Role of DR-70 immunoassay in suspected malignant pleural effusion

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ABSTRACT

Context: A good proportion of patients with undiagnosed pleural effusion (PE) turn into malignancy over a period of time. Identification of positive biomarker may help in selecting the individuals who require close follow-up. Aims: The aims of this study were to evaluate the role of DR-70 immunoassay in suspected malignant PE. Settings and Design: We conducted a cross-sectional study among 89 patients of suspected malignant PE and 50 normal subjects (NS) were taken as control. Materials and Methods: Patients with exudative PE; who had pleural fluid lymphocyte count greater than 50% and adenosine deaminase less than 30 U/L were taken as cases. We had selected NSs among relatives of patients having normal blood chemistry and radiological investigations. Sensitivity and specificity of the test to differentiate malignant and non-malignant PE and also to identify PE with underlying malignancy was analyzed. Results: Mean value of DR-70 in NS was found to be 0.83 ± 0.273 mg/L without any significant difference between males (0.82 mg/L) and females (0.85 mg/L). Mean value of DR-70 in PE with underlying cancer was 5.03 ± 3.79 mg/L. Sensitivity (80%) and specificity (77.78%) of the test was maximum in PE with underlying cancer using cut-off value of 2 mg/L. Mean value DR-70 in malignant PE was 5.18 ± 3.75 mg/L and in non-malignant PE was 3.73 ± 3.74 mg/L without any statistically significant difference (P = 0.08). Conclusions: DR-70 assay has high sensitivity in detecting underlying lung cancer, but has no role in differentiating malignant PE from non-malignant PE.

KEY WORDS: Bronchogenic carcinoma, DR-70 immunoassay, pleural effusion, sensitivity, specificity

INTRODUCTION

Cancer is one of the most common causes of death, posing significant health concern world-wide. More than 11 million people are diagnosed with cancer every year. It is estimated that there will be 16 million new cases every year by 2020.1 Stage of cancer at the time of diagnosis governs treatment decisions.2 Recent technological advancement has generated tremendous interest in searching of a suitable blood, sputum or exhaled breath biomarker for the detection of early lung cancer.3 Pleural diseases are common affecting 3000 people/million population each year.4 A good proportion of patients with undiagnosed pleural effusion (PE) turns into malignancy over a period of time. Identification of positive biomarker may help in selecting the individuals who require close follow-up. Although India has started using cancer biomarkers, it has not reached international level yet. To the best of our knowledge, this is the first literature in India evaluating the role of AMDL-ELISA DR-70 fibrinogen degradation products (FDP) in suspected cases of malignant PE.

MATERIALS AND METHODS

We conducted a cross-sectional study a medical college of Kolkata from July 2011 to June 2012 to evaluate the role of (FDP) DR-70 in detection of malignant PE. The study was conducted among 50 normal persons (control) and 89 patients of suspected malignant PE (cases). Among
control 28 were males and 22 were females. Cases consisted of 89 patients with 55 males and 34 females.

We had selected normal subjects (NSs) among relatives of admitted patients in our hospital on the basis of normal blood chemistry reports and radiological investigations. Patients with PE were first classified into transudates and exudates according to Light’s criteria.\(^5\) According to literature, tubercular PE patients usually have pleural fluid lymphocyte-to-neutrophil ratio of 0.75 or more and rarely have adenosine deaminase (ADA) below 30 U/L.\(^6,4\) We enrolled patients with exudative PE with pleural fluid lymphocyte count greater than 50% and ADA less than 30 U/L and there by removed tuberculosis as a confounding factor of the study. Patients who had a fever or peripheral white blood cell count greater than 11,000/mm\(^3\) or <4,000/mm\(^3\) were excluded. Moreover patients with parapneumonic effusion usually have neutrophilic, exudative pleural fluid with high ADA.\(^9\) Other causes of lymphocytic exudative effusions such as rheumatoid pleurisy, post coronary artery bypass grafting, sarcoidosis, yellow nail syndrome, and chylothorax were also excluded from the study.\(^8,9\) Among these selected cases, patients with conditions that may affect the FDP level in the blood and so the DR-70 test results were excluded. Conditions which can affect DR-70 (FDP) level in the blood are pregnancy and pregnancy related complications; history of receiving prior chemotherapy or radiotherapy; sputum positive cases of tuberculosis or sputum negative cases with suggestive radiology and a positive tubercular skin testing, recent surgery, trauma, burns, renal diseases; acute and chronic infections; history of recent blood transfusion or therapy for coagulopathic conditions and hypercholesterolemia.\(^10\)

After selecting cases of lymphocytic PE with low ADA, a diagnostic approach for etiological evaluation was undertaken parallel to the evaluation of value of DR-70 in serum. The investigations which were used to arrive at the etiological diagnosis of PE and underlying malignancy if any were contrast enhanced computer tomography of thorax, fiber optic bronchoscopy and related procedures, closed pleural biopsy or radiologically guided pleural biopsy, thoracoscopy or video assisted thoracoscopy (VATS) guided pleural biopsy. Samples were drawn from normal persons and patients and samples were sent without any bias or clinical background to the respective laboratory.

Method of estimation of DR-70 (FDP)

Test kit was AMDL DR-70 kit, supplied by Super Religare Laboratories, Kolkata. Name of the test was Onko-sure (DR-70 Elisa Test) and manufactured at Tustin, California, USA by AMDL Diagnostics & Jaiva Technologies, Inc. Test kit batch number was DR 2101193. This is an ELISA based assay, which uses affinity purified rabbit antiDR-70 polyclonal antibodies coated 96 micro titer plate in a well format. The DR-70 antigen in diluted patient serum (1:200) was captured by these antibodies and after a wash step, these antibodies conjugated to horseradish peroxidase (HRP) were added to the wells. In presence of the DR-70 antigen, the HRP labeled antiDR-70 antibodies would bind to the captured tumor marker to form an immunological sandwich with the immobilized antibodies. After a second wash step, the enzyme substrate 3,3’,5,5’-tetramethylbenzidine (TMB) was added to the well. The end point of the test was read in a micro plate reader at 450 nm, when the reaction was stopped with 0.1 N HCL. The amount of DR-70 in serum was proportional to the intensity of color formed during the test and it was quantified by interpolation from a standard curve using the calibrators provided with the kit.

Statistical analysis

Cases (n) were selected from the total number of NSs (control) + patients with suspected malignant PE (N) by linear systematic sampling. The sample mean is being used to estimate the mean of a population (number of patients) almost equal to the true value designated as unbiased assessment. Using the Central Limit Theorem, the mean value of the sample means equals the population means. Therefore, the sample mean is an unbiased estimator of the population mean. The design and methodology of the study is carefully drawn using the scientific and statistical principles to ensure reliable and unbiased results.

Statistical analysis was performed using the SPSS package for Windows, version 13.0. Mean, standard deviation, confidence interval was used at various occasions. We used unpaired t-test to determine the level of significance between the two means and P value <0.05 was considered to be statistically significant. Sensitivity and specificity of the test with positive and negative predictive values were analyzed.

RESULTS

NSs were within the age range of 25-70 years with the median age 45 years. DR-70 values of NSs and PE patients were mentioned in Table 1. Mean value (±SD) of DR-70 in 50 NSs was found to be 0.83 ± 0.273 mg/L (range was 0.3 to 1.2 mg/L and 95% confidence interval for the mean was 0.7544 to 0.9096). Mean value (±SD) of DR-70 in male NS were 0.82 ± 0.274 mg/L (range was 0.3 to 1.2 mg/L and 95% confidence interval for the mean was 0.7255 to 0.9745). There was no statistically significant difference between the male and female NS regarding DR-70 value (P = 0.7513). The average mean value (±SD) of DR-70 in NS below 60 years and ≥60 years was 0.76 ± 0.29 mg/L (range was 0.4 to 1.2 mg/L and 95% confidence interval for the mean was 0.8165 to 1.0835) and 0.95 ± 0.23 mg/L (range was 0.3 to 1.2 mg/L and 95% confidence interval for the mean was 0.6733 to 0.8579) respectively. The difference between these two age groups was statistically significant (P = 0.02). Mean value (±SD) of DR-70 in smokers and non-smokers were 0.9 ± 0.26 mg/L.
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Table 1: Average value of DR-70 in control and cases

| Total no. of subjects | Average value of FDP DR70(mg/L) |
|-----------------------|---------------------------------|
| Normal subjects       |                                 |
| Overall               | 50                              |
| Male                  | 28                              |
| Female                | 22                              |
| <60 years             | 32                              |
| ≥60 years             | 18                              |
| Non-smokers           | 33                              |
| Smokers               | 17                              |
| Overall               | 89                              |
| With underlying malignancy | 80                    |
| Lung cancer           | 66                              |
| Overall               | 95                              |
| Adenocarcinoma        | 30                              |
| Squamous cell carcinoma | 10                        |
| Small cell carcinoma  | 24                              |
| Poorly differentiated  | 2                               |
| Without underlying malignancy | 9         |
| Pleural fluid M cell positive or metastasis in pleural biopsy | 59 |
| Pleural fluid M cell and pleural biopsy for metastasis negative | 30 |

Table 2: Sensitivity and specificity of DR-70 in detecting underlying malignancy of PEs patients

| Types of underlying malignancy | No. of patients | FDP DR 70 level (mg/L) | Sensitivity (%) using different cut-off level | Specificity (%) using different cut-off level |
|-------------------------------|-----------------|------------------------|----------------------------------------------|----------------------------------------------|
|                               |                 | >1                     | >2   | >3   | >1   | >2   | >3   | >1   | >2   | >3   | >1   | >2   | >3   | >1   | >2   | >3   |
| Bronchogenic carcinoma        | 66              | 63                     | 56   | 37   | 95.45| 84.85| 56.06| 52.17| 56.6 | 65.21| 66.67| 66.67| 66.67| 52.17| 56.6 | 62.5 |
| Breast carcinoma              | 5               | 3                      | 3    | 2    | 60   | 60   | 40   | 14.94| 24.13| 47.12| 15.56| 24.44| 34.78| 15.56| 24.44| 47.78|
| Gastrointestinal tract malignancy | 3          | 2                      | 2    | 2    | 66.67| 66.67| 66.67| 15.73| 24.7 | 46.06| 15.73| 24.7 | 46.06| 15.73| 24.7 | 46.06|
| Genitourinary tract malignancy | 2              | 1                      | 1    | 1    | 50   | 50   | 50   | 15.56| 24.44| 47.78| 15.56| 24.44| 47.78| 15.56| 24.44| 47.78|
| Other malignancy              | 4               | 2                      | 2    | 2    | 88.75| 80.00| 55.00| 66.67| 77.78| 88.89| 66.67| 77.78| 88.89| 66.67| 77.78| 88.89|
| Total malignancy              | 80              | 71                     | 64   | 44   | 88.75| 80.00| 55.00| 66.67| 77.78| 88.89| 66.67| 77.78| 88.89| 66.67| 77.78| 88.89|

Table 3: Sensitivity and specificity with positive and negative predictive value of DR-70 using different cut-off levels

| Cut off value of FDP DR 70 (mg/L) | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|-----------------------------------|-----------------|-----------------|---------|---------|-----------------|-----------------|---------|---------|
| 1                                 | 88.75           | 66.67           | 95.95   | 40      | 95.45           | 52.17           | 85.14   | 80      |
| 2                                 | 80              | 77.78           | 96.97   | 30.43   | 84.85           | 56.6            | 84.85   | 56.52   |
| 3                                 | 55              | 88.89           | 97.78   | 18.19   | 56.06           | 65.21           | 82.22   | 34.09   |
| 4                                 | 46.25           | 88.89           | 97.37   | 15.69   | 50              | 78.26           | 86.84   | 35.29   |
| 5                                 | 41.25           | 88.89           | 97.05   | 14.55   | 45.45           | 82.63           | 88.23   | 34.54   |
| 6                                 | 36.25           | 88.89           | 96.67   | 13.56   | 37.88           | 86.96           | 89.29   | 32.79   |
| 7                                 | 27.5            | 100             | 100     | 13.43   | 31.81           | 95.65           | 95.45   | 32.84   |

PPV: Positive predictive value, NPV: Negative predictive value, FDP: Fibrinogen degradation products

(range was 0.3 to 1.2 mg/L and 95% confidence interval for the mean was 0.7511 to 1.0606) and 0.79 ± 0.28 mg/L (range was 0.3 to 1.2 mg/L and 95% confidence interval for the mean was 0.7040 to 0.8839) respectively among NS without any statistically significant difference (P = 0.17).

Among 89 cases of PE, 66 were diagnosed with lung cancer. Breast carcinoma, gastrointestinal tract malignancy, genitourinary tract malignancy, rhabdomyosarcoma, unknown primary constituted 5, 3, 2, 1, and 3 cases respectively. Diagnosis of tubercular PE and rheumatoid arthritis was made in 3 and 2 cases respectively. No etiological diagnosis of PE was made in 4 cases. Cut off value of 1 mg/L was taken as a positive value based on the tests conducted in normal individuals. Mean value (±SD) of DR-70 in lung cancer was 5.47 ± 3.96 mg/L with 95% of the confidence interval of 3.76-7.18. Among 66 cases, 3 cases were found to be negative with value <1 mg/L. Sensitivity and specificity of the DR-70 assay in PE with different types of malignancy are depicted in Table 2. Sensitivity (84.85%) and specificity (56.6%) of the test were maximum in PE with underlying lung cancer using the cut-off value of 2 mg/L. At this cut-off value positive predictive value of the test to detect PE with underlying lung cancer was 84.85% and to detect PE with underlying cancer was 96.97%. DR-70 was positive (≥1 mg/L) in 3, 2, 1, 1 and 1 case of Breast carcinoma, gastrointestinal tract malignancy,
genitourinary tract malignancy, rhabdomyosarcoma, and unknown primary respectively. Mean value (±SD) of DR-70 in cancer patients with PE was 5.03 ± 3.79 mg/L (range was 0.6 to 13.8 mg/L and 95% confidence interval for the mean was 4.1870 to 5.8730). Sensitivity and specificity of DR-70 with positive and negative predictive values using the cut-off value of 1-7 in PE with cancer as a whole and with lung cancer has mentioned in Table 3 and receiver operating characteristic curve for PE with underlying malignancy and PE with lung cancer has drawn in Figure 1. Among 9 non-malignant cases result was positive in one case of tuberculosis PE and 2 cases of undiagnosed PE. Mean value (±SD) in this 9 non-malignant effusion was 1.66 ± 2.17 mg/L (range was 0.4 to 7 mg/L and 95% confidence interval for the mean was -0.01004 to 3.3212). There was statistically significant difference ($P < 0.0001$) between levels of DR-70 values between cancer patients and NSs as well as between bronchogenic carcinoma patients and NSs. There was statistically significant difference of DR-70 ($P < 0.01$) value between patients of PE with underlying malignancy and without underlying malignancy. There was also statistically significant difference of DR-70 ($P = 0.05$) in lung cancer patients and PE with other cancer patients. A total of 59 patients were found to have malignant cells positive in pleural fluid or metastasis in pleural biopsy. Mean value of DR-70 in malignant PEs was 5.18 ± 3.75 mg/L (range was 0.6 to 13.8 mg/L and 95% confidence interval for the mean was 4.1992 to 6.1534) and in non-malignant PEs was 3.73 ± 3.74 mg/L (range was 0.4 to 13.7 mg/L and 95% confidence interval for the mean was 2.3321 to 5.1279). The difference was found to be statistically insignificant ($P = 0.08$). Among lung cancer patients: there was 30 cases of adenocarcinoma, 24 cases of small cell carcinoma, 10 cases of squamous cell carcinoma and 2 cases of poorly differentiated carcinoma. Mean value of DR-70 in adenocarcinoma, small cell carcinoma, and squamous cell carcinoma was 5.37 ± 4.73 mg/L (range was 0.6 to 13.8 mg/L and 95% confidence interval for the mean was 3.9289 to 6.8177), 5.51 ± 2.69 mg/L (range was 0.7 to 13.7 mg/L and 95% confidence interval for the mean was 3.7191 to 7.3059) and 4.9 ± 2.3 mg/L (range was 0.6 to 10.5 mg/L and 95% confidence interval for the mean was 2.4645 to 7.3355) respectively. There was no statistically significant difference ($P > 0.05$) between observed mean DR-70 levels among adenocarcinoma, small carcinoma, and squamous cell carcinoma patients.

**DISCUSSION**

Biological markers are urgently needed for improving the early detection, diagnosis, and treatment of carcinomas. Various efforts to find a suitable blood, sputum or exhaled breath biomarker for the detection of early lung cancer are ongoing at different parts of the world. The DR-70 (FDP) immunoassay is the first new cancer test to be approved by the US FDA for monitoring colorectal cancer since January 14, 1982 when carcinoembryonic antigen (CEA) was approved. In 1970, Donald Rounds discovered DR-70 culture medium of cells undergoing malignant transformation. Later on, ring shaped particles were found in the serum of cancer patients. The name of the tumor maker DR-70 was derived from the first letter of his first and second names and the year of discovery to honor him. In 1991, AMDL, Inc., in the USA, suggested that DR-70 is a maker DR-70 was derived from the first letter of his first and second names and the year of discovery to honor him. In 1991, AMDL, Inc., in the USA, suggested that DR-70 is a group of cancer related proteins, and it is a protease secreted by the cancer. Unlike CEA, DR-70 floats freely in blood and abundant in serum acts as a “barometer for cancer” by simultaneously measuring the multiple FDP species that may be underestimated by other tests. DR-70 detects all of the breakdown products of Fibrin and Fibrinogen, including a unique “IPDP” cancer-related breakdown product. DR-70 is different from estimation of D-dimer as D-dimer values alone would greatly underestimate cancer and miss some altogether. Wu et al., had conducted the study among 277 healthy subjects and 136 cancer patients including 13 different types of cancer. They concluded that sensitivity of the assay was 87.8%, 92.6%, 65.2% and 66.7%, respectively for lung, stomach, breast, and rectum cancer at 95% specificity level. Wu et al. had told that, at 95% of specificity, a sensitivity of 87% was obtained using 335 control subjects and 83 lung cancer patients. Fields et al., had said that mean DR-70 level of cancer subjects were 3 times higher compared to the NSs. Results of our study were relatively consistent with the results of above mentioned literatures. Contrary to Fields et al., Stieber et al., had reported lack of success in evaluating lung cancer with DR-70. In a study conducted in a high-risk Chilean population for early detection of lung cancer, Adonis et al., had found 90% of sensitivity of DR-70 in confirmed cases of lung cancer. The study also revealed that a high percentage of patients who were positive for DR-70 also showed suspicious lesions when using imaging techniques, which were later confirmed as pre-malignant lesion. A recent study had mentioned the role of DR-70 in early diagnosis of lung cancer found a cut point of 1.0 ug/ml provided optimal differentiation between the

![Figure 1: Receiver operating characteristic curve of DR-70 immunoassay for pleural effusion (PE) with underlying malignancy and PE with lung cancer discriminating them from control subjects](image-url)
control and cancer groups yielding a sensitivity of 87% and specificity of 95%. [25]

It was seen that even after complete investigations including thoracoscopic biopsies, a significant proportion of the patients remained diagnosed with non-specific pleuritis and no specific diagnosis could be established. A retrospective study revealed about 8.3% of the subjects turned out to be malignant over a 2 year follow-up period. [26] Gieseler et al., had evaluated several coagulation and thrombin activation effectors and markers in a series of 136 malignant effusions. They found a high level of highly activated coagulation system in blood and their malignant effusions, as suggested by high levels of prothrombin fragments 1 + 2 and D-dimers. [27] Another study conducted by Hatton et al., suggested that the concentrations of fibrinolytic factors and their products in PEs was reflective of the tumor burden of the rabbit. [28] Conceivably, the components of a malignant effusion contained much information about the extent of tumor growth.

The results of our study demonstrated high sensitivity in detection of PEs with underlying malignancy if we took 1 mg/L as cut off value for positivity. However, it also gave false positive results in a substantial proportion of PEs without underlying malignancy. No specific cut-off values of DR-70 are available in the literature above which it is considered to be positive. We recommend 2 mg/L as the cut-off value in which DR-70 has a sensitivity of 80% and specificity of 77.78% in PE patients with underlying cancer. Our study results also showed maximum sensitivity (84.85%) and specificity (56.6%) at 2 mg/L cut off value of DR-70 in patients of PE with underlying lung cancer. However, studies involving larger subjects are required to give a precise cut-off value.

It can serve as a pantumor marker in suspected cases of malignant PEs but unable to help in identifying the primary origin of the tumor. As with other tumor, DR-70 test also gave varying degree of false positives, this may be due to the fact that DR-70 is not a protein of cancer gene expression, and it's relation to cancer needs to be studied. Current investigations showed elevated levels of DR-70 in subjects suffering from tuberculosis, rheumatoid arthritis, which may lead to false positive results. As with other cancer diagnostic products, false positive and false negative test results could pose a small risk to patient health if the physician is not vigilant in following up the results with other clinically relevant diagnostic modalities. Any positive results should lead to a battery of investigations to have a correct diagnosis. Performing imaging procedures in individuals with a high level of DR-70 will lead to detection of cancer at an early stage. In order to have a reliable result with the DR-70 assay, the assay control procedure described in the product insert must be strictly maintained and samples should be taken in the fasting state as well as tested in non-hemolysis state. Patients who are suffering from infections should not take part while the infection is still active and ongoing.

**Limitation**

Stage wise relationship of carcinoma with DR-70 was not carried out by us. As it was a cross-sectional study, role of DR-70 as a prognostic marker during treatment could not be evaluated.

**CONCLUSION**

DR-70 immunoassay has a significant role to identify underlying malignancy specially lung cancer. Serial DR-70 assay can detect early cases of malignancy in high-risk group for lung cancer. It has no role in differentiating malignant from non-malignant PE but in cases of suspected malignant PE with non-specific pleuritis in pleural biopsy, serial DR-70 assay can detect the underlying malignancy early as non-specific pleuritis often turned into malignancy later on.

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