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## Clinical utility of pleural fluid YKL-40 as a marker of malignant pleural effusion



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### A B S T R A C T

Pleural effusion is a common presenting feature of malignancy. Malignant pleural effusion is primarily diagnosed by pleural fluid cytology, pleural biopsy, and tumor markers. The glycoprotein YKL-40 is a new tumor marker that has shown to have a good diagnostic accuracy to detect malignant pleural effusion. However, there are only a few studies that have evaluated pleural fluid YKL-40 for detecting malignant pleural effusions. Hence, we conducted this study to evaluate the utility of pleural fluid YKL-40 to detect malignant pleural effusion. This is a cross-sectional study conducted between February 2016 and December 2017 in a tertiary care referral hospital. One hundred and forty-seven consecutive patients with pleural effusion were included in the study. These patients were divided into 3 groups, viz malignant, tuberculous, and parapneumonic pleural effusion, based on clinical features, radiological examination, and pleural fluid analysis. Pleural fluid YKL-40 levels were measured using enzyme-linked immunosorbent assay. Out of the 147 consecutive patients included in the study, 47 patients (31.97%) had malignant pleural effusion, 51 patients (34.69%) had tuberculous pleural effusion, and 49 patients (33.33%) had parapneumonic pleural effusion. The median pleural fluid YKL-40 level was higher in malignant pleural effusion (114.80 ng/mL) compared to tuberculous (93.17 ng/mL) and parapneumonic pleural effusion (89.87 ng/mL;  $P < 0.05$ ). A diagnostic cut-off for pleural fluid YKL-40 value of 99.76 ng/mL detected malignant pleural effusion with 83% sensitivity, 87% specificity, positive predictive value (PPV) of 75%, negative predictive value (NPV) of 91.58%, and diagnostic accuracy of 85.71%. The level of pleural fluid YKL-40 is significantly elevated in malignant pleural effusion. In lymphocytic pleural effusions presenting with low adenosine deaminase levels and high YKL-40 levels, a thorough diagnostic search for malignancy is warranted.

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## Introduction

Diagnosis of malignant pleural effusion is done mainly by pleural fluid cytology and pleural biopsy. Pleural fluid cytology has a sensitivity of 60% to diagnose malignant pleural effusion.<sup>1</sup> Patients with a negative pleural fluid cytology are subjected to a pleural biopsy that can detect malignancy only in 7%–13% of cytology negative malignant pleural effusion.<sup>2,3</sup> Pleural biopsy being an invasive procedure is associated with morbidity and mortality due to which efforts are being taken to develop reliable and less-invasive tools like tumor markers to detect malignant pleural effusions.

Earlier studies found that tumor markers like carbohydrate antigen 125 (CA 125), Carbohydrate antigen 15-3 (CA 15-3), carbohydrate antigen 19-9 (CA 19-9), and cytokeratin fragment 21-1 (CYFRA 21-1) had poor sensitivity and organ specificity for diagnosing malignant pleural effusion.<sup>4,5</sup> Hence, in the quest for discovering new tumor markers, the role of a new protein YKL-40 as a tumor marker was studied.

YKL 40 is a secreted biomarker released mainly by macrophages in the setting of inflammation and malignancy.<sup>6,7</sup> It is a glycoprotein, protein secreted in vitro by the human osteosarcoma cell line, and was named based on its NH<sub>2</sub>-terminal amino acids tyrosine (Y), lysine (K), and leucine (L) and its molecular weight of 40 kDa.<sup>8</sup> This glycoprotein is highly expressed in tissues undergoing rapid proliferation and differentiation.<sup>9</sup>

YKL-40 was evaluated initially as a marker of inflammation and is currently used to study exacerbation in bronchial asthma, chronic obstructive pulmonary disease (COPD) and rheumatoid arthritis.<sup>10-12</sup> As this glycoprotein was also found to be overexpressed in solid tumors like breast carcinoma, colorectal cancer, osteosarcoma, and glioblastoma multiforme, experiments were undertaken to evaluate its role as a tumor marker. An important observation was that a higher serum level of YKL-40 was associated with a shorter survival, hence making this tumor marker of prognostic value. However, this new tumor marker was lacking organ specificity.<sup>13-15</sup> This finding of elevated serum YKL-40 in solid tumors was extrapolated to malignant pleural effusion. A few studies were done to compare serum and pleural fluid YKL-40 in different types of pleural effusions and to see if this tumor marker was useful in diagnosing malignant pleural effusion. As the results obtained from these studies were contradicting, no definite conclusion could be drawn regarding the utility of this marker for the diagnosis of malignant pleural effusion.<sup>16-19</sup> So the definitive role of this protein as a tumor marker for malignant pleural effusion is still being explored. Hence, this study was planned with this background to evaluate the diagnostic accuracy of YKL-40 protein to detect malignant pleural effusions.

## Methodology

### Study design

This is cross-sectional study conducted between February 2016 and December 2017 in a tertiary care referral hospital. This study was duly approved by the Institute Ethics Committee.

One hundred and forty seven consecutive patients with diagnosis of pleural effusion made by a clinical examination and chest X-ray were included in the study. Patients with age <18 years, cases of bronchial asthma or COPD, patients on steroids (>3 months) and those with transudative pleural effusion were excluded from the study.

### *Number of groups to be studied with definition*

Patients with diagnosis of pleural effusion were divided into 3 groups based on clinical features, radiological examination, and pleural fluid analysis into malignant, tuberculous, and parapneumonic pleural effusion.

#### *Group 1*

In the present study, the malignant pleural effusion was defined by the presence of malignant cells either by pleural fluid cytology or pleural biopsy, and this was considered as the gold standard for the diagnosis of malignant pleural effusion.<sup>20</sup>

#### *Group 2*

Tuberculous effusion diagnosed by pleural fluid adenosine deaminase (ADA) above 60 IU (or) Ziehl-Neelsen positive in pleural fluid (or)  
Pleural biopsy showing caseating granuloma (or)  
Sputum Acid-Fast Bacilli positive with concurrent pleural effusion.

#### *Group 3*

Parapneumonic effusion defined as occurring with community acquired pneumonia defined according to the American Thoracic Society criteria as new onset respiratory symptoms, fever, abnormal breath sounds, a new pulmonary infiltrate on chest X-ray, and neutrophilic pleural effusion.

### *Study procedure*

Patients with pleural effusion were subjected to diagnostic thoracentesis under sterile aseptic precautions as a part of standard patient care. Pleural fluid sample was sent for estimation of protein, lactate dehydrogenase (LDH), ADA, cell count, bacterial culture, mycobacterial culture, and pleural fluid cytology, and 3 mL of pleural fluid was collected for the estimation of YKL-40 protein. The pleural fluid samples collected for estimation of YKL-40 were subjected to centrifugation within 3 hours and the supernatant was collected and stored in deep freezer (–80°C). In patients with 3 consecutive negative pleural fluid cytology, ultrasound or computed tomography-guided pleural biopsy was done as standard of care procedure.

### *Estimation of YKL-40 protein*

The samples were analyzed using enzyme-linked immunosorbent assay (ELISA) as was done in previous studies.<sup>16-19</sup> ELISA kits for YKL-40 were obtained from BT Lab, Shanghai Korain Co. Ltd. Pleural fluid samples and the reagents were warmed naturally to room temperature for 30 minutes prior to performing the test. Pleural fluid sample, anti-YKL-40 antibody, and streptavidin-HRP is added to the wells and incubated at 37°C for 60 minutes. The ELISA plate is washed with buffer solution 5 times. Solutions A and B are added to the wells and incubated at 37°C for 10 minutes. The wells will turn blue and the intensity of the color developed is proportional to the amount of YKL-40 in the pleural fluid. Stop solution is added to terminate the reaction and the color of the wells becomes yellow. The optical density of each well was determined at 450nm with 30 minutes using an automated analyzer. Based on the optical density of the well, the pleural fluid YKL-40 was quantitated.

### *Statistical analysis*

Statistical analysis was done using IBM PASW statistics (SPSS) version 19.0. Categorical data like gender, smoking, and alcohol consumption were expressed as frequency and percentages.

**Table 1**  
Baseline characteristics of study groups.

| S. no. | Baseline parameters                             | Malignant pleural effusion(n=47) | Tuberculous pleural effusion(n= 51) | Parapneumonic pleural effusion (n=49) |
|--------|---|----------------------------------|-------------------------------------|---------------------------------------|
| 1      | Age in years<br>Mean $\pm$ SD                   | 60 $\pm$ 12                      | 41 $\pm$ 13                         | 44 $\pm$ 14                           |
| 2      | Male (%)  | 24 (51.06)                       | 43 (84.30)                          | 37 (75.50)                            |
| 3      | Female (%)                                      | 23 (48.93)                       | 8 (15.70)                           | 12 (24.50)                            |
| 4      | Smoker (%)                                      | 14 (29.78)                       | 21 (41.20)                          | 18 (36.70)                            |
| 5      | Alcohol consumption (%)                         | 10 (21.27)                       | 29 (56.90)                          | 22 (44.90)                            |
| 6      | Serum protein (g/dL)<br>Mean $\pm$ SD           | 6.33 $\pm$ 0.89                  | 6.38 $\pm$ 0.82                     | 6.21 $\pm$ 1.17                       |
| 7      | Pleural fluid protein (g/dL)<br>Mean $\pm$ SD   | 4.47 $\pm$ 1.10                  | 4.11 $\pm$ 1.20                     | 4.26 $\pm$ 1.36                       |
| 8      | Pleural fluid LDH (IU/L)<br>Median with IQR     | 1286 (108-11146)                 | 1337 (19-10429)                     | 3200 (388-17520)                      |
| 9      | Pleural fluid ADA (IU/L)<br>Median with IQR     | 15 (4-103)                       | 70 (13-215)                         | 20 (2-329)                            |
| 10     | Pleural fluid YKL-40 (ng/mL)<br>Median with IQR | 114.80 (75.37-152)               | 93.17 (78-107.60)                   | 89.87 (78.65-106.15)                  |

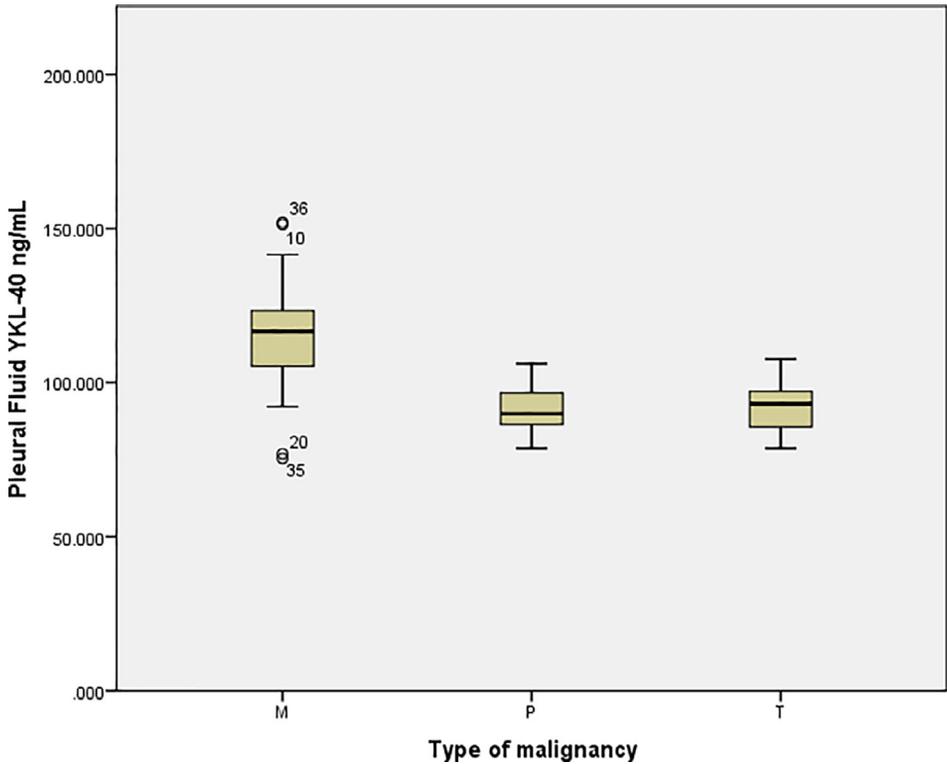
ADA, adenosine deaminase; IQR, interquartile range; LDH, lactate dehydrogenase; SD, standard deviation.

The continuous data was expressed as mean with standard deviation (Normal data) or median with interquartile range (Skewed data). The comparison of levels of pleural fluid YKL-40 was done by Kruskal-Wallis test. The comparison pleural fluid YKL-40 between pleural fluid cytology positive and negative malignant pleural effusion was done using Mann-Whitney *U* test. The comparison of level of pleural fluid YKL-40 according to histopathologic type of malignancy was done using Kruskal-Wallis test. Receiver-operating characteristic (ROC) curve was used to identify the optimum cut-off values of YKL-40 for differentiating malignant and nonmalignant pleural effusions using Youden index. All statistical analysis was carried out at 5% level of significance and  $P < 0.05$  was considered as significant.

## Results

A total of 147 patients were included in the study, out of which 47 (31.97%) were malignant pleural effusion, 51 (34.69%) were tuberculous pleural effusion, and 49 (33.33%) were parapneumonic pleural effusion. Out of 147 patients, 70.75% were males and 29.25% were females. The mean age of patients in the malignant, tuberculous, and parapneumonic pleural effusion groups were 60  $\pm$  13 years, 41  $\pm$  13 years, and 44  $\pm$  14 years, respectively. The median pleural fluid LDH was 1286 IU/L, 1337 IU/L, and 3200 IU/L in the malignant, tuberculous, and parapneumonic pleural effusion groups, respectively. The median pleural fluid ADA was 15 IU/L, 70 IU/L, and 20 IU/L in the malignant, tuberculous, and parapneumonic pleural effusion groups, respectively (Table 1).

Among the 47 patients with malignant pleural effusion, 29 patients had pleural fluid malignant cytology positive (61.70%) and 18 patients had pleural biopsy showing malignancy (38.30%). The median pleural fluid YKL-40 level in malignant, tubercular, and parapneumonic groups were 114.80 ng/mL, 93.17 ng/mL, and 89.87 ng/mL, respectively. A box and whisker plot was used to



**Fig. 1.** Box and whisker plot depicting pleural fluid YKL-40 in malignant, tubercular, and parapneumonic pleural effusion. M, malignant pleural effusion; P, parapneumonic pleural effusion; T, tuberculous pleural effusion.

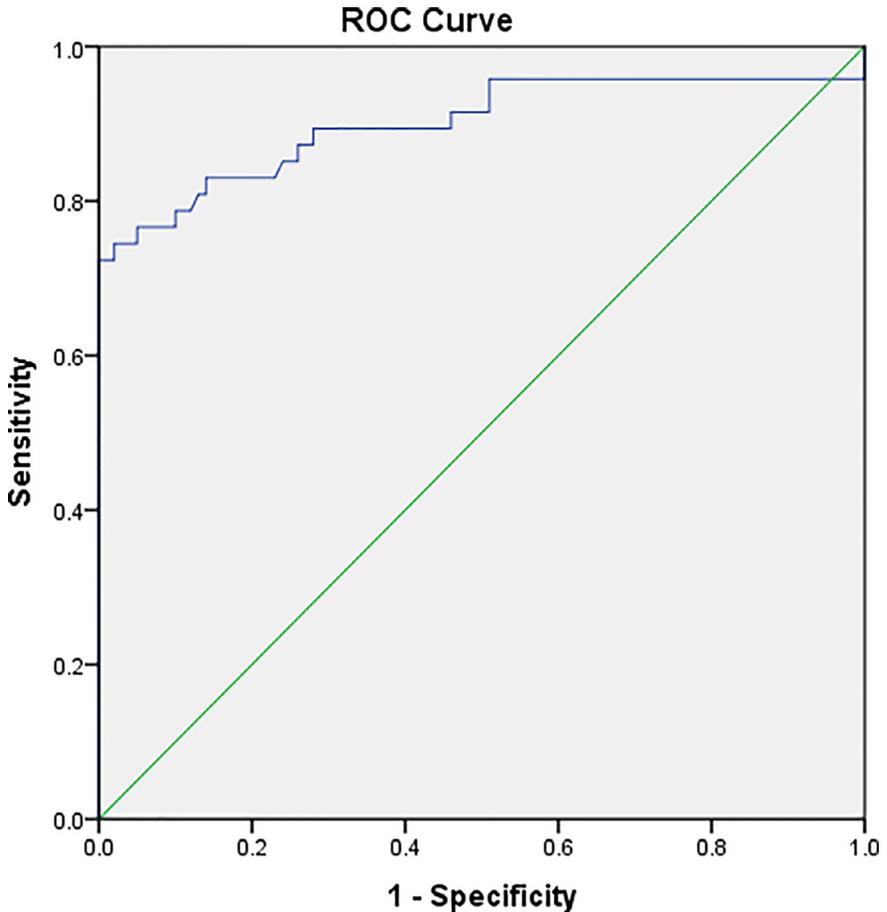
compare the pleural fluid YKL-40 among the 3 groups (Fig 1). The area under the curve (AUC) for malignant pleural effusion was 0.90 with 95% confidence interval 0.833–0.968 (Fig 2). The diagnostic cut-off value for pleural fluid YKL-40 of 99.76 ng/mL was considered positive for malignant pleural effusions. Out of 147 patients, 52 patients (35.37%) had positive pleural fluid YKL-40 protein and 95 patients (64.63%) had negative pleural fluid YKL-40 protein. Positive pleural fluid YKL-40 protein detected malignant pleural effusion with a sensitivity of 83%, specificity of 87%, PPV of 75%, NPV of 91.58%, and diagnostic accuracy of 85.71% compared to gold standard.

In patients with malignant pleural effusion, the pleural YKL-40 was positive in 13 of 13 patients (100%) of metastatic adenocarcinoma with unknown primary, 9 of 9 patients (100%) of breast cancer, and 13 of 13 patients (100%) of adenocarcinoma lung. Though the number of patients positive for pleural fluid YKL-40 was high in patients with metastatic adenocarcinoma with unknown primary, breast, and lung carcinoma, this finding was not significant due to the small number of patients in each subgroup (Table 2).

**Discussion**

In the present study, we found that positive pleural fluid YKL-40 protein had a good sensitivity and specificity to diagnose malignant pleural effusion. The pleural fluid YKL-40 did not vary significantly among the histopathologic subgroups. The median pleural fluid LDH and ADA levels were lower in the malignant pleural effusion group.

Malignant pleural effusion poses a diagnostic challenge because the conventional tumor markers like CEA, CA-125, CA 19-9, CA 15-3, and CYFRA 21-1 are not reliable for diagnosing



**Fig. 2.** Receiver-operating characteristics (ROC) curve depicting sensitivity and specificity of pleural fluid YKL-40 in malignant pleural effusion. AUC 0.90 (95% CI 0.833-0.968).

**Table 2**

Positivity rate by pleural fluid YKL-40 in different subgroups of malignant pleural effusion.

| S. no | Type of malignancy                             | Frequency | Positive pleural fluid YKL-40 |
|-------|--|-----------|-------------------------------|
| 1     | Metastatic adenocarcinoma with unknown primary | 13        | 13                            |
| 2     | Adenocarcinoma lung                            | 13        | 13                            |
| 3     | Adenocarcinoma breast                          | 9         | 9                             |
| 4     | Adenocarcinoma ovary                           | 6         | 4                             |
| 5     | Small cell carcinoma of lung                   | 4         | 0                             |
| 6     | Squamous cell carcinoma of lung                | 1         | 0                             |
| 7     | Renal angiosarcoma                             | 1         | 0                             |
|       | Total  | 47        |                               |

malignant pleural effusion due to the poor sensitivity and specificity of these markers.<sup>4,5</sup> In a pursuit to discover an ideal tumor marker for diagnosing malignant pleural effusions, chitinase-like protein YKL-40 was studied. This protein has been suggested to play a role in cell proliferation and tumor angiogenesis, and protects cells from apoptosis.<sup>21</sup> Though YKL-40 is largely studied as a tumor marker with prognostic significance in numerous solid tumors, it is also be-

ing studied in the serum of patients with nonmalignant conditions like bronchial asthma, COPD, and rheumatoid arthritis for detecting exacerbation.<sup>13–15</sup> Hence, in the present study, patients with bronchial asthma and COPD were excluded to reduce the confounding effect of these inflammatory conditions on pleural fluid YKL-40.

The study by Attia et al evaluated pleural fluid YKL-40 in 88 patients with pleural effusion, out of which 34 were malignant pleural effusions. They reported a cut-off value of 256ng/mL was shown to diagnose malignant pleural effusion with a sensitivity of 85.3% and specificity of 90.7%.<sup>16</sup> In the present study, pleural YKL-40 cut-off value of 99.76 ng/mL had a sensitivity of 83% and specificity of 87%, which is as high as the previous study. Two studies from Greece and Turkey found that the mean levels of pleural fluid YKL-40 showed a higher trend in malignant pleural effusion compared to tubercular and parapneumonic pleural effusion but this observation was not statistically significant due to a small sample size.<sup>17,18</sup> Another study had reported that pleural fluid YKL-40 was significantly elevated in tuberculous pleural effusion fluid compared to malignant pleural effusion.<sup>19</sup> The reason for this finding was thought to be due to elevated interferon gamma (Th1 cytokine), which is expressed in tuberculous pleural effusion which was found to be a potent inducer of YKL-40 mRNA.<sup>22,23</sup> Malignant pleural effusion displays both Th1 and Th2 immune reaction with the former being predominant due to production of soluble factors which attenuate Th1 response.<sup>24</sup> But specificity protein 1 (Sp1), specificity protein 3 (Sp3), upstream stimulatory factor 1 (USF1), runt-related transcription factor 1 (RUNX1), and CCAAT/enhancer-binding protein (C/EBP) are transcription factors involved in cellular proliferation and malignant transformation. These soluble factors enhance the expression of YKL-40 mRNA.<sup>25</sup> Hence, it can be deduced that YKL-40 can be induced by factors other than interferon gamma. There are a few recent studies that have proved that serum YKL-40 is a useful prognostic marker to assess treatment response and survival in malignancy, thus indicating the role of carcinogenic transcription factors in the regulation of YKL-40 expression.<sup>26–28</sup> These studies found that there was a significant reduction in serum YKL-40 following chemotherapy and had reported that higher pretreatment level of serum YKL-40 was associated with a reduced survival. However, in the present study, we had not evaluated the prognostic value of pleural fluid or serum YKL-40 because malignant pleural effusion represents metastatic malignancy with a poor survival. Hence, pleural fluid or serum YKL-40 may not provide additional information on the survival of patients with malignant pleural effusion.

In the present study, we had analyzed the relationship of pleural fluid YKL-40 and the various histologic types of malignancy like the previous studies.<sup>16,17</sup> In one of the study, it was observed that pleural fluid YKL-40 was elevated in pleural effusion due to metastatic malignancy of non-pulmonary origin, which is same as the present study where pleural YKL-40 was found to be elevated in metastatic adenocarcinoma of unknown origin, breast and lung cancer. However, another study from Egypt had not found significant difference in pleural fluid YKL-40 among the histologic subtypes of malignant pleural effusion.<sup>17</sup>

The clinical implication of the present study will be important in developing countries where tuberculosis is still prevalent and the incidence of malignancy is also steadily increasing over the past few decades due to the increasing aging population and environmental exposure. Lymphocytic pleural effusion has many causes with tuberculosis and malignancy being the most important differential diagnoses in developing countries. On one hand, tuberculous pleural effusion can be diagnosed by assessing ADA, which is a very reliable diagnostic marker, but no such marker exists for malignant pleural effusion as of now. Perhaps a positive pleural fluid YKL-40 can aid in differentiating infection and malignancy in countries with high prevalence of tuberculosis. YKL-40 can be used as a diagnostic marker for malignancy in patients presenting with a lymphocytic pleural effusion when tests for tuberculosis are negative.

Though the present study showed that pleural fluid YKL-40 levels were higher in malignant pleural effusion, the cut-off obtained was lower than that reported in previous studies. The reason for this discrepancy could be attributed to small sample size used in the previous studies.<sup>16,17</sup>

Hence, we conclude that pleural fluid YKL-40 is a reliable diagnostic marker for detecting malignant pleural effusion. However, further studies with a larger sample size are required to establish the relationship between pleural fluid YKL-40 and histologic subtypes of malignancy.

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## References

- Garcia LW, Ducatman BS, Wang HH. The value of multiple fluid specimens in the cytological diagnosis of malignancy. *Mod Pathol*. 1994;7:665–668.
- Prakash UB, Reiman HM. Comparison of needle biopsy with cytologic analysis for the evaluation of pleural effusion: analysis of 414 cases. *Mayo Clin Proc*. 1985;60:158–164.
- Nance KV, Shermer RW, Askin FB. Diagnostic efficacy of pleural biopsy as compared with that of pleural fluid examination. *Mod Pathol*. 1991;4:320–324.
- Hackbarth JS, Murata K, Reilly WM, Algeciras-Schimmich A. Performance of CEA and CA19-9 in identifying pleural effusions caused by specific malignancies. *Clin Biochem*. 2010;43:1051–1055.
- Porcel JM, Vives M, Esquerda A, Salud A, Pérez B, Rodríguez-Panadero F. Use of a panel of tumor markers (carcinoembryonic antigen, cancer antigen 125, carbohydrate antigen 15-3, and cytokeratin 19 fragments) in pleural fluid for the differential diagnosis of benign and malignant effusions. *Chest*. 2004;126:1757–1763.
- Chupp GL, Lee CG, Jarjour N, et al. A chitinase-like protein in the lung and circulation of patients with severe asthma. *N Engl J Med*. 2007;357:2016–2027.
- Létuvé S, Kozhich A, Arouche N, et al. YKL-40 is elevated in patients with chronic obstructive pulmonary disease and activates alveolar macrophages. *J Immunol*. 2008;181:5167–5173.
- Johansen JS, Williamson MK, Rice JS, Price PA. Identification of proteins secreted by human osteoblastic cells in culture. *J Bone Miner Res*. 1992;7:501–512.
- Johansen JS, Høyer PE, Larsen LA, Price PA, Møllgård K. YKL-40 protein expression in the early developing human musculoskeletal system. *J Histochem Cytochem*. 2007;55:1213–1228.
- Holmgaard DB, Mygind LH, Titlestad IL, et al. Plasma YKL-40 and all-cause mortality in patients with chronic obstructive pulmonary disease. *BMC Pulm Med*. 2013;13:77.
- Väänänen T, Vuolteenaho K, Kautiainen H, et al. Glycoprotein YKL-40: a potential biomarker of disease activity in rheumatoid arthritis during intensive treatment with csDMARDs and infliximab. Evidence from the randomised controlled NEO-RACo trial. *PLoS One*. 2017;12.
- Gon Y, Maruoka S, Ito R, et al. Utility of serum YKL-40 levels for identification of patients with asthma and COPD. *Allergol Int*. 2017;66:624–626.
- Johansen JS, Christensen IJ, Riisbro R, et al. High serum YKL-40 levels in patients with primary breast cancer is related to short recurrence free survival. *Breast Cancer Res Treat*. 2003;80:15–21.
- Qin G, Li X, Chen Z, et al. Prognostic value of YKL-40 in patients with glioblastoma: a systematic review and meta-analysis. *Mol Neurobiol*. 2017;54:3264–3270.
- Cintin C, Johansen JS, Christensen IJ, Price PA, Sørensen S, Nielsen HJ. High serum YKL-40 level after surgery for colorectal carcinoma is related to short survival. *Cancer*. 2002;95:267–274.
- Attia A, Rasmy A, Amin A, Alanazi M. Evaluation of pleural fluid YKL-40 as a marker of malignant pleural effusion. *Egypt J Chest Dis Tuberc*. 2015;64:489–495.
- Adamidi T, Soultziz N, Neofytou E, et al. Expression of YKL-40 and MIP-1a proteins in exudates and transudates: biomarkers for differential diagnosis of pleural effusions? A pilot study. *BMC Pulm Med*. 2015;15:150.
- Kayhan S, Gumus A, Cinarka H, et al. The clinical utility of pleural YKL-40 levels in diagnosing pleural effusions. *J Thorac Dis*. 2013;5:634–640.
- Kim H-R, Jun C-D, Lee K-S, et al. Levels of YKL-40 in pleural effusions and blood from patients with pulmonary or pleural disease. *Cytokine*. 2012;58:336–343.
- Light R. Pleural effusions related to metastatic malignancies. In: *Pleural Diseases*. 6th ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins Health; 2013:159–162.
- Kzhyshkowska J, Gratchev A, Goerd S. Human chitinases and chitinase-like proteins as indicators for inflammation and cancer. *Biomark Insights*. 2007;2:128–146.
- Barnes PF, Fong SJ, Brennan PJ, Twomey PE, Mazumder A, Modlin RL. Local production of tumor necrosis factor and IFN-gamma in tuberculous pleuritis. *J Immunol*. 1990;145:149–154.
- Kzhyshkowska J, Mamidi S, Gratchev A, et al. Novel stabilin-1 interacting chitinase-like protein (SI-CLP) is upregulated in alternatively activated macrophages and secreted via lysosomal pathway. *Blood*. 2006;107:3221–3228.
- Oshikawa K, Yanagisawa K, Ohno S, Tominaga S, Sugiyama Y. Expression of ST2 in helper T lymphocytes of malignant pleural effusions. *Am J Respir Crit Care Med*. 2002;165:1005–1009.
- Rehli M, Niller H-H, Ammon C, et al. Transcriptional regulation of CHI3L1, a marker gene for late stages of macrophage differentiation. *J Biol Chem*. 2003;278:44058–44067.
- Batista KMP, de Eulate-Beramendi SA, de Piña KYÁR, et al. Mesenchymal/proangiogenic factor YKL-40 related to glioblastomas and its relationship with the subventricular zone. *Folia Neuropathol*. 2017;55:14–22.

27. Wan G, Xiang L, Sun X, et al. Elevated YKL-40 expression is associated with a poor prognosis in breast cancer patients. *Oncotarget*. 2017;8:5382–5391.
28. Darr C, Krafft U, Hadaschik B, et al. The role of YKL-40 in predicting resistance to docetaxel chemotherapy in prostate cancer. *Urol Int*. 2018;101:65–73.