/2				10.3 ± 2.6	
Ambade et al. (2015)	India	COPD	96	67.7 ± 8.9	73/23	531.1 ± 583.4	Serum	ELISA	149.6 ± 53.5	8
		Control	96	59.8 ± 12.2	73/23	555.2 ± 321.3			74.8 ± 30.3	
Ito et al. (2015)	Japan	COPD	20	74.3 ± 7.5	18/2	NR	Serum	ELISA	47.1 ± 33.6	7
		Control	33	70.5 ± 7.0	22/11				54.3 ± 39.0	
Güzel et al. (2014)	Turkey	COPD	30	68.5 ± 10.5	30/0	54.9 ± 40.1	Serum	ELISA	118.6 ± 102.4	7
		Control	27	42.5 ± 12.6	18/9	13.2 ± 20.4			7.8 ± 5.2	
Gagnon et al. (2014)	Canada	COPD	37	65.0 ± 6.0	25/12	44.0 ± 21.0	Serum	ELISA	15.8 ± 14.6	8
		Control	19	62.0 ± 8.0	13/6	36.0 ± 17.0			12.1 ± 7.5	
Liu et al. (2014)	China	COPD	65	66.6 ± 8.1	61/4	41.7 ± 19.7	Serum	ELISA	45.5 ± 37.8	8
		Control	26	66.7 ± 10	22/4	22.5 ± 2.8			31.7 ± 12.0	
Ozyurek et al. (2013)	Turkey	COPD	40	62.1 ± 9.1	37/3	51.0 ± 31.0	Serum	ELISA	119.0 ± 69.0	7
		Control	20	44.9 ± 5.8	12/8	23.0 ± 13.0			86.2 ± 49.0	
Deek et al. (2013)	Egypt	COPD	64	59.1 ± 8.5	64/0	NR	Serum	ELISA	314.8 ± 103.0	8
		Control	26	58.0 ± 7.1	26/0				122.8 ± 31.9	
Ju et al. (2012)	China	COPD	111	65.5 ± 6.5	92/19	NR	Serum	ELISA	182.9 ± 46.5	7
		Control	60	64.0 ± 5.8	21/39				103.1 ± 25.0	
Ishii et al. (2012)	Japan	COPD	188	70.2 ± 7.7	174/14	73.1 ± 45.6	Serum	ELISA	74.6 ± 58.0	7
		Control	82	64.3 ± 12.0	69/13	55.5 ± 46.4			78.8 ± 74.7	
Lomas et al. (2009)	UK	COPD	1,888	63.4 ± 7.2	1,222/666	49.2 ± 27.3	Serum	ELISA	121.1 ± 14.9	7
		Control	497	54.1 ± 8.8	235/262	19.2 ± 17.1			101.3 ± 13.0	
Shakoori et al. (2009)	Pakistan	COPD	27	61.0 ± 12.2	27/0	64.4 ± 34.3	Serum	ELISA	187.6 ± 104.6	7
		Control	54	36.0 ± 11.0	54/0	16.0 ± 20.0			127.0 ± 65.0	
Mutti et al. (2006)	Italy	COPD	50	65.6 ± 2.1	36/14	28.9 ± 4.3	Serum	ELISA	126.0 ± 77.0	8
		Control	80	50.7 ± 2.0	58/22	6.6 ± 1.4			101.3 ± 68.6	

Abbreviations: N - sample size, M - male, F - female, ELISA - enzyme-linked immunosorbent assay, NR - not reported.

ignorable heterogeneity among studies was observed (I^2 = 95.9%) and random-effects model was used in this meta-analysis. To reveal possible sources of the heterogeneity, we further performed a multivariate meta-regression analysis. The results demonstrated that publication year, as well as the sample size ratio of controls and case groups as confounding factors did not substantially affect the heterogeneity (adjusted p-values were 0.602 and 0.995, respectively, for COPD).

Table 2. Characteristics of studies involving in the comparison of serum SP-D levels in AECOPD and stable COPD.

Study	Group	N	Age	Gender (M/F)	SP-D (ng/mL)
Alaabden et al. (2015)	SCOPD	28	58.8 ± 8.3	22/6	337.9 ± 86.3
	AECOPD	28	64.5 ± 8.2	23/5	508.7 ± 102.8
Ju et al. (2012)	SCOPD	71	65.2 ± 6.8	54/17	153.5 ± 45.2
	AECOPD	40	66.1 ± 5.7	38/2	235.2 ± 48.3
Shakoori et al. (2009)	SCOPD	14	62.0 ± 11.0	14/0	151.0 ± 83.0
	AECOPD	13	60.0 ± 13.0	13/0	227.0 ± 120.0

Abbreviations: N - sample size, M - male, F - female, SCOPD - stable COPD, AECOPD - acute exacerbation of COPD.

Table 3. Characteristics of studies involving in the comparison of serum SP-D levels in smokers and nonsmokers in healthy population.

Study	Group	N	Age	Gender (M/F)	SP-D (ng/mL)
Ito et al. (2015)	Smokers	15	68.8 ± 7.3	10/5	68.2 ± 49.1
	Nonsmokers	18	72.0 ± 6.6	12/6	42.7 ± 26.5
Deek et al. (2013)	Smokers	14	58.0 ± 7.1	14/0	144.4 ± 26.1
	Nonsmokers	12	58.0 ± 7.1	12/0	97.5 ± 14.2
Lomas et al. (2009)	Smokers	296	54.7 ± 8.9	161/135	114.3 ± 14.5
	Nonsmokers	201	53.2 ± 8.6	74/127	82.2 ± 10.3
Mutti et al. (2006)	Smokers	30	43.6 ± 1.8	20/10	130.0 ± 65.0
	Nonsmokers	50	54.9 ± 2.1	38/12	84.0 ± 70.0

Abbreviations: N - sample size, M - male, F - female.

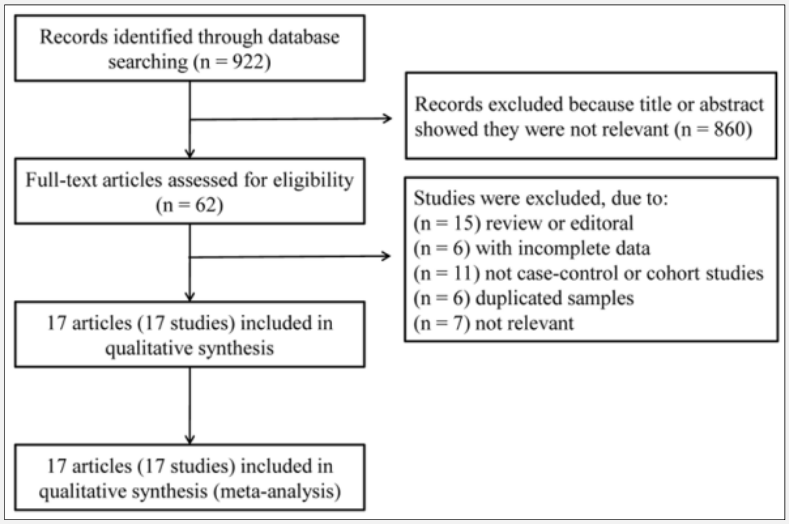

Figure 1. Flowchart shows study selection procedure.

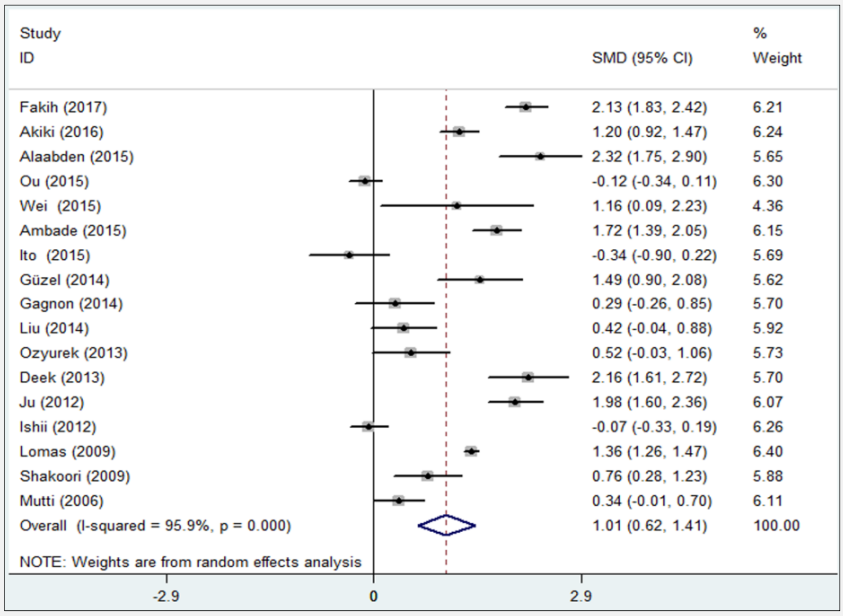

Figure 2. Forest plot for serum SP-D levels in COPD patients compared with those in controls.

SMD - standardized mean difference, CI - confidence interval.

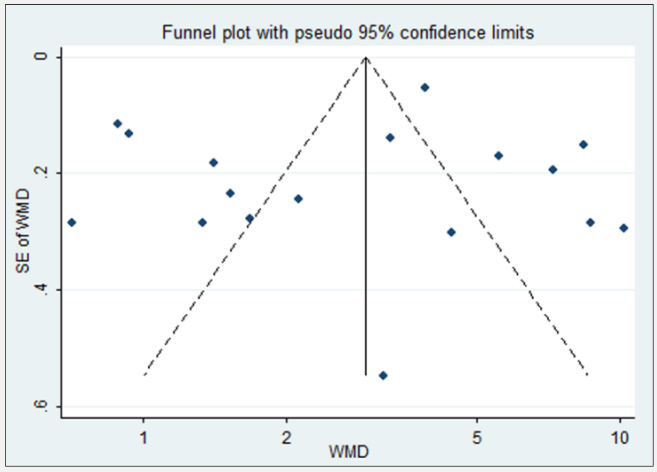

Figure 3. Funnel plot for serum SP-D levels in COPD patients compared with those in controls.

Publication bias and sensitivity analysis

The results of Begg's test (p = 0.902) and Egger's test (p = 0.628) showed no presence of publication bias. The funnel plot is presented in Figure 3. Sensitivity analysis was also performed to explore the potential influence of each individual study on the overall results by deleting one single study each time from the pooled analysis. As shown in Figure 4, no substantial change was demon-

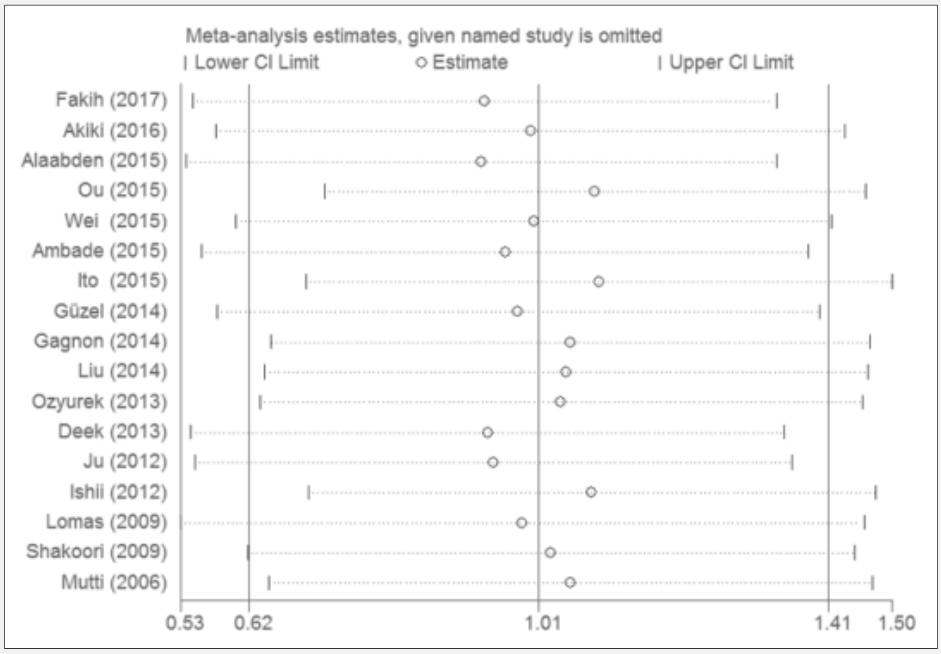

Figure 4. Sensitivity analysis for serum SP-D levels in COPD patients compared with those in controls.

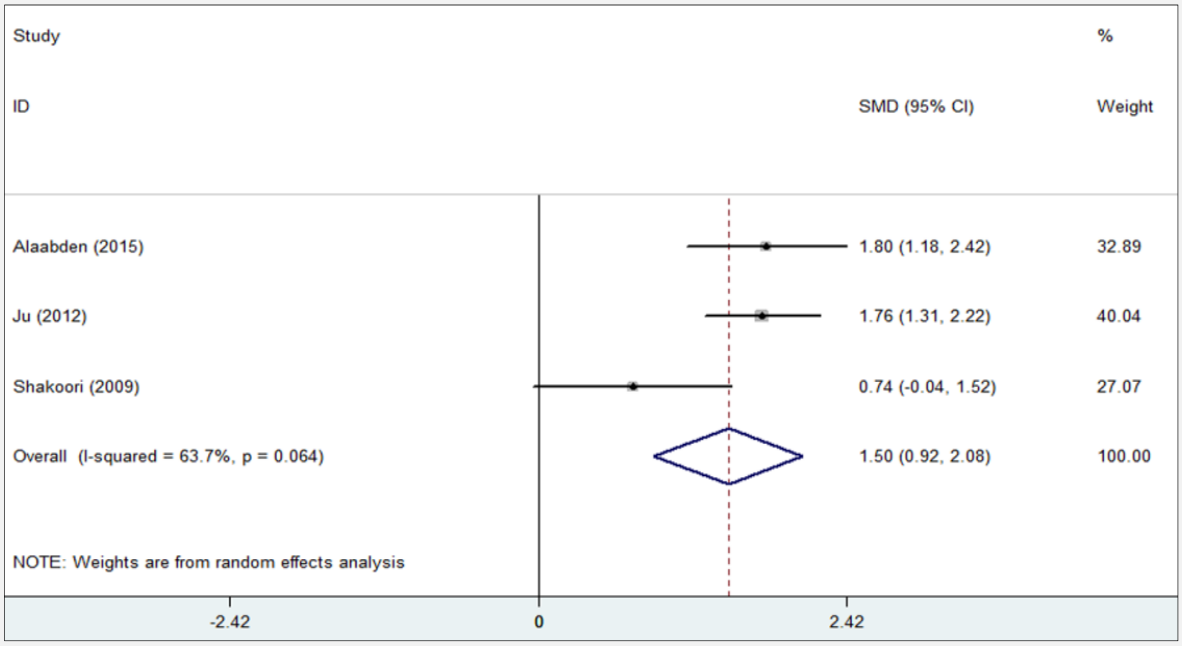

Figure 5. Forest plot for serum SP-D levels in AECOPD patients compared with those in stable COPD patients.

SMD - standardized mean difference, CI - confidence interval.

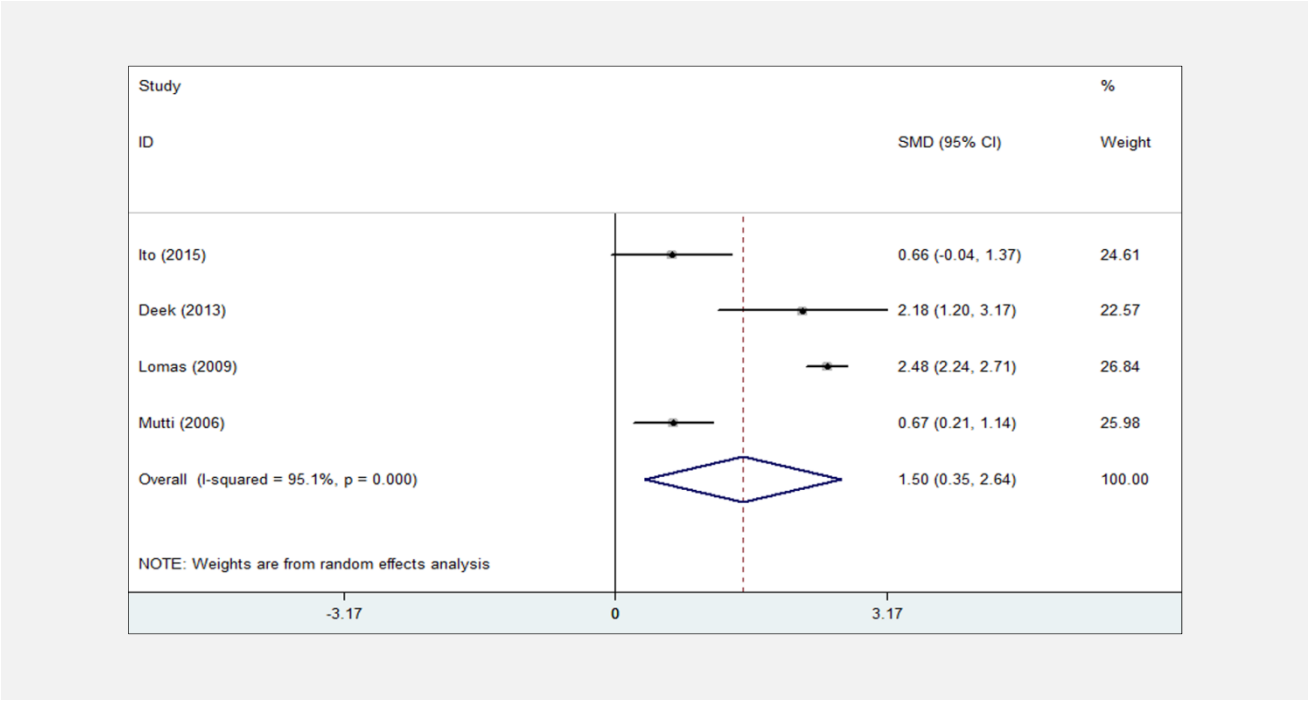

Figure 6. Forest plot for serum SP-D levels in healthy smokers compared with those in healthy nonsmokers.

SMD - standardized mean difference, CI - confidence interval.

strated in the overall studies, indicating that no individual study could affect the pooled SMD significantly.

Subgroup meta-analysis

To explore the source of heterogeneity, we further conducted a subgroup analysis. There were three studies involving in the effects of disease status on serum SP-D levels. The serum SP-D concentration in AECOPD patients and stable COPD patients is shown in Table 2. The results of the forest plot showed that serum SP-D concentration in AECOPD patients was significantly higher than that in stable COPD patients (SMD = 1.50, 95% CI = 0.92 - 2.08, $p < 0.001$), as presented in Figure 5. In addition, we investigated the effects of smoking on serum SP-D concentration in the control group. As shown in Table 3, four studies stratified for smoking status in healthy population: smokers and nonsmokers. Figure 6 found that serum SP-D concentration was higher in smokers than that in nonsmokers in healthy population (SMD = 1.50, 95% CI = 0.35 - 2.64, p = 0.025).

DISCUSSION

A number of studies have been conducted to investigate the association between serum SP-D concentration and COPD risk [19-25]. Güzel et al. indicated that serum SP-D levels in COPD patients were significantly higher than those in controls [19,21]. However, Gagnon et al. pointed out that there was no significant difference in serum SP-D concentration between COPD patients and controls [20]. Therefore, it is critical to systematically evaluate all studies and quantify the overall association between serum SP-D concentration and COPD. The main findings of this meta-analysis were as follows: (1) serum SP-D concentration in COPD patients was significantly higher than that in controls; (2) serum SP-D concentration was significantly higher in patients with AECOPD than that in patients with stable COPD; (3) serum SP-D concentration was higher in smokers than that in nonsmokers in healthy population.

SP-D plays an important role in regulating innate immunity through two ways: direct killing of specific bacteria and fungi, and binding pathogens and facilitating phagocytosis [26,27]. Studies have demonstrated that the elevation of serum SP-D levels is associated with chronic inflammatory conditions such as asthma, interstitial pulmonary fibrosis, acute respiratory distress syndrome, and COPD [8,9]. SP-D has been thought to protect the lung against oxidative and inflammatory stress in the pathogenesis of COPD as part of the host's innate immune system [12]. To some extent, these findings are consistent with the increased serum SP-D levels in COPD patients and suggest that serum SP-D is a promising biomarker for COPD.

The precise mechanism leading to higher serum SP-D levels in AECOPD compared with stable COPD is still

unclear. Studies have demonstrated that the severity of AECOPD correlates with airway inflammation, and increased intrapulmonary inflammation during AECOPD contributes to elevation of serum SP-D levels; another explanation for elevated serum SP-D levels during AECOPD is that intrapulmonary SP-D expression may increase to protect the lung against pathogens and regulate the inflammatory response in airways, where serum SP-D levels may respond to the raised lung expression [24,27]. In addition, higher serum SP-D levels were found in smokers compared with nonsmokers in healthy population. The underlying mechanism may be that smoking increases the alveolar-capillary permeability, causing SP-D to leak from lung compartments into systemic circulation [28].

A non-ignorable heterogeneity among studies should be noted in the present meta-analysis, which may be attributed to many factors: First, different disease status (exacerbation or stable) and smoking history (smokers or nonsmokers) were included in the study. Second, the participants included had different baseline characteristics, such as age, gender, body mass index in each study. Third, available data was accessed through statistics transformation but not direct provision in several studies. Based on the results of sensitivity analysis, meta-regression analysis and subgroup analysis, we speculated that the heterogeneity might be derived from different disease status and smoking history to some extent in this present meta-analysis.

Several limitations should be considered when interpreting the results. First, only published studies with sufficient data were included, thus publication bias may have occurred even though the results of Begg's test or Egger's test did not detect it. Second, due to lack of sufficient data in several primary studies, we failed to further investigate the effects of other factors (gender, age, body mass index) on serum SP-D levels, which may have affected our results. Third, heterogeneity was not resolved after sensitivity analysis and meta-regression analysis.

CONCLUSION

In conclusion, the current meta-analysis indicates that serum SP-D levels may be a promising biomarker for COPD. In particular, increased serum SP-D levels appear to be associated with acute exacerbation of COPD and smoking in healthy population.

Acknowledgment:
This work was supported by Natural Science Foundation of Gansu Province of China (No. 18JR3RA322).

Author Contributions:
Hong Wang and Yixin Wan conceived and designed the study; Huirong Huang, Fanqi Wu and Lijun Chen analyzed and interpreted the data; Degang Zhang and Tianming Zhang organized the results; Fangwei Li wrote the manuscript.

Declaration of Interest:
There is no conflict of interest.

References:

1. Stolz D, Barandun J, Borer H, et al. Diagnosis, prevention and treatment of stable COPD and acute exacerbations of COPD: The swiss recommendations 2018. Respiration 2018;96(4):382-98 (PMID: 30138943).
2. Vicedo-Cabrera AM, Roosli M, Radovanovic D, et al. Cardiorespiratory hospitalisation and mortality reductions after smoking bans in Switzerland. Swiss Med Wkly 2016;146:w14381 (PMID: 28102874).
3. Stoleski S, Minov J, Karadzinska-Bislimovska J, Mijakoski D, Tutkun L. C-reactive protein concentrations among crop and dairy farmers with stable chronic obstructive pulmonary disease. Open Access Maced J Med Sci 2017;5(6):724-9 (PMID: 29104 680).
4. Zhang J, Bai C. The significance of serum interleukin-8 in acute exacerbations of chronic obstructive pulmonary disease. Tanaffos 2018;17(1):13-21 (PMID: 30116274).
5. Brusselle G, Pavord ID, Landis S, et al. Blood eosinophil levels as a biomarker in COPD. Respir Med 2018;138:21-31 (PMID: 29 724389).
6. Arroyo R, Martin-Gonzalez A, Echaide M, et al. Supramolecular assembly of human pulmonary surfactant protein SP-D. J Mol Biol 2018;430(10):1495-509 (PMID: 29626540).
7. Hartl D, Griese M. Surfactant protein D in human lung diseases. Eur J Clin Invest 2006;36(6):423-35 (PMID: 16684127).
8. Mackay RM, Grainge CL, Lau LC, Barber C, Clark HW, Howarth PH. Airway surfactant protein D deficiency in adults with severe asthma. Chest 2016;149(5):1165-72 (PMID: 26836907).
9. Ikeda K, Shiratori M, Chiba H, et al. Serum surfactant protein D predicts the outcome of patients with idiopathic pulmonary fibrosis treated with pirfenidone. Respir Med 2017;131:184-91 (PMID: 28947028).
10. Fakih D, Akiki Z, Junker K, et al. Surfactant protein D multimerization and gene polymorphism in COPD and asthma. Respirology 2018;23(3):298-305 (PMID: 28960651).
11. Akiki Z, Fakih D, Jounblat R, et al. Surfactant protein D, a clinical biomarker for chronic obstructive pulmonary disease with excellent discriminant values. Exp Ther Med 2016;11(3):723-30 (PMID: 26997985).
12. Zien Alaabden A, Mohammad Y, Fahoum S. The role of serum surfactant protein D as a biomarker of exacerbation of chronic obstructive pulmonary disease. Qatar Med J 2015;2015(2):18 (PMID: 26942111).
13. Ou CY, Chen CZ, Hsiue TR, Lin SH, Wang JY. Genetic variants of pulmonary sp-D predict disease outcome of COPD in a Chinese population. Respirology 2015;20(2):296-303 (PMID: 25376 584).

14. Ito E, Oka R, Ishii T, et al. Fucosylated surfactant protein-D is a biomarker candidate for the development of chronic obstructive pulmonary disease. J Proteomics 2015;127(Pt B):386-94 (PMID: 26206179).

15. Wei L, Xu D, Qian Y, et al. Comprehensive analysis of gene-expression profile in chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2015;10:1103-9 (PMID: 26089660).

16. Ambade VN, Sontakke AN, Barthwal MS, Tyagi R, Basannar DR. Diagnostic utility of biomarkers in COPD. Respir Care 2015; 60(12):1729-42 (PMID: 26106205).

17. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: Checklist and explanations. Ann Intern Med 2015;162(11):777-84 (PMID: 260 30634).

18. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7(3):177-88 (PMID: 3802833).

19. Guzel A, Karadag A, Okuyucu A, Alacam H, Kucuk Y. The evaluation of serum surfactant protein D (SP-D) levels as a biomarker of lung injury in tuberculosis and different lung diseases. Clin Lab 2014;60(7):1091-8 (PMID: 25134376).

20. Liu W, Ju CR, Chen RC, Liu ZG. Role of serum and induced sputum surfactant protein D in predicting the response to treatment in chronic obstructive pulmonary disease. Exp Ther Med 2014;8(4):1313-7 (PMID: 25187846).

21. El-Deek SE, Makhlouf HA, Saleem TH, Mandour MA, Mohamed NA. Surfactant protein D, soluble intercellular adhesion molecule-1 and high-sensitivity C-reactive protein as biomarkers of chronic obstructive pulmonary disease. Med Princ Pract 2013; 22(5):469-74 (PMID: 23860258).

22. Ishii T, Hagiwara K, Kamio K, et al. Involvement of surfactant protein D in emphysema revealed by genetic association study. Eur J Hum Genet 2012;20(2):230-5 (PMID: 21934714).

23. Lomas DA, Silverman EK, Edwards LD, et al. Serum surfactant protein D is steroid sensitive and associated with exacerbations of COPD. Eur Respir J 2009;34(1):95-102 (PMID: 19164344).

24. Shakoori TA, Sin DD, Ghafoor F, Bashir S, Bokhari SN. Serum surfactant protein D during acute exacerbations of chronic obstructive pulmonary disease. Dis Markers 2009;27(6):287-94 (PMID: 20075511).

25. Mutti A, Corradi M, Goldoni M, Vettori MV, Bernard A, Apostoli P. Exhaled metallic elements and serum pneumoproteins in asymptomatic smokers and patients with COPD or asthma. Chest 2006;129(5):1288-97 (PMID: 16685021).

26. Carreto-Binaghi LE, Aliouat el M, Taylor ML. Surfactant proteins, SP-A and SP-D, in respiratory fungal infections: Their role in the inflammatory response. Respir Res 2016;17(1):66 (PMID: 27250970).

27. Moreno D, Garcia A, Lema D, De Sanctis JB. Surfactant protein D in chornic obstructive pulmonary disease (COPD). Recent Pat Endocr Metab Immune Drug Discov 2014;8(1):42-7 (PMID: 245 06680).

28. Papaioannou AI, Papiris S, Papadaki G, et al. Surfactant proteins in smoking-related lung disease. Curr Top Med Chem 2016;16 (14):1574-81 (PMID: 26420367).