**Original Article**

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TANAFFOS

**Comparative Study of Vascular Endothelial Growth Factor in Exudative and Transudative Pleural Effusion**

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**Background:** Increased vascular permeability is one of the main mechanisms in the production of pleural effusion (PE) and vascular endothelial growth factor (VEGF) has a significant role in its pathogenesis. This study aimed to compare pleural levels of VEGF in transudative and exudative PEs besides the other pleural markers.

**Materials and Methods:** In this prospective cross-sectional study, 80 patients with PE were divided into 4 groups as transudative (N=15), parapneumonic (N=15), tuberculosis (N=25), and malignant (N=25) PE. Biochemical tests measured the pleural protein, LDH, cholesterol, glucose, polymorphonuclear cell (PMN), and lymphocyte. ELISA measured the pleural VEGF level. **Results:** Out of 80 patients, 51 were male, and the total mean age was 55.34±18.53. There were significant differences in pleural VEGF between exudative and transudative effusion (P<0.001) and between malignant and benign effusion (P=0.014). The highest mean difference in pleural VEGF levels was seen in the comparison of transudative and malignant groups (Mean difference=-136.56; P<0.002). The VEGF level in 3 groups was not significantly different; transudative vs tuberculous, parapneumonic vs tuberculous, and parapneumonic vs malignant. Furthermore, VEGF higher than 73.09 pg/ml had a 64% sensitivity and 82% specificity for the diagnosis of malignancy. Among pleural markers (VEGF, protein, LDH, and glucose), VEGF had the highest area under curve (AUC=0.734). Moreover, pleural protein, LDH, and glucose levels significantly correlated with pleural VEGF; however, pleural cholesterol, PMN, and lymphocyte were not correlated.

**Conclusion:** VEGF is assumed as an important factor in the pathogenesis of exudative PE, especially malignant effusion. It can distinguish between

lymphocytic exudative PEs.

*Email address: javidaz@mums.ac.ir* **Key words:** Pleural Effusion, Exudate, Transudate, Vascular Endothelial Growth Factor (VEGF)

INTRODUCTION affected by PE (3). PE results from an impaired balance Pleural effusion (PE) is a common medical between pleural fluid production and absorption; arising

complication and a significant provenance of morbidity (1), and is described as excessive fluid retention in the pleural

cavity (the mean normal amount of pleural fluid is 8.4±4.3

from increased vascular permeability, resulting in plasma leakage, and lack of drainage of the pleural space due to

obstruction of vessels and lymphatics of the lung and

ml) (2). It’s estimated more than 400 people per 100,000 are pleura (4). About 30-40% of PE is idiopathic or

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indeterminate, but in 60-70% of cases, PE can be caused by pathological, and clinical findings. Biochemical analysis of more than *50* diseases, including lung disease, systemic the liquid acquired by a thoracentesis (including

disease, organ dysfunction, drug‑induced PE, and tumor differential leukocyte counts, glucose, total proteins,

metastasis (5). PEs are classically categorized into "transudates" and "exudates" based on the mechanism of fluid formation. Transudative effusions (TEs) result from an imbalance in oncotic and hydrostatic pressure in pleural capillaries (e.g. Hypoproteinemia), increased negative intrathoracic pleural pressure (e.g. Atelectasis), or the progress of ascitic fluid from the peritoneal cavity to the pleural cavity, through defects in the diaphragm or lymph

vessels (e.g. Hepatic hydrothorax) (2-5). Systemic diseases

albumin, lactate dehydrogenase (LDH), cholesterol, pH,

amylase, adenosine deaminase, and tumor markers for

malignancy) is mostly the first procedure to separate TEs

from EEs (2). Cytological examination, thoracoscopic and

different radiological procedures are other methods (with

its own benefits and concerns) used to differentiate TEs

from EEs (11-13). The criteria most frequently used to

distinguish transudates from exudates is related to the

such as heart failure, renal failure, and liver cirrhosis can measurement of LDH and protein in both pleural fluid

cause transudative PEs as well (6). In contrast, exudative

effusions (EEs) are the result of inflammation of the pleura,

and serum, namely Light's criteria (7).

Studies indicated that VEGF level is consistently higher

increased capillary permeability, decreased lymphatic in exudative PEs than in transudative PEs (14). It is

drainage, or other local conditions of the pleural surface, like tuberculosis, pneumonia, pancreatitis, malignancy, pulmonary infarction, collagen diseases, or systemic lupus

erythematosus (7).

reported that pleural fluid VEGF levels in patients with PE due to malignancies are higher than those due to benign diseases (15, 16). However, studies assessing various types

of PE and comparing VEGF with other pleural markers are

Vascular endothelial growth factor (VEGF) is a required.

pluripotent, cell-specific, and multi-functional cytokine

that plays an important role in angiogenesis and vascular

permeability. VEGF is 10,000 times more effective than

histamine as a permeability-enhancer. VEGF causes

proliferation, migration, and differentiation of endothelial

cells, as well as the formation of malignant pleural and

peritoneal fluid. Increased VEGF level is also seen in

chronic respiratory diseases such as asthma and cystic

fibrosis (8).

The initial step in the management of PE is recognizing

the origin of pleural fluid, which is necessary to ensure

optimum treatment by determining the pathophysiological

Overall, clinicians need more accurate and sensitive tests to diagnose the underlying cause of PE among suspected patients. Regarding the weakness and limitations of current methods and the importance of differentially diagnosing the type of PEs, we designed this study aiming to compare the pleural VEGF levels in all types of PEs in an effort to improve the accuracy of pleural fluid categorization.

MATERIALS AND METHODS

In this prospective cross-sectional study, we studied inpatients and outpatients admitted to Ghaem Hospital

(Mashhad, Iran). We included those with PE until the

process and clinical features (5,9). As a result, required sample for each group was completed. The

misclassification of transudates as exudates can lead to

inappropriate patient handling or possibly unnecessary

and invasive diagnostic investigations that increase health

sample size was considered according to recent studies. We excluded patients with coagulation disorder (INR more

than 2 and platelets less than 100,000 per microliter)

care costs and morbidity (10). The second step of PE and/or patients with malignancy undergoing management is analyzing the fluid using biochemical, chemotherapy with anti-VEGF drugs.

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Our study was approved by the Mashhad University of employed for comparison of pleural VEGF levels of four

Medical Science Ethics Committee. Demographic groups. The level of significance was set at *P=0.05*. Data information, medical history, and medication history were were analyzed using SPSS, version *15*. Moreover, the ROC obtained. Before thoracentesis, all cases signed the (Receiver Operating Characteristic) curve was used to

informed consent. Pleural fluid was tapped and prepared

for biochemical markers analysis. Also, 5 ml of the samples

were heparinized, centrifuged, and frozen at -20 ° C for

subsequent VEGF testing. Biochemical tests measured the

serum and pleural protein (g/dl), LDH (U/l), cholesterol

(mg/dl), glucose (mg/dl), polymorphonuclear cell (PMN),

and lymphocytes.

assess the sensitivity and specificity of VEGF, protein,

LDH, and glucose in the diagnosis of malignancy.

RESULTS

In this survey, 80 patients with the diagnosis of PE

were included: 15 patients with transudative PE, 15

patients with parapneumonic PE, and 50 patients with

We categorized PEs as exudative (65 cases) and lymphocytic exudative PE including tuberculosis (TB)

transudative (15 cases) according to Light’s criteria (7). We

separated parapneumonic (15 cases) pleural effusion,

related to pneumonia, according to biochemical tests,

clinical signs, and predominance of neutrophils. A

malignant (25 cases) pleural effusion was diagnosed if the

pleural biopsy or pleural fluid cytology found malignant

cells. A tuberculous (25 cases) pleural effusion was

described as one when granuloma was found on the

pleural biopsy specimen.

**Laboratory analysis**

The level of pleural VEGF (pg/ml) was measured using

the enzyme-linked immunosorbent assay (ELISA) (AviBion

Human VEGF ELISA Kit, Finland). The assays were done

according to the manufacturer’s instructions at Bu Ali

Research Institute. The detection limit was between 0.148

(n=25), and malignancy (n=25). Fifty-one of these

participants were male (63.75%) and 29 were female

(36.25%) with a mean age of 55.34 ± 18.53 years (range, 21-

86 years). It is described in Table 1.

Pleural VEGF level was not correlated with age,

gender, and positive cytology rate (P=0.402, P=0.109, and

P=0.146, respectively). Pleural VEGF levels in patients with

exudative effusions were significantly higher than

transudative (P<0.001), and also in effusions related to

malignancies than benign groups (P=0.014). The

comparison of the studied PE groups based on VEGF is

presented in Table 2. Pleural fluid markers and VEGF

levels differed significantly among studied groups with

P<0.001, as these levels based on the types of PE, are

and 12 (pg/ml). shown in Table 3. Moreover, pleural VEGF was **Statistical analysis** significantly correlated with pleural protein, LDH, and Continuous data are reported as mean±standard glucose levels, while there was no significant correlation

deviation (SD). We used Spearman/Pearson’s correlation

coefficients to calculate the correlation of VEGF with other

with pleural cholesterol, PMN, and lymphocytes (Table 4).

In the calculation of sensitivity and specificity of pleural

variables (Pleural protein, Pleural LDH, Pleural markers, VEGF≥7309 had a sensitivity of 64% and a

cholesterol, Pleural glucose, Pleural PMN, Pleural lymph).

Chi-square, independent t-test, ANOVA, and Kruskal–

Wallis tests were used as appropriate (each test mentioned

below the tables). POST-HOC analysis of ANOVA test was

specificity of 82% for the diagnosis of malignancy (Table 5,

Figure 1). Also, the area under the curve (AUC) was higher

for VEGF than protein, LDH, and glucose levels (AUC =

0.734, 95% CI [0.617-0.851]) (Table 5).

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**Table 1.** Age and gender distribution of patients according to the type of pleural effusion

**Gender**

**Male** **Female**

**Age**

**Mean ± SD\***

**Transudate Parapneumonic Tuberculosis**

**Malignancy**

**No.** **Percent (%)** 8 53.3

13 86.7 15 60

15 60

**No.** **Percent (%)** 7 46.7

2 13.3 10 40

10 40

65.27 ± 12.30 52.40 ± 21.94 44.64 ± 18.37

61.84 ± 13.90

**p-value in result of test** 0.220C 0.001A

\*SD: Standard deviation C=Based on Chi-squared test A=Based on Anova test

**Table 2.** Comparison of studied groups according to VEGF

**Comparison of groups in terms of VEGF** Transudate and parapneumonic group Transudate and tuberculosis group Transudate and malignancy group Parapneumonic and tuberculosis group Parapneumonic and malignancy group Tuberculosis and malignancy group

\*Based on POST-HOC analysis of ANOVA test

**Mean difference (pg/ml)** -121.1013 -29.8938 -136.5618 91.2074 -15.4605

-106.6680

**p-value\*** 0.018 0.860 0.002 0.063 0.973

0.005

**Table 3.** Evaluation of pleural fluid markers and VEGF in the studied patients based on the type of pleural effusion

**Pleural fluid markers**

**VEGF (pg/ml) Protein (g/d1) LDH\*\* (u/l) Cholesterol (mg/dl) Glucose (mg/dl) PMN\*\*\* (%)**

**Lymphocyte (%)**

**Study groups\*** Transudate 7.1773± 7.6582 1.38 ± 0.37 120 ± 54.70 39.40 ± 27.99 157.93 ± 64.04 18.66 ± 11.87

81.33 ± 11.87

Parapneumonic 128.2786±136.8250 4.26 ± 0.85 2174.26 ± 4751.34 64.86 ± 18.63

66 ± 34.66 79.66 ± 12.8

20.33 ± 12.88

Tuberculosis 37.0712±33.4691 4.5 ± 0.74

4.5 ± 0.74 422.44 ±172.12 83.08 ± 13.71 84.12 ±18.62

22.60 ± 18.77

Malignancy 143.7392±162.5413 4.10 ± 0.61

641.8 ± 924.34 99.28 ± 13. 74 86.64 ± 22.74 17.0 ± 11.27

83.0 ± 11.27

**p-value**

0.000A 0.000A 0.000K 0.000A 0.000A 0.000A

0.000A

\*Data based on mean ± Standard deviation \*\* Lactate dehydrogenase

\*\*\* Polymorphonuclear

K: Based on Kruskal–wallis A= Based on ANOVA test

**Table 4.** Comparison of the relationship between pleural fluid markers and VEGF

**Correlation of the studied variables with the level of pleural fluid VEGF** **r\*** Pleural protein 0.248 Pleural LDH 0.461 Pleural cholesterol 0.151 Pleural glucose -0.251 Pleural PMN (%) 0.147 Pleural lymph (%) -0.147

\*r: Correlation coefficient SP: Based on Spearman

P= Based on Pearson test

**p-value** 0.027P 0.000SP 0.180P 0.025P 0.193P

0.193P

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**Table 5.** Evaluation of sensitivity and specificity of VEGF and other pleural markers in the diagnosis of malignancy

**VEGF (pg/ml) Protein (g/dl) LDH (u/l)**

**Glucose (mg/dl)**

**Area under the curve** 0.734

0.532 0.698

0.457

**Confidence Interval 95%** 0.617-0.851

0.407-0.657 0.585-0.811

0.332-0.582

**Sensitivity** 0.64

0.96 0.96

0.80

**Specificity** 0.82

0.31 0.42

0.40

**Cut off point** 7309≤

3.2≤ 330≤

80.5≤

DISCUSSION

Undiagnosed PE is a major clinical concern. The

available methods can be inefficient in up to 40% of cases

comparison of various subtypes of exudative effusion, found a higher concentration of pleural VEGF in malignant

than tuberculous, parapneumonic, and collagen exudative

(17). These put forward the need for more diagnostic effusions. The exact underlying mechanism for this approaches. Regarding deficiency of assessment of four PE association is not known. However, it is proposed that types and comparison of sensitivity and specificity of VEGF functions through tyrosine kinase receptors VEGF with common pleural markers, we explored the primarily expressed on endothelial cells, pleural tissue,

diagnostic potential of VEGF in four PE types and

compared it with other pleural markers.

and most tumor cells (22). Moreover, it is suggested that

VEGF plays an important role in increasing vascular

The results of this prospective cross-sectional study on

80 patients with PE indicated that VEGF had the highest

permeability thus resulting in PE in malignant

patients (23).

potential in the diagnosis of pleural effusions compared with protein, LDH, and glucose solely. Moreover, the level of pleural protein, pleural LDH, and pleural glucose was correlated with the level of pleural fluid VEGF. Also, the mean value of pleural fluid VEGF in malignant patients

was 143.73 pg/ml, which was significantly higher than

In this study ROC analysis showed that by considering the cut-off value of 73.09 pg/ml, pleural fluid VEGF had a sensitivity of 64% and specificity of *82%* in the diagnosis of malignant PE. Hariyanto et al. reported a sensitivity and specificity of 85.29% and 84.22% at cut-off value of 416.60

pg/ml for VEGF-A level in pleural fluid for the diagnosis

tuberculous PE (37.07 pg/ml), and transudative PE of malignant PE (24). Gad et al. found sensitivity and (7.17 pg/ml); but the difference with parapneumonic PE specificity of pleural fluid VEGF (cut-off value 1590 pg/ml) was insignificant (128.27 pg/ml). The mean value of of 96.2% and 98.7%, respectively, in differentiating pleural fluid VEGF in malignant patients in previous malignant exudative from benign exudative PE (25). Fathy studies vary between 19.56 to 3208 pg/ml (18, 19). et al. found a sensitivity of 95% and specificity of 96% in Consistent with previous studies, this study found higher the diagnosis of malignant PE (cut-off value of

pleural VEGF levels in exudative effusions compared to

transudates. Fathy et al. (18) reported the mean value of

1800 pg/ml)(18). Khalil et al. (21) reported specificity of

53.3% and sensitivity of 100.0 % at cut-off value of

pleural fluid VEGF in malignant patients (median 720 pg/ml. A possible explanation for the inconsistency of 3208 pg/mL) was significantly higher than tuberculous PE these numbers is the different cut-off points assessed in (median 364 pg/ml) and infectious PE (median each study. According to high VEGF levels in 974 pg/ml). Economidou et al found that VEGF level was parapneumonic PE, probably the specificity and sensitivity significantly higher in exudates than in transudates. of the VEGF test are higher among lymphocyte-However, reported no significant differences of pleural predominant PEs; future studies should assess this point. VEGF levels between malignant and inflammatory **Limitations**

effusions(20). Khalil et al. (21) reported higher pleural fluid

VEGF levels in exudates than transudate effusions. Also,

This study had two limitations. First, the high cost of

this procedure makes it only proper for suspected cases.

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Second, this study should be performed on a larger population.

CONCLUSION

In conclusion, our results show that pleural fluid VEGF is an important biomarker in the differential diagnosis of effusions, especially in differentiating malignant effusions. Regarding the cut-off value of 73.09 pg/ml, pleural fluid VEGF has a sensitivity of 64% and specificity of 82% in the diagnosis of malignant PE. Considerably, further research

is required to investigate the implications of anti-VEGF

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