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# Investigating the Efficiency of D-Dimer Test in Diagnosis of Aortic Dissection: A Systematic Study and Meta-Analysis

Iraj Ahmadi [1], Samira Mis Qavam [2], Kourosh Sayehmiri [3], Mohamad Golitaleb [4], Hamed Tavan [5,*]

[1] Department of Physiology, Faculty of Medicine, Ilam University of Medical Sciences, Ilam, IR Iran
[2] Department of Cardiology, Faculty of Medicine, Ilam University of Medical Sciences, Ilam, IR Iran
[3] School of Medicine, Psychosocial Injuries Research Center, Ilam University of Medical sciences, Ilam, IR Iran
[4] Department of Nursing, Arak University of Medical Sciences, Arak, Ilam, IR Iran
[5] Student Research Committee, Ilam University of Medical Sciences, Ilam, IR Iran

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ABSTRACT

Background: Aortic dissection is a rare and important emergency condition, which usually involves a high mortality rate. Yet, early diagnosis of the disorder would increase the survival rate significantly.

Objectives: The present systematic study and meta-analysis aimed at investigating the efficiency of D-dimer test in diagnosis of aortic dissection.

Materials and Methods: The data used in this study were extracted from PubMed, Scopus, Elsevier, Springer, and Willey databases. Specificity, D-dimer, Sensitivity, and Aortic Dissection were the valid keywords used to extract the related articles. Totally, 11 papers published during 1998 - 2007 were selected. I2 index was used to assess heterogeneity across the studies.

Results: A total of 596 subjects (averagely 54.5 ones in each study) were examined in the present research and 11 articles were entered into the final meta-analysis. According to the findings, the mean of the specificity test was 0.66 (0.54 - 0.78), with I2 index = 74.9% and p-value = 0.001. Additionally, the mean of the sensitivity test was 0.98 with I2 index = 606% and p-value = 0.381. Moreover, the mean D-dimer plasma level was 18.6 ug/mL in patients suffering from aortic dissection.

Conclusion: This study showed the high efficiency of D-dimer test in diagnosis of aortic dissection. Thus, physicians are recommended to apply this quick and inexpensive method when a final diagnosis has not been made yet. Early diagnosis of aortic dissection via D-dimer test would result in implementation of the necessary treatments, eventually leading to a significant decrease in mortality rate.

## 1. Background

Acute aortic dissection is a rare and important emergency condition, which usually involves a high mortality rate. In this condition, severe pain emerges suddenly, which has been described as sharp, tearing, or migratory pain by patients in different situations (1, 2). Although medical and surgical emergency treatments may be possible, early diagnosis of the condition could lead to a significant increase in the survival rate (3, 4). Sensitive clinical tests are a way to diagnose acute aortic dissection. Various diagnostic tests, such as Computed Tomography (CT), Transesophageal Echocardiography (TEE), and Magnetic Resonance Imaging (MRI), have also been used based on the patients' clinical symptoms. However, these methods are expensive and limited to access. Hence, physicians usually employ clinical findings and tests, such as Electrocardiogram (ECG) and Chest X-Ray (CXR). In order to get to a final diagnosis in patients suffering from acute aortic dissection, clinicians are required to perform advanced imaging studies and screening to determine high-risk patients (5-7).

Acute aortic dissection leads to damage to the vascular tissue, blood coagulation disorder, and formation of fibrin (8). D-dimer is the product of fibrin. According to various studies, patients with acute aortic dissection have high D-dimer levels (9, 10). Accordingly, recent researches have

*Corresponding author: Hamed Tavan, Faculty of Nursing and Midwifery, Student Research Committee, Ilam University of Medical Sciences, Ilam, Iran, PO Box: 69391-77143. Tel: +98-9187474221; Fax: +98-8412227134; E-mail: hamedtavan@gmail.com.

shown that D-dimer plasma level might function as a useful screening measure to overcome acute aortic dissection and to save time and money (11-15). Based on different experiments conducted on D-dimer plasma level and acute aortic dissection as well as application of sensitivity and specificity tests, a meta-analysis is required to validate the obtained data and provide precise results for scientists and researchers (16-19).

## 2. Objectives

The present systematic study and meta-analysis aims to investigate the efficiency of D-dimer test in diagnosis of aortic dissection.

## 3. Materials and Methods

In the present systematic review and meta-analysis, the required data were extracted from PubMed, Scopus, Elsevier, Springer, and Willey databases. Specificity, D-dimer, Sensitivity, and Aortic Dissection were the valid keywords used to extract the related articles.

### *3.1. Study Selection and Data Extraction*

First, all papers related to D-dimer, sensitivity, specificity, and aortic dissection were collected and a list of some relevant abstracts was prepared. Then, all papers whose titles included D-dimer and aortic dissection were entered into the primary list and other papers that focused on aortic dissection treatment were excluded from the study. Afterwards, a checklist was provided to implement the final assessment with the following items: researcher's name, study title, publication year, location of study, sample size, number of female participants, number of male participants, sensitivity, specificity, D-dimer, aortic dissection, location code, age group, risk factors, and subgroups. Next, the researchers examined the checklist and the papers related to the topic of the research were entered into the meta-analysis. At this stage, 60 papers whose keywords were similar to the main topic were found and 30 papers were qualified based on the prepared checklist. Finally, qualitative assessment was done using the checklist, with the main criteria being sample size, study conduction time, and the relationship between D-dimer and aortic dissection. Accordingly, 11 papers were entered into the final meta-analysis and their full texts were closely investigated.

### *3.2. Statistical Analysis*

Since the relationship between D-dimer and aortic dissection, and sensitivity and specificity was mentioned in the extracted papers, the sample sizes were closely anatomized and binomial distribution was used to calculate the variance in each study. Each study was weighed in the reverse proportion to its variance. Due to the large difference in the prevalence rates in various studies (heterogeneity of studies) and the significance of the heterogeneity index (I2), random effects model was used in the meta-analysis. Heterogeneity rate was 90.6% in the present study, which ranked among very diverse studies (I2 index lower than 25%, between 25% and 75%, and above 75% signifies low, medium, and high heterogeneity, respectively).

Meta-regression was used to examine the relationship between D-dimer and aortic dissection, and sensitivity and specificity as well as the reason for heterogeneity of the results. The relationship between D-dimer and aortic dissection was determined based on risk factors, age groups, and sex through analyzing subgroups. All analyses were performed using STATA 11.1 software.

## 4. Results

In the present study, 60 articles were found in the systematic review. After examining the articles, 30 studies were entered into the checklist. Finally, 11 papers were selected and their full texts became available to the researcher. The flowchart of the study has been depicted in Figure 1.

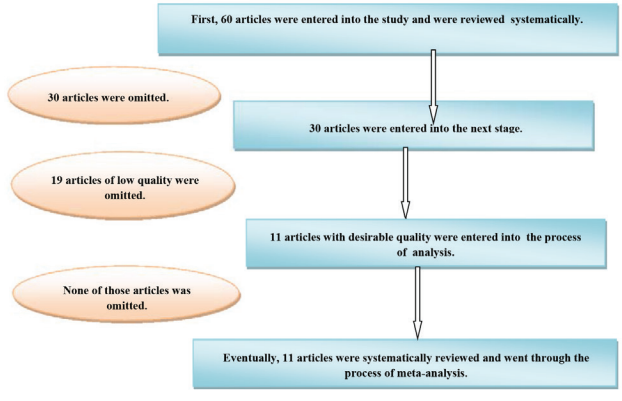


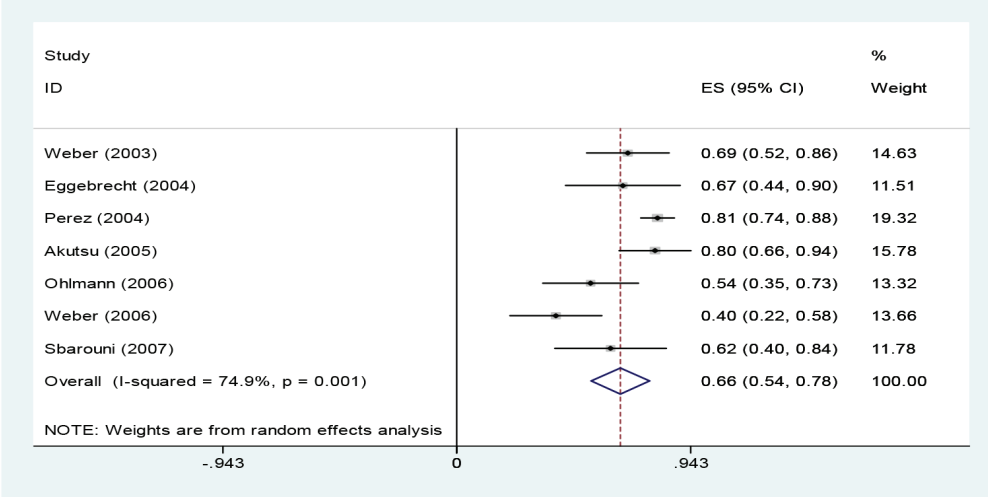

**Figure 1.** Flowchart of the Systematic Review and Meta-Analysis Processes

The selected papers were conducted from 1998 up to 2007. A total number of 596 subjects (averagely 54.5 subjects in each study) were examined. Additionally, 36.36%, 36.36%, 18.18%, and 9.09% of the studies were conducted in Asia, Europe, Australia, and America, respectively. All studies (cohort, case series, and case control) were conducted in a sectional approach and the qualified subjects were selected based on lists. The relationship between D-dimer and aortic dissection was assessed and sensitivity and specificity rates were recorded. The lowest specificity rate (40%) was related to Weber's study (2006), while the highest rate (81%) was related to Peres' study (2004) (Figure 2). The total specificity rate was 0.66 (0.54 - 0.78), with I2 index = 74.9% and P value = 0.001. Considering sensitivity, the lowest rate (92%) was related to Hazui's study (2006) and the highest rate (100%) was related to Sbarouni's research (2007) (Figure 3). The total sensitivity rate was 0.98, with I2 index = 6.6% and P value = 0.381.

The characteristics of the papers examining the relationship between D-dimer and aortic dissection through sensitivity and specificity tests have been presented in Table 1. Considering the heterogeneity of studies (I2 = 90.6%), the confidence interval of each individual study and all studies according to the random effects model has been depicted in the Forest Plot in Figure 1.

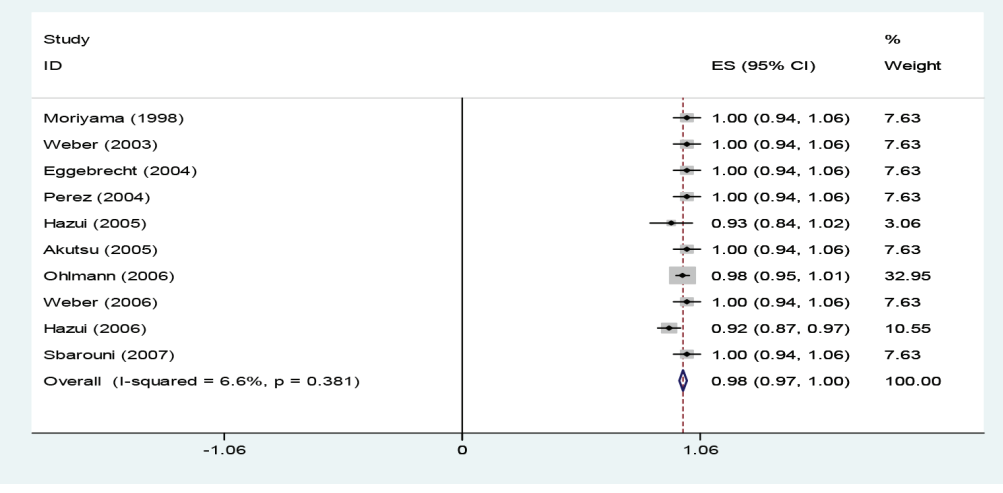
In this study, the meta-regression figure was determined based on the publication year with regard to specificity. The results indicated that increase in the year of publication was accompanied with a lower article specificity. Accordingly,

**Figure 2.** Forest Plot of the Specificity Rate regarding the Relationship between D-Dimer and Aortic Dissection with 95% Confidence Interval based on the Random Effects Model.




Lines signify the specificity confidence interval in each study and the midpoint of each segment shows the rate of specificity in each study. The diamond symbol represents the total specificity rate, which was estimated as 0.66 (0.54 - 0.78), with I2 index = 74.9% and P value = 0.001.

**Figure 3.** Forest Plot of the Sensitivity Rate regarding the Relationship between D-Dimer and Aortic Dissection with 95% Confidence Interval.




The sensitivity rate was calculated for individual studies separately and for all studies based on the random effects model. The segments signify sensitivity confidence interval in each study. The midpoint of each segment shows an estimation of the prevalence rate in each study. The diamond symbol represents the total sensitivity rate, which was 0.98 (0.97 - 0.100), with I2 index = 6.6% and P value = 0.381.

**Table 1.** Characteristics of the Studied Articles with Regard to the Relationship between D-Dimer and Aortic Dissection

| D-Dimer Test (N) | D-Dimer Test (N) | Specificity | Sensitivity | Dissection Diagnosis | Year | Location | Author |
|---|---|---|---|---|---|---|---|
| **7** | 19 | 0 | 100 | CT, MRI | 1998 | Japan | Moriyama (3) |
| **30** | 24 | 69 | 100 | TTE, CT, MRI | 2003 | Austria | Weber (4) |
| **0** | 16 | 67 | 100 | TEE, CT | 2004 | Germany | Eggebrecht (7) |
| **133** | 7 | 81 | 100 | CT, EKG | 2004 | USA | Perez (6) |
| **0** | 29 | 0 | 93 | CT | 2005 | Japan | Hazui (5) |
| **1** | 30 | 80 | 100 | CT | 2005 | Japan | Akutsu (8) |
| **26** | 94 | 54 | 98 | TEE, CT, MRI | 2006 | France | Ohlmann (9) |
| **0** | 27 | 40 | 100 | CT, EKG | 2006 | Austria | Weber (10) |
| **0** | 113 | 0 | 92 | CT | 2006 | Japan | Hazui (11) |
| **9** | 13 | 0 | 15 | CT | 2006 | Italy | Monaco (15) |
| **0** | 18 | 62 | 100 | CT, echocardiogram | 2007 | Greece | Sbarouni (14) |

specificity rate was 0.83 in 2005 and 0.40 in 2007 (Figure 4). The meta-regression figure was also calculated based on the publication year with regard to sensitivity. The results showed that increase in the year of publication was accompanied with a decrease in the sensitivity rate. Accordingly, sensitivity rate was 100% in 2000 and 97% in 2007 (Figure 5).

Publication bias of the obtained results has been presented in Figures 6 and 7. According to the results, publication bias had no roles in these articles, which has been presented as symmetry in a funnel figure. The size of circles signifies the weight of studies; bigger circles signify larger sample sizes and smaller circles represent smaller ones.

Aortic dissection was diagnosed through CT scan in 66.66% and via MRI, ECG, and echocardiogram in 33.33% of the studies. Furthermore, the mean serum level of D-dimer was 18.6 ug/mL in patients suffering from aortic dissection.

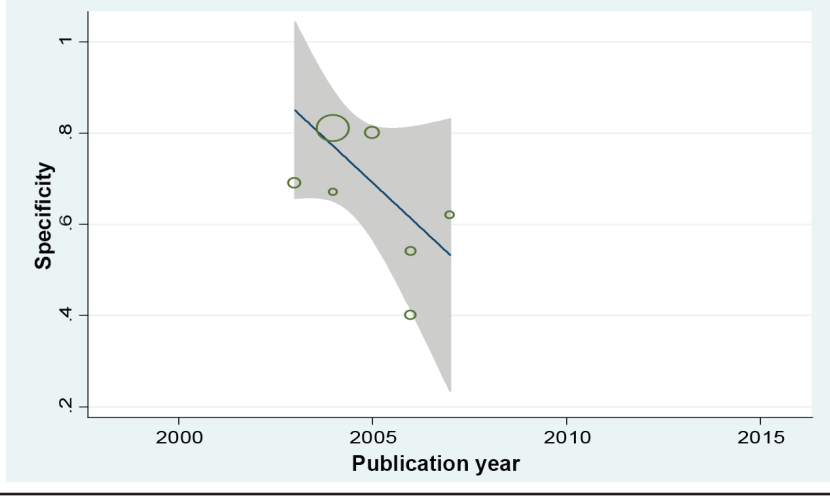
## 5. Discussion

The results of this study showed that the mean specificity rate was 0.66 (0.54 - 0.78), with I2 index = 74.9% and P value = 0.001. It seems that specificity rate did not benefit from high validity in definite diagnosis of aortic dissection. These findings were also confirmed by other researchers (1, 7). In contrast, some other studies reported specificity rates above 0.80% (6). The reason for such inconsistency can be differences in research communities and publication years.

The results of this study revealed that the overall sensitivity rate was 0.98 (0.97 - 0.100), with I2 index = 6.6% and P value = 0.381. It seems that the findings of sensitivity tests were extremely important in definite diagnosis of aortic dissection. Similar findings were also reported by other studies (10, 11, 14, 15).

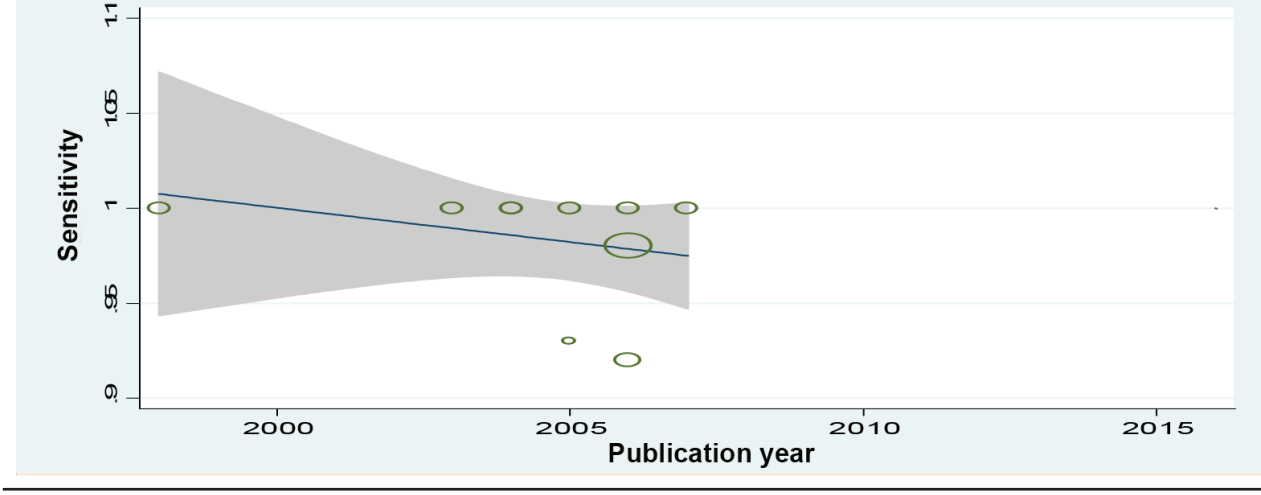
Aortic dissection was diagnosed through CT scan in 66.66% and via MRI, ECG, and echocardiogram in 33.33% of the cases. Indeed, D-dimer plasma level was measured in all studies, the reason being the low cost and high precision of this diagnostic test (5-8, 14). The results revealed that D-dimer plasma level was 18.6 ug/mL in patients with aortic dissection, which might be due to vascular tissue damage, activation of extrinsic coagulation cascade pathway, and formation of fibrin. Studies have shown the high level of D-dimer to be a common phenomenon in patients suffering

**Figure 4.** Meta-Regression of Studies based on the Publication Year.



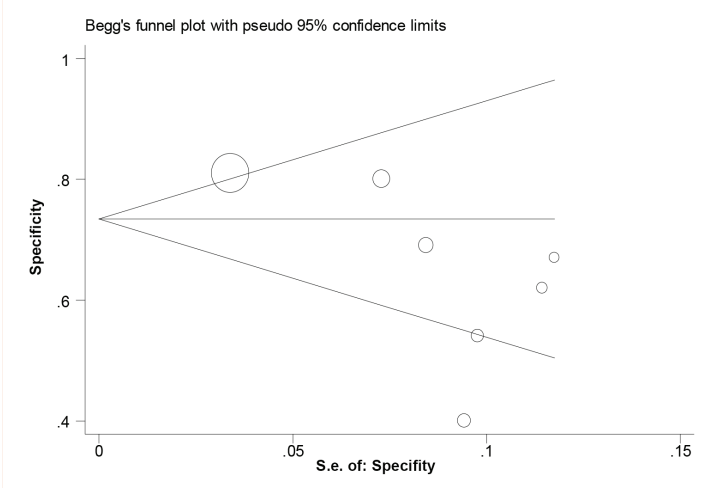

Circles signify the sample size; the bigger the circle, the larger the sample size, and vice versa.

**Figure 5.** Meta-Regression of Studies based on the Publication Year.



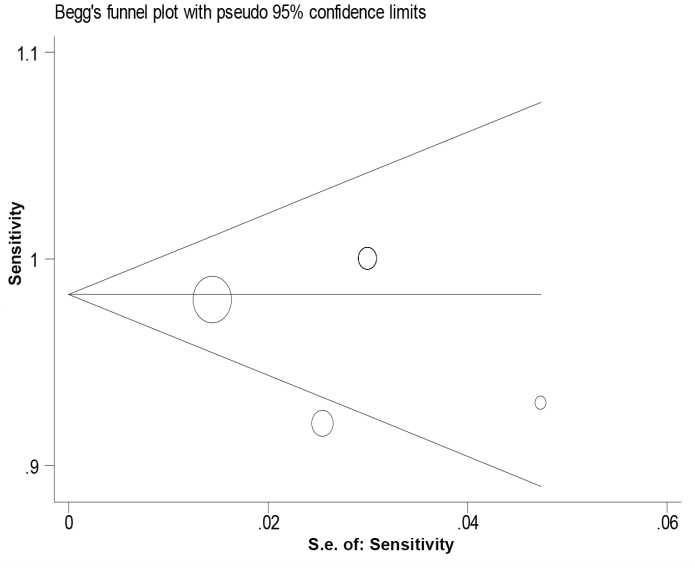

Circles signify the sample size; the bigger the circle, the larger the sample size, and vice versa.

**Figure 6.** Publication Bias with regard to Specificity in the Relationship between D-Dimer and Aortic Dissection.




The size of the circles shows the weight of studies; bigger circles represent larger sample sizes and smaller circles signify smaller ones.

**Figure 7.** Publication Bias with regard to Sensitivity in the Relationship between D-Dimer and Aortic Dissection.




The size of the circles shows the weight of studies; bigger circles signify larger sample sizes and smaller circles represent smaller ones.

from aortic dissection. Thus, the high rate of D-dimer could be a definite symptom of aortic dissection. Similar results have also been obtained in other studies conducted on the issue (1, 2).

In the current systematic review, 60 articles were found 30 of which were eliminated and the other 30 were qualified based on a prepared checklist. After precise assessment, 11 articles were finalized and their full texts became available to the researchers. The heterogeneity rate of the studies was 90.6%, which is a high value according to the classification of heterogeneity (values less than 25%, between 25% and 75%, and above 75% represent low, medium, and high heterogeneity, respectively (20, 21). Thus, the random effects model was used in further investigations. This model indicated that the differences in findings could be attributed to various sampling methods and measurement parameters regarding the relationship between D-dimer and aortic dissection with respect to sensitivity and specificity.

*5.1. Limitations of the Study*

One of the main limitations of the present study was that the majority of samples were not randomly selected, which caused inefficiency in the subjects selection process. Another limitation was the small number of variables investigated in the research. Some studies that had recorded sensitivity and specificity tests did not include risk factors and symptoms. Additionally, some studies had just reported the treatments without mentioning the causes. Some other studies had not considered the differences among various diagnostic methods, such as CXR, ECG, MRI, and CT scan, and the data were presented generally without comparison of various high-risk age groups. Besides, none of the studies had suggested the best diagnostic method. Finally, the prevalence of aortic dissection had not been stated in the

five continents, which caused deficiency in equal calculation of the prevalence rates in all locations. Another limitation of the research was that due to the lack of true positives, false positives, true negatives, and false negatives, a binomial distribution had to be employed to calculate the confidence intervals and to combine the results. Indeed, specific analyses could not be utilized for diagnostic studies.

*5.2. Conclusion*

The study results indicated that the mean D-dimer plasma level was 18.6 ug/mL in patients suffering from aortic dissection. Thus, D-dimer could be used as an efficient laboratory test in patients with equivocal symptoms of aortic dissection.

*5.3. Suggestions*

According to the results, D-dimer test is one of the most efficient methods in diagnosis of aortic dissection. Hence, physicians are recommended to apply this quick and inexpensive method in cases without definite final diagnoses.

*5.4. Research Findings in the Clinic*

Early diagnosis of aortic dissection by D-dimer test could result in implementation of necessary treatments, eventually decreasing the mortality rate.

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**Authors' Contribution**

All authors: data collection; Hamed Tavan, Iraj Ahmadi Mohamad Golitaleb: statistical analysis; Kourosh Sayehmiri,: study design; Samiramis Qavam, Hamed Tavan: quality assessment; all authors: final revision and grammar editing.

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The authors declare that there is no conflict of interests.

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