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D-dimer Levels in COVID-19 Patients and Its Correlation with Age and Gender: A Retrospective Analysis

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ABSTRACT

Raised levels of coagulation parameters indicate thrombotic disorders which need to be managed as soon as possible. Radiological findings are confirmatory diagnosis in these cases however the increased load and risk of spread of COVID-19 infections makes pathological findings the sole basis to start treatment. D-dimer is a widely used fibrin degradation product test used for initial diagnosis of thrombotic disorders. Studies have shown that a four-fold increase in its levels is a strong indicator of mortality in active COVID-19 cases. In this study we had retrospectively analysed D-dimer data level from patients admitted in tertiary COVID care centre. The final data set obtained comprised of 153 patients out of which 93 were male (60.78%) and 60 were female (39.22%). Numbers of males with elevated D-dimer levels (above 250 ng/ml) were 64 (68.81%). Numbers of females with elevated D-dimer levels (above 250 ng/ml) were 44 (73.33%). Numbers of pre-menopausal females were 23 (38.33%) and numbers of post-menopausal females were 37 (61.67%). Number of pre-menopausal females and having elevated D-dimer levels (above 250 ng/ml) were 16 (69.56%). Number of post-menopausal females and having elevated D-dimer levels (above 250 ng/ml) were 28 (75.67%).From our study we concluded that women and older individuals are at a higher risk of developing thrombotic disorders in COVID-19 infection. Men are comparatively at a lower risk.

Keywords: COVID-19; D-dimer; coagulation parameters; risk; women

INTRODUCTION

As of writing this article, coronavirus disease (COVID-19) has infected 1,31,50,645 globally. [1] The huge toll on humanity in terms of mortality, economic losses and stress cannot be ignored. While the quest for its treatment and vaccine continues, management of patients actively infected by it is imperative. COVID-19 progresses to "atypical" acute respiratory distress syndrome (ARDS). [2] Pathological studies in China conducted at the beginning of this pandemic indicated to abnormal coagulation parameters. [3] Raised levels of coagulation parameters indicate thrombotic disorders which need to be managed as soon as possible. [4] Radiological findings are confirmatory diagnosis in these cases however the increased load and risk of spread of infections makes pathological findings the sole basis to start treatment. D-dimer is a widely used fibrin degradation product test used for initial diagnosis of thrombotic disorders. [5] Studies have shown that a four-fold increase in its levels is a strong indicator of mortality in active COVID-19 cases. [6][7] In this study we have retrospectively analysed D-dimer data level from patients admitted in tertiary COVID care centre.

METHODOLOGY

D-dimer data from patients between time period of May,2020 and mid-July,2020 was used. These values had been measured

using Tulip diagnostics' Turbodyne SC machine. Since the data comprised of both COVID as well as non-COVID patients, an inclusion and exclusion criteria were drawn. Inclusion criteria were defined as patients infected with COVID-19 and had been confirmed by RT-PCR. Age and gender of the patient was mandatorily required. If a patient had been more than once for d-dimer levels, only the higher value was retained. Other repetitions were excluded. Patients for which age or gender or both were missing were excluded. Threshold of the machine used to measure D-dimer levels in ng/ml was 10,000. Data for which results showed excess value was removed. In case levels were not reported due to clotted sample or haemolysed sample, such records were excluded. Samples reporting a value "less than 100" were converted to value equal to 100 ng/ml. Names of the patients after completing the above procedure were removed from data to maintain anonymity. The final data set obtained contained three parameters, age, gender and d-dimer level (in ng/ml).

MS-Excel 2016 and IBM-SPSS version 25 software [8] were used for analysis of data. The data set was divided into five subsets as follows:

1. Age and D-dimer level (irrespective of gender)
2. Age of males and D-dimer level (females excluded)
3. Age of females and D-dimer levels (males excluded)
4. Age of pre-menopausal females and D-dimer levels (males and post-menopausal females excluded)
5. Age of post-menopausal females and D-dimer levels (males and pre-menopausal females excluded)

The age for menopause was taken as 47 years [9] and the normal value of D-dimer level was taken as 250 ng/ml. [10]

For all the above subsets, MS-Excel was used to draw a scatter plot with age on x-axis and D-dimer levels (in ng/ml) on y-axis. A linear trendline was predicted with y-intercept at 250 ng/ml. Equation of the line and co-efficient of determination (R^2) was calculated.

To provide correlation between variables in each subset, IBM-SPSS software was used to calculate co-relation (r) and p-value using Pearson's co-efficient and two-tailed test of significance. A scatter plot was drawn and quadratic or cubic plot graphs were plotted with confidence interval of mean at 95%. The equation was obtained for the plot.

RESULTS

The final data set obtained comprised of 153 patients out of which 93 were male (60.78%) and 60 were female (39.22%). Numbers of males with elevated D-dimer levels (above 250 ng/ml) were 64 (68.81%). Numbers of females with elevated D-dimer levels (above 250 ng/ml) were 44 (73.33%). Numbers of pre-menopausal females were 23 (38.33%) and numbers of post-menopausal females were 37 (61.67%). Number of pre-menopausal females and having elevated D-dimer levels (above 250 ng/ml) were 16 (69.56%).Number of post-menopausal females and having elevated D-dimer levels (above 250 ng/ml) were 28 (75.67%). The entire data set is listed in table 1 below.

Table 1: Data set of 153 COVID infected individuals with their age, gender and D-dimer levels. M represents male and F indicates female.

Age (years)	Sex	D-dimer(ng/ml)
11	M	100
20	M	100
21	F	1896.5
21	F	248.42
21	F	100
23	F	1690.3
24	F	291.9
24	M	101.6
24	F	1376.3
25	F	100
25	F	364.5
25	M	2905.3
25	F	2723.26
26	M	100
27	M	392.29
27	M	2206.4
27	M	100
28	F	833.91
29	F	388.26
30	M	1950
30	F	4286.4

30	M	155.8
30	M	4545.1
30	M	100
30	F	114.6
30	M	1519.66
31	M	675.23
31	M	100
31	M	265.23
32	M	100
35	M	439.35
35	M	100
35	F	1522.82
36	M	139.59
38	M	157.16
38	M	964.12
38	M	180.4
38	F	664.87
38	F	100
38	F	100
39	M	1237.02
40	M	856.8
40	M	5473.1
40	M	1467.85
40	M	8717.79
40	M	100
41	M	554.6
41	M	100
42	M	973.94
42	M	1890
42	M	669.18
43	F	526.9
43	F	647.7
43	F	100
45	M	315.9
45	F	4082.4
45	M	132
45	M	433.9
45	M	169.7
45	M	290.2
45	F	285
47	F	975.63
48	M	253.22
48	M	100
48	M	372.22
49	M	1844.1
49	M	100
50	F	1209.43
51	M	100
51	M	4538.7
51	M	1225.62
52	M	686.2
52	M	287.4
52	M	150.6
52	M	1866.57
52	F	122.94
53	F	1103.02
53	F	100
54	M	236.54
55	M	207.34
55	M	7736.51
55	M	490.89
55	F	337.15
55	M	367.1
55	M	122.6
55	M	4587
55	M	733.9
55	M	659.2
55	F	2419.3
55	M	426.9
55	F	176.1
56	M	1307.8
56	M	269.8
56	M	5463.5
56	M	264.7
56	F	1340.2
58	M	1008.26
58	M	723.9
58	M	162.6
59	F	626.2
59	M	759
60	F	148.82
60	M	1879.82
60	M	363.5
60	F	392.8
60	F	2329.8
60	F	4708
60	F	3172.7
60	F	100
60	M	479.4
60	F	242.5
62	M	100
64	M	1130.3
65	F	326.07
65	M	3953.1
65	M	231.7
65	F	339.7
65	F	449.4
65	F	5578
65	F	2865.6
65	M	4764.2
65	M	100
65	F	100
67	M	5331.09
67	F	1047.3
67	M	810.5
67	M	5117
67	F	100
68	M	341.84
68	F	3099.4
68	F	4310
69	M	3176
69	M	5024
70	F	100
71	F	1009.6
72	F	5287.8
73	M	413.6
74	M	3405.2
75	M	839.81
75	M	388.46
75	F	1739.9
75	F	4068.2
75	F	4446.9
75	F	711.8
77	F	2001.33
77	F	1811.9
78	F	661.19
79	M	3923.4
80	F	4229.9
80	M	3318
83	M	324.8
84	M	3635.9
88	M	122.4

Subset 1: Age and D-dimer levels (irrespective of gender)
Scatter plot and linear equation from MS-Excel 2016 is shown in figure 1 below.

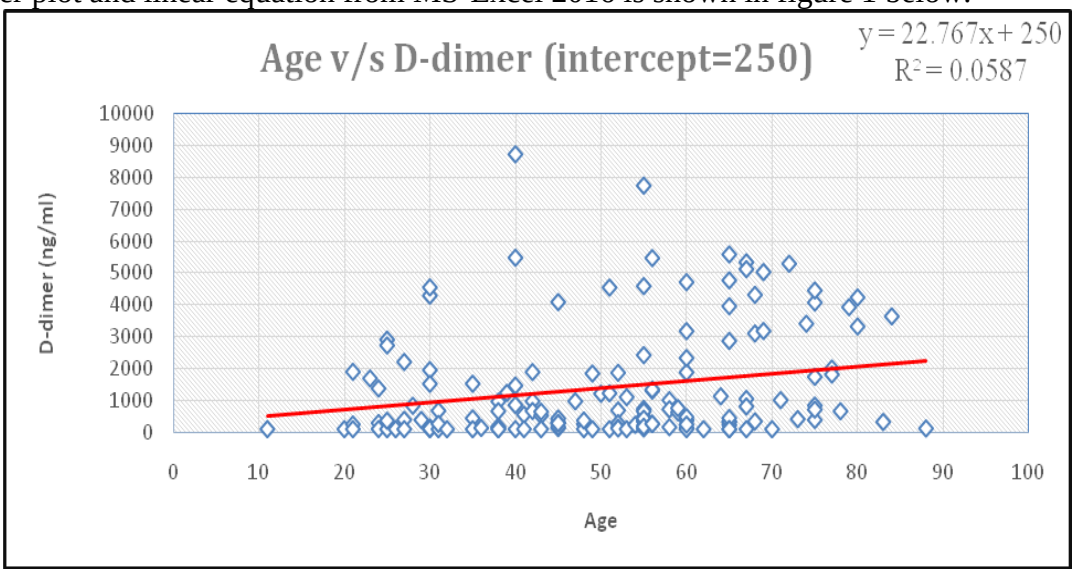

Figure 1: Age v/s D-dimer level scatter plot and linear trendline plotted in MS-Excel 2016. Line is coloured in red and squares indicate plots.

Equation of line in first subset is $y = 22.767x + 250$where y is value of D-dimer in ng/ml and x is age is years. y-intercept is set at 250 to represent normal D-dimer level. The slope of line is positive and the coefficient of determination R^2 is 0.0587.

Using IBM-SPSS software, there was significant correlation between age and D-dimer r(151) = 0.244 [p=0.02(<0.05)]. A quadratic equation plot was drawn with age on x-axis and D-dimer level on y-axis at 95% mean confidence level (Figure 2).

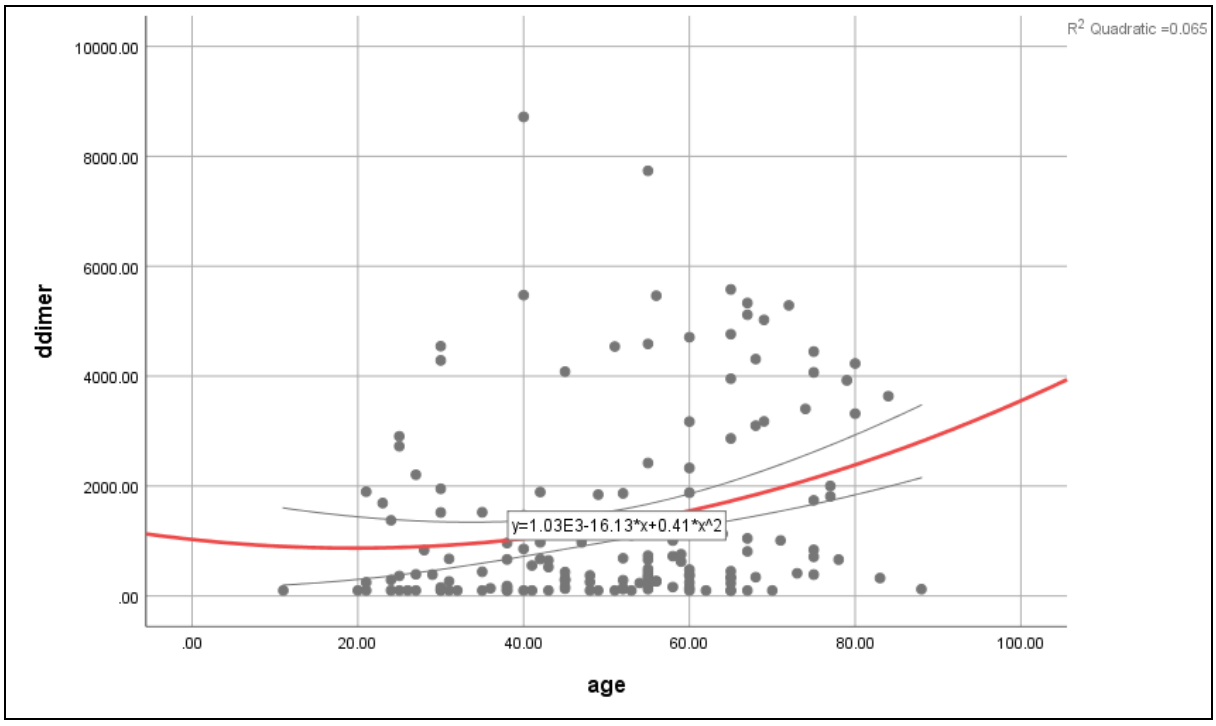

Figure 2: Age v/s D-dimer level scatter plot and quadratic trendline plotted in IBM-SPSS. Line is coloured in red and circles indicate plots.

The quadratic equation obtained is as follows: $y=0.41x^2-16.13x+1030$

Subset 2: Age of males and D-dimer level (females excluded)
Scatter plot and linear equation from MS-Excel 2016 is shown in figure 3 below.

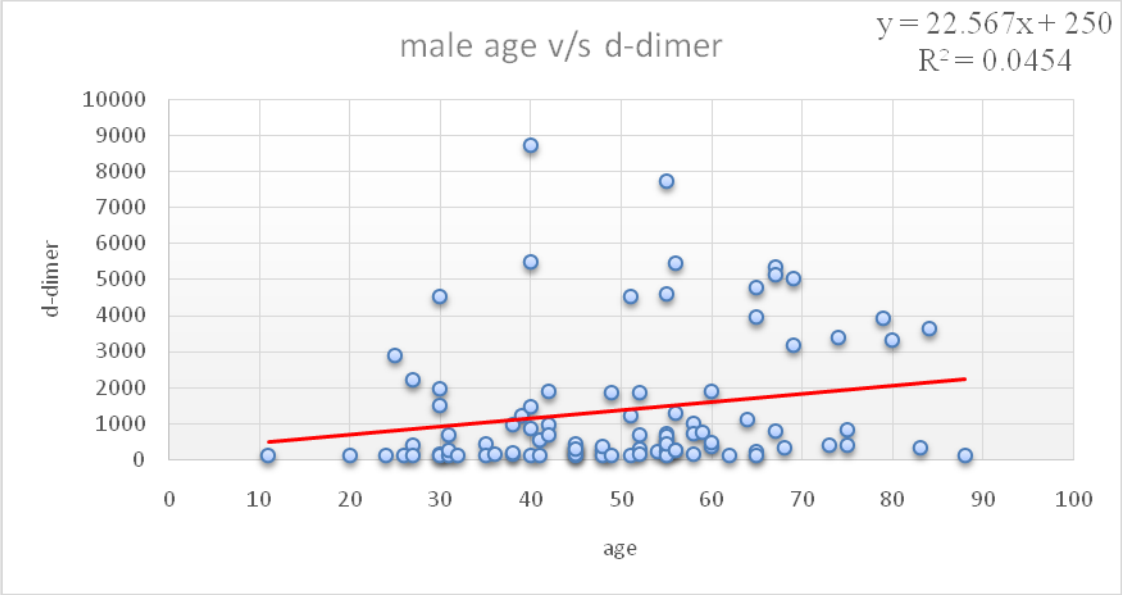

Figure 3: Age of males' v/s D-dimer level scatter plot and linear trendline plotted in MS-Excel 2016. Line is coloured in red and circles indicate plots.

Equation of line in second subset is *y = 22.567x + 250*where y is value of D-dimer in ng/ml and x is age is years. y-intercept is set at 250 to represent normal D-dimer level. The slope of line is positive and the coefficient of determination R^2 is 0.0454.
Using IBM-SPSS software, there was significant correlation between male age and D-dimer r(91) = 0.214 [p=0.039(<0.05)]. A cubic equation plot was drawn with age on x-axis and D-dimer level on y-axis at 95% mean confidence level (Figure 4).

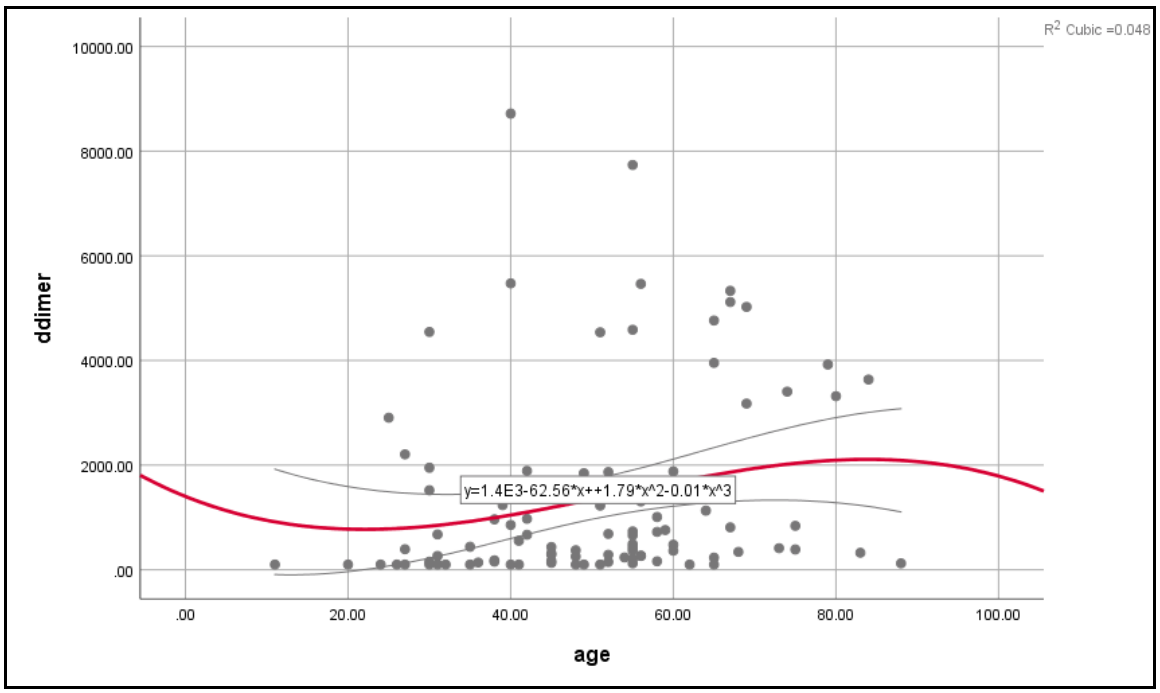

Figure 4: Male age v/s D-dimer level scatter plot and cubic trendline plotted in IBM-SPSS. Line is coloured in red and circles indicate plots.

The cubic equation obtained is as follows: $y=1400-62.56x+1.79x^2-0.01x^3$

Subset 3: Age of females and D-dimer levels (males excluded)
Scatter plot and linear equation from MS-Excel 2016 is shown in figure 5 below.

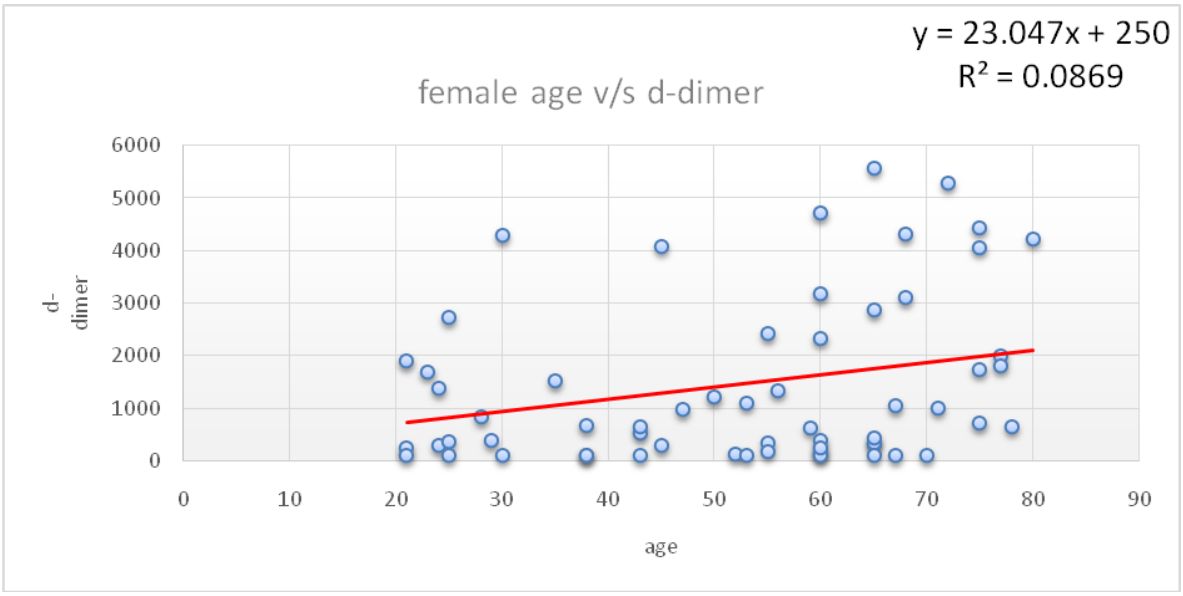

Figure 5: Female age v/s D-dimer level scatter plot and linear trendline plotted in MS-Excel 2016. Line is coloured in red and circles indicate plots.

Equation of line in third subset is $y = 23.047x + 250$where y is value of D-dimer in ng/ml and x is age is years. y-intercept is set at 250 to represent normal D-dimer level. The slope of line is positive and the coefficient of determination R^2 is 0.0869.
Using IBM-SPSS software, there was significant correlation between female age and D-dimer r (58) = 0.297 [p=0.021(<0.05)]. A quadratic equation plot was drawn with age on x-axis and D-dimer level on y-axis at 95% mean confidence level (Figure 6).

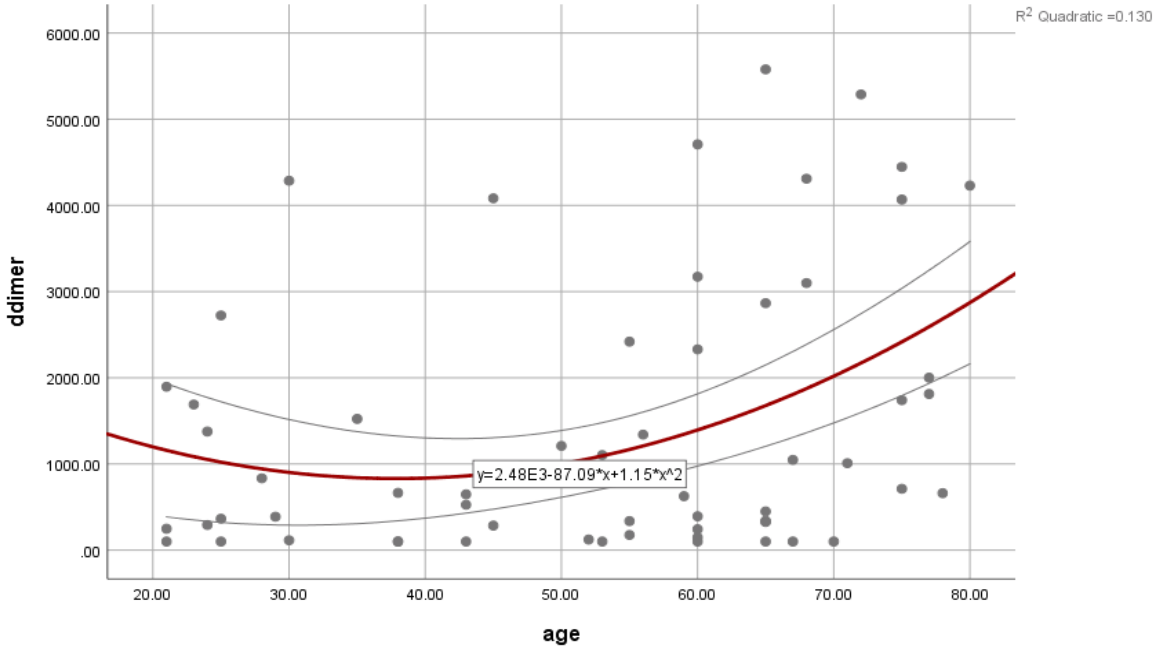

Figure 6: Female age v/s D-dimer level scatter plot and quadratic trendline plotted in IBM-SPSS. Line is coloured in red and circles indicate plots.

The quadratic equation obtained is as follows: $y=1.15x^2-87.09x+2480$

Subset 4: Age of pre-menopausal females and D-dimer levels (males and post-menopausal females excluded)
Scatter plot and linear equation from MS-Excel 2016 is shown in figure 7 below.

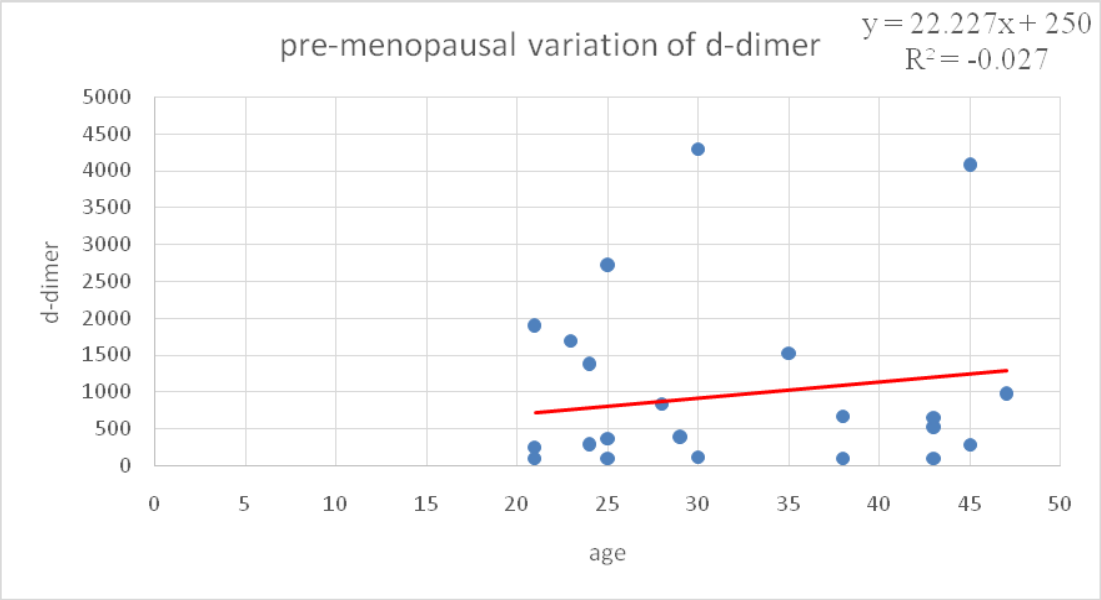

Figure 7: Pre-menopausal female age v/s D-dimer level scatter plot and linear trendline plotted in MS-Excel 2016. Line is coloured in red and circles indicate plots.

Equation of line in third subset is $y = 22.227x + 250$where y is value of D-dimer in ng/ml and x is age is years. y-intercept is set at 250 to represent normal D-dimer level. The slope of line is positive and the coefficient of determination R^2 is -0.027.
Using IBM-SPSS software, there was no significant correlation between pre-menopausal female age and D-dimer r (21) = 0.005 [p=0.982(>0.05)]. No plot was drawn for this subset.

Subset 5: Age of post-menopausal females and D-dimer levels (males and pre-menopausal females excluded)
Scatter plot and linear equation from MS-Excel 2016 is shown in figure 8 below.

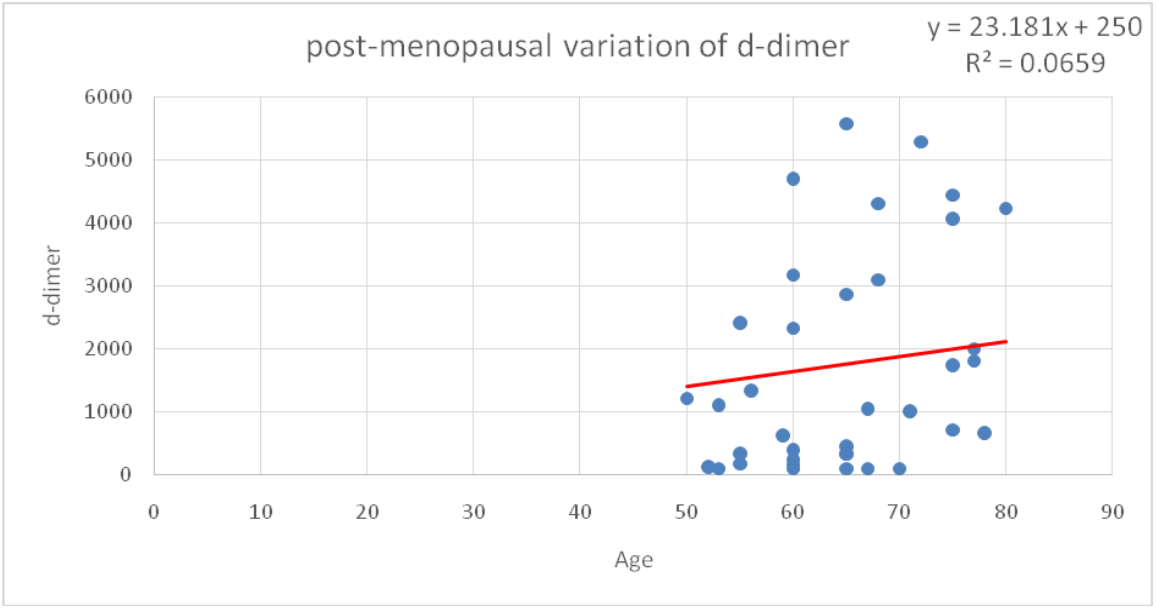

Figure 8: Post-menopausal female age v/s D-dimer level scatter plot and linear trendline plotted in MS-Excel 2016. Line is coloured in red and circles indicate plots.

Equation of line in third subset is $y = 23.181x + 250$where y is value of D-dimer in ng/ml and x is age is years. y-intercept is set at 250 to represent normal D-dimer level. The slope of line is positive and the coefficient of determination R^2 is 0.0659.

Using IBM-SPSS software, there was significant correlation between post-menopausal female age and D-dimer r (35) = 0.353 [p=0.032(<0.05)]. No plots were drawn for this subset.

DISCUSSION

The results obtained in subset 1, 2 and 3 in which there is significant co-relation between age and D-dimer level. The increase in d-dimer levels in COVID-19 patients is consistent with other studies. [7][3] Women are at a higher risk of developing thrombotic disorders than men as seen from results drawn by elevated D-dimer levels from table 1. Variation in d-dimer level with age in female is by a factor of 0.0869 and in male is by factor of 0.0454. Variation in d-dimer level after menopause is by factor of 0.0659 and in pre-menopausal women is by factor of -0.027. This negative value in pre-menopausal age group indicatesfactors which are absent in post-menopausal women. [11][12] This is also being depicted by data from the table. These factors need to be investigated further in the two age groups on a larger scale. We haven't co-related clinical condition and co-morbidities in our study and can be incorporated in future studies. Normal values of D-dimer and menopause age is variable [13] and therefore studies like this will need to use more extensive data to provide a more accurate prediction. Co-relation of most of the subsets proved to be significant and indicates towards more studies like these to be conducted. There might be factors present in pre-menopausal women protecting them from thrombotic disorders in general and progression in COVID-19 specifically. Such factors are absent in post-menopausal women and pregnant women [14] where there in variation in D-dimer level [15] with reported cases. The above hypothesis however needs further investigation.

CONCLUSION

From our study we conclude that women and older individuals are at a higher risk of developing thrombotic disorders in COVID-19 infection. Men are comparatively at a lower risk. Clinical co-relation is required to be incorporated in future. Factors in pre-menopausal women need to be investigated for their protective role. Studies like these are important to be conducted on a larger and more extensive scale to help in effective patient management and policy making.

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Conflict of interest: None.

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