Evaluation of variation of D-dimer levels in COVID-19 patients to predict the disease outcome in a hospital based study

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Abstract

Objectives: D-dimers is a sensitive indicator in COVID-19 patients. We aimed to determine the contribution of demographic factors (age and gender) toward an elevated d-dimer values, and to determine the probability of surviving in different age groups in COVID-19, with d-dimer > 0.5 μg/ml.

Methodology: A total of 193 patients were enrolled from COVID-19 isolation units of Hayatabad Medical Complex Peshawar, whose d-dimer levels were performed as per instructions of the treating physician and were followed. Relevant information's were recorded on a pre-designed performa prepared in accordance with the objectives of the study.

Results: Out of total 193 patients 152 (78.8%) were males and 41 (21.2%) females. 94(48.7%) patients were in the age range 35-55 y while 76(39.4%) patients had age more than 55 y. Regarding d-dimer readings, 162 (83.9%) had d-dimer levels more than 0.5 μg/ml. The mean with standard deviation of age of the patients was 52 ± 13 yrs. The mean with standard deviation of d-dimer values of the patients was 4.9 ± 13.3 μg/ml. It was observed that, the relative risk of deranged values of d-dimers was 1.18 *(rr = 1.18)* in patients with age > 55 yrs. Similarly, in female gender the relative risk of higher values of d-dimers above normal was 1.26 *(rr = 1.26)* without reaching a statistically significant p-value *(p = 0.48).* The probability of worse outcome in term of death was 2.06 times more in patients with d dimers > 0.5 μg/ml *(OR = 2.06).* Furthermore the probability of surviving was 90-100% by age ≤ 50 y, 80% in age range 51-60 y, 45% in age range 61-70 y and 30% at age ≥ 80 y.

Conclusion: The deranged d-dimer levels were noted in 84% of the COVID-19 patients. Age > 55 y and female gender are at higher risk of deranged d-dimers and further consequences. Survival rate of patients with deranged d-dimers drops to 30% in patients with age ≥ 80 y, 45% at age ≤ 70 y.

Key word: COVID-19, D-dimers, survival rate, prognostic values

1. Introduction

COVID-19 is pandemic respiratory infectious disease with unknown etiology, was first reported to the WHO office on 31st Dec 2019, from Wuhan, a metropolitan city in the province of Hubei China.[1] Case fatality rate of 2.3% has been reported from china that is lower than SARS (9.5%) , MERS (34.4%) and H7N9 (39%).[2]

Regarding the transmissibility of the COVID-19, the basic reproductive number (R0), which is a measure of the expected number of cases generated from one positive case, is 1.5-3 for SARS-CoV, compared to 1.5-5 for MERS-CoV.[3] The majority of the infected cases are asymptomatic. However, 20% of the cases develop viral pneumonia characterized by fever, cough shortness of breath, and acute lung injury, with an overall mortality rate of 2.3%.[4]

Since the early epidemic, the scientist suggested that the COVID-19 may directly has an impact on the cardiovascular system, either by increasing the mortality specially in patient with cardiac manifestations of COVID-19 has some association with cardiovascular complication most importantly causing venous throboembolism.[5]

Potentially the linkage of COVID-19 and venous thromboembolism is well described and reported by number of authors with significant alteration of the hematological parameters in corona infection. Some have described the association of these hematological abnormalities with an increase in the level of d-dimers in COVID-19.[6,7,8]

D-dimer on admission greater than 2.0 µg/mL (four-fold increase) could effectively predict in-hospital mortality in patients with Covid-19, which indicated D-dimer could be an early and helpful marker to improve management of Covid-19 patients.[9]

Yu B et al reported from China that there was a fold increase in hospital mortality associated with an increasing d-dimers level more than 1 µg/mL at time of admission.[10]

Present study was therefore designed with the objectives to,

1. Determine the variation of d-dimers in COVID-19.

2. Determine the contribution of demographic factors (age and gender) toward elevated d-dimers values.

3. Determine the probability of surviving in different age groups in COVID-19, with d-dimer > 0.5 µg/ml in a hospital based study.

2. Methodology

This cross-sectional study was conducted from 8th may to 2nd June 2020 in a tertiary care hospital of Peshawar. A total of 193 COVID-19 patients were included.

2.1. Population & Sampling

Assuming 4% prevalence of COVID-19 in general population from the study of Zhou X et al;8 a reference population of 100,000 patients was estimated to reside in the catchment area of our teaching hospital, Hayatabad Medical Complex Peshawar, Khyber Pakhtunkhwa, Pakistan. A sample size of 193 was calculated through Open-epi software, an online sample size calculator, with Absolute precision of 5%, confidence interval of 95%, and a drop out of 10%.

Only patients hospitalized with COVID-19 in isolation unit of HMC were included. Only covid-19 patients where d-dimers were advised by the treating consultant were included irrespective of age and gender.

Similarly those patients were observed for disease outcome in terms of satisfactory discharge or case fatality due to COVID-19.

COVID-19 patients where d-dimers were not advised were excluded. Similarly all patients with any type of symptoms came to emergency or outdoor patients department or even confirmed patients of COVID-19 in isolation department where d-dimers were not advised were also excluded.

The samples for laboratory testing were collected under aseptic techniques using venous blood 3 ml from hospitalized patients. D-dimer assays was performed with use of citrated, heparinized or EDTA plasma (Pathfast®, Tina-quant® (Roche, technology). D-dimer test was conducted on COBAS-511 (Roche Diagnostics), using particle-enhanced immunoturbidimetric assay (Tina-quant®). A value of < 0.5 µg/ml was taken as normal.

2.2. Ethical endorsement

Ethical endorsement was obtained from the institutional ethical review board of Post-Graduate Medical Institute, Hayatabad Medical Complex under notification No (316/HEC/B & PSC/2020 Dated 15th May 2020).

Prior informed consent was obtained from all suspects and they were assured of confidentiality.

For COVID confirmation, PCR results of the naso-pharyngeal swab duly reported in Public health research laboratory of the Hospital and also of the Khyber medical University (a designated Lab for PCR

of 2019nCoV by the Government of Khyber Pukhtunkhwa) were considered only.

2.3. Operational definitions

Child: Article 1 of The United Nations Convention on the Rights of the Child defines a child as "for the purposes of the present Convention, a child means every human being below the age of 18 yr unless under the law applicable to the child, majority is attained earlier".[11]

Adult: Young adult 19-35 yr, middle-aged adult 36-55 yr and older adult > 56 yr.[12]

2.4. Data analysis

Data was entered in SPSS 25th version and descriptive and correlation statistics were applied. Numerical variables like age of patients and d-dimer values were presented as Mean with standard deviation and range.

Correlation tests using spearman ranked correlation was used to determine the correlation of d-dimers with age and gender categories and disease outcome.

Chi-square test was used to show a relationship of the elevated d-dimers with age categories, gender groups and disease outcome in COVID-19 patients.

Relative risk analysis was done for risk estimation in age and gender groups and for case fatality with elevated d-dimers levels.

Kaplan Meir test was used for survival analysis to compare the mortality rate in COVID-19 patients under the influence of the elevated d-dimers levels

3. Results

The mean with standard deviation of age of the patients was 52 ± 13 yr. A minimum of 10 y with a maximum of 80 y of age was recorded with age range of 70 y. Mode of age was 55 yr. The mean with standard deviation of d-dimer values of the patients was 4.9 ± 13.3 µg/ml. The minimum of the recorded values was 0.04 to a maximum of 109 µg/ml. (Table 1)

Out of total 193 patients 152 (78.8%) were males and 41 (21.2%) females. 94 (48.7%) patients were in the age range 35-55 y while 76 (39.4%) patients had age more than 55 y. Regarding d-dimer readings, 162 (83.9%) had d-dimer levels more than 0.5 µg/ml. 161 (83.4%) of the patients were discharged satisfactorily.

Table 1: Descriptive Statistics

Value	D-dimer	Age
Number of patients	193	193
Mean	4.94	52
Median	1.60	54
Mode	0.70	55
Standard deviation	13.50	13
Range	109.00	70
Minimum	0.04	10
Maximum	109.00	80

We observed patients in isolation only whose d-dimer was advised and hence the death rate here (32 cases out of 193) does not reflect the mortality rate as we did not follow all positive cases, we followed only the COVID-19 cases who were advised d-dimers by the treating physician (Table 2).

We observed a significant difference in the levels of d-dimers in age groups. In patients with age > 55 yr the relative risk of higher values of d-dimers above normal was 1.18 *(rr = 1.18)* without reaching a statistically significant p-value *(p = 0.47)*. The relative risk values

Table 2:

Variables	Frequency	Percent
2.1. Gender		
Male	152	78.8
Female	41	21.2
Total	193	100.0
3.2. Age brackets		
< 18 yr	1	0.5
19-35 yr	22	11.4
36-55 yr	94	48.7
> 55 yr	76	39.4
Total	193	100.0
3.3. D-dimer categories		
< 0.5 µg/ml	31	16.1
> 0.5 µg/ml	162	83.9
Total	193	100.0
3.4. Disease outcome		
Discharged satisfactorily	161	83.4
Died	32	16.6
Total	193	100.0

Table 3: Inferential statistics for significance, correlation and relative risk of d-dimer values in COVID-19

3.1. D-dimer values and age factor in COVID-19

D-dimer (µg/ml)	Age categories		Total	Asymptotic Significance (2-sided)-Chi square test	Odds Ratio (OR)	Relative risk (rr)	Pearson Correlation(r)
	< 55 y	> 55 y					
< 0.5	17	14	31			Age > 55 y = 1.18	
> 0.5	100	62	162	p = 0.47	0.8	Age < 55 y = 0.8	0.06
Total	117	76	193				

3.2. D-dimer values and gender factor in COVID-19

D-dimer (µg/ml)	Gender		Total	Asymptotic Significance (2-sided)-Chi square test	Odds Ratio (OR)	Relative risk	Pearson Correlation
	Male	Female					
< 0.5	23	8	31			Females = 1.26	
> 0.5	129	33	162	p = 0.48	0.7		0.08
Total	152	41	193			Males = 0.9	

3.3. D-dimer values and Disease Outcome in COVID-19

D-dimer (µg/ml)	Disease Outcome		Total	Asymptotic Significance (2-sided)-Chi square test	Odds Ratio (OR)	Relative risk	Pearson Correlation
	Satisfactory	Died					
< 0.5	28	3	31			Died = 1.1	
> 0.5	133	29	162	p = 0.25	2.06	Discharged satisfactorily = 0.5	0.08
Total	161	32	193				

Table 4: Cross-tabulation of Dichotomous variables of age, d-dimer and disease outcome

| Age as dichotomous variable			D-dimer categories		Total	Death rate in patient with d-dimer > 0.5 µg/ml
			< 0.4 µg/ml	> 0.4 µg/ml		
< 55 y	Disease outcome	Satisfactory	16	86	102	44%
		Died	1	14	15	
	Total		17	100	117	
> 55 y	Disease outcome	Satisfactory	12	47	59	47%
		Died	2	15	17	
	Total		14	62	76	
Total	Disease outcome	Satisfactory	28	133	161	Overall 29/32 (91%)
		Died	3	29	32	
	Total		31	162	193	

above 1 indicates age > 55 yr as a risk factor in prognosis. When gender groups was analyzed for the

d-dimer values we observed that in female gender the relative risk of higher values of d-dimers above normal was 1.18 *(rr = 1.26)* without reaching a statistically significant p-value *(p = 0.48)*. The relative risk values above 1 indicates gender as a risk factor in prognosis.

We observed that the probability of worse outcome in term of death was 2.06 times more in patients with d-dimers > 0.5 µg/ml *(OR = 2.06)* with a relative risk of 1.1. (Table 3). It was noted that in patients with age < (14/32) 44% of 55 yr and d-dimers > 0.5 µg/ml the death rate was the highest.

We used Kaplan Meir test to calculate the median survival in COVID-19 patients in present study under

the influence of the d-dimer values. We observed that the probability of surviving was 90-100% by age ≤ 50 yr , 80% in age range 51-60 yr, 45% in age range 61-

70 yr and astonishingly the survival plot touched the line of 30% when the age of the patients was 80 yr or more (Figure-1).
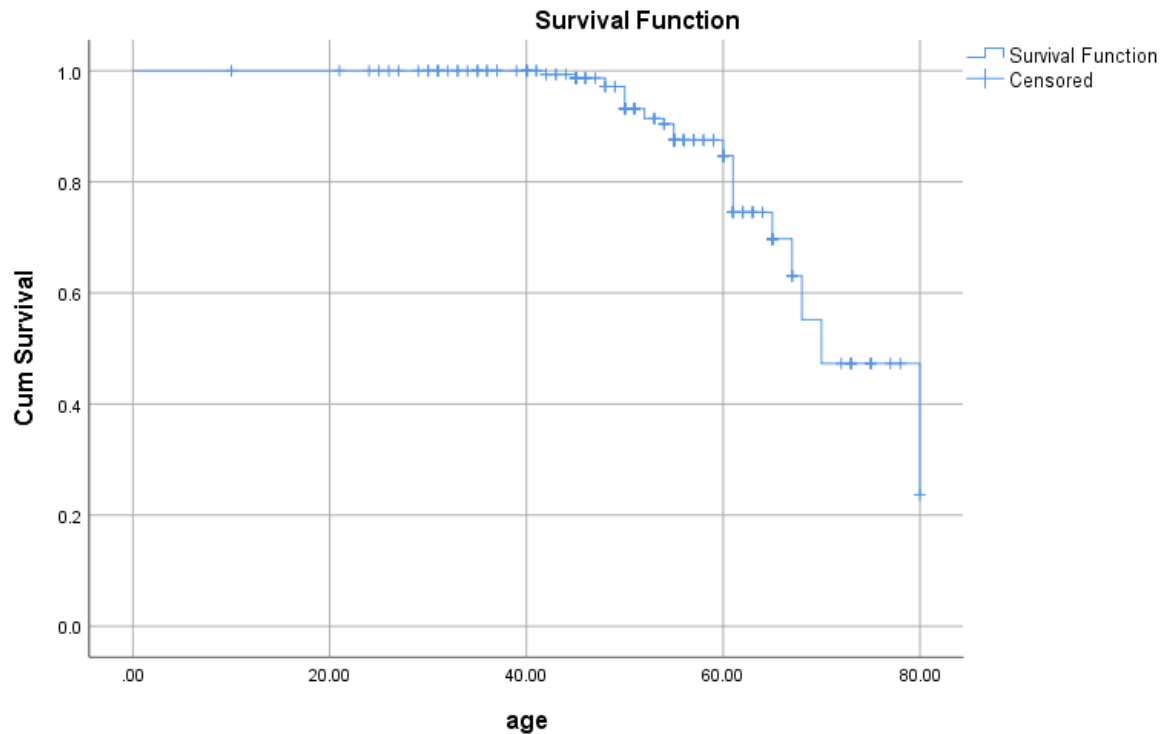
Figure 1: Survivability of COVID-19 patients plotted against age

4. Discussion

An elevated d-dimers in COVID-19 is the hallmark predictor of mortality and septic shock.[13] The prominent feature of the COVID-19 is the coagulopathy and prothrombotic stage with homeostatic derangement representing the major clinic-pathological manifestation of this deadly disease. The severity of the abnormality in the coagulation parameters in corona patients is associated with the severity of the disease and poor prognosis.[14]

The mean d-dimer values of the patients was 4.9 ± 13.3 µg/ml in present study. Our findings are higher than Garcia-Olivé I et al,[15] who reported Mean d-dimer levels as 1.16 on admission, and higher at 5.1 µg/ml in patients with suspicion of pulmonary embolism. We observed that the d-dimer readings, 162 (83.9%) had d-dimer levels more than 0.5 µg/ml. Zhou F et al[13] reported from a multi-centered cohort study from the mainland China that a higher level of d-dimers more than 0.5 µg/ml shows the severity of the disease while

the levels of d-dimers > 1 µg/ml at time of admission are associated with higher mortality in COVID-19.

In present study we noted a significant difference in the levels of d-dimers in age groups. In patients with age > 55 yr the relative risk of higher values of d-dimers above normal was 1.18 *(rr = 1.18)* without reaching a statistically significant p-value *(p = 0.47).* Similarly Survival rate of patients with deranged d-dimers drops to 30% in patients with age ≥ 80 yr and 45% at age ≤ 70 yr using Kaplan Meir test. Yao, Y et al.[16] concluded that age > 60 yr and high levels of d-dimers (more than 1 µg/ml) can help clinicians to identify the patients at risk of worse outcome in term of death.

Another study published in JAMA, reported that it would be more beneficial to use the age adjusted cut off values of the d-dimers for the specific populations specially in the scenario of COVID-19 and must be added as part of the national surveillance system for detection of corona cases as mortality and severity of

the disease increases with an increase in age of patients[17] that matches our findings.

We further noted that the total deaths, 29/32 (91%) were recorded in patients with d-dimers > 0.5 µg/ml, with (15/32) 47% in patients with age > 55 yr and d-dimers > 0.5 µg/ml.

The trial published in JAMA concluded that d-dimer levels of more than 2 µg/ml is the only trusted and reliable indicator/variable associated with increased odds (ten times higher probability) of case fatality in COVID-19 (OR = 10.7, p = 0.04).[17] CDC report from China showed 80% of the causalities (deaths) due to COVID-19 were in the adults aged > 60 yr as compared to 0.1% in person aged < 19 yr.[9] Similarly Italy is the second mostly affected country in the world, with more than 80000 cases of SARS-CoV infection. They reported a higher mortality in aged people as compared to younger population that identifies an immunity gap.[18] An elevation of d-dimers indicates the activation of fibrinolytic process and is of diagnostic and prognostic values in COVID-19 patients.[19]

5. Conclusion

We concluded that the deranged d-dimers levels were observed in 84% of the COVID-19 patients. Age > 55 yr and female gender are at higher risk of deranged d-dimers and further consequences. Survival rate of patients with deranged d-dimers drops to 30% in patients with age $\geq$ 80 yr and 45% at age $\leq$ 70 yr.

Therefore despite the difference in opinion of the scientist the present pooled analysis of the so for available data shows that a higher d-dimer level indicates a higher risk of mortality due to COVID-19. It is therefore suggested on the basis of the findings that an early advising d-dimer levels in COVID-19 patients which is a rapid test, non expensive, accessible and affordable, can be of significant help with better satisfaction of the clinicians working on the management of COVID-19 patients.

6. Conflict of interest

None declared by the authors

7. Authors' contribution

SK- Data Collection, conduct of Study, critical review, concept

HK- Data analysis, writing the manuscript, concept, critical review

SK- Data Collection, conduct of study

MA- Data analysis, manuscript writing

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