

## FDP and D-Dimer in Patients of H1N1 Pneumonia: Association with Hypoxia and Mortality?

Dr. Aradhna Singh<sup>1</sup>, Dr. Laxmi Kant Goyal<sup>2\*</sup>, Dr. Sujata Agrawal<sup>3</sup>, Dr. Kamlesh Sharma<sup>4</sup>, Dr. Debajyoti Maji<sup>5</sup>, Dr. Komal Jangir<sup>6</sup>

<sup>1</sup>Assistant Professor, Department of Medicine, SMS Medical College, Jaipur India

<sup>2</sup>Assistant Professor, Geriatric Medicine SMS Medical College, Jaipur India

<sup>3</sup>Assistant Professor, Department of Medicine, SMS Medical College, Jaipur India

<sup>4</sup>Assistant Professor, Department of Medicine, SMS Medical College, Jaipur India

<sup>5</sup>Senior Resident, Department of Medicine, SMS Medical College, Jaipur India

<sup>6</sup>Senior Resident, Department of Medicine, SMS Medical College, Jaipur India

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#### \*Corresponding author

Dr. Laxmi Kant Goyal

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**Abstract:** Influenza an infection has been found to be associated with disseminated intravascular coagulation (DIC) and pulmonary micro embolism. This study assesses marker of thrombus formation (FDP, D-dimer levels) in H1N1 patients and their association with morbidity (hypoxia) and mortality. The preliminary data of an ongoing, analytical, case-control study among H1N1 infected are presented. Twenty H1N1 infected patient having radiographic evidence of pneumonia, having age >18 years and less than 60 years were included in this study, after taking informed consent (the case). Twenty age and sex matched were also included in this study that had bilateral pneumonia, but were H1N1 negative (the control). The patients who had heart disease, cerebro-vascular diseases, haemorrhagic disorder, coagulation disorder, diabetes, hypertension, received injection recently, hepatic disorder, malignancy, recent surgery or infections other than H1N1 were excluded. Pregnant females were also excluded from this study. The nasopharyngeal-swab specimens were collected from each study participants at the time of hospitalization and analysed by of a real-time reverse-transcriptase-polymerase- chain-reaction (RT-PCR) assay. The venous blood samples were taken for FDP and D-dimer at same time. Among the 20 cases, 13/20 were FDP positive, and 5/20 controls were FDP positive (P<0.05). Hypoxia was higher in cases (17/20) as compared to controls (7/20) (P<0.05). FDP positivity was associated with significantly higher frequency of hypoxia (15/20) and high mortality (10/20) (P<0.05 for each). D-dimer positivity was associated with significantly higher frequency of hypoxia (15/20) and high mortality (10/20) (P<0.05 for each). D-dimer/FDP positivity was associated with significantly higher frequency of hypoxia and high mortality in H1N1 infected patients.

**Keywords:** H1N1 Flu, D-dimer, FDP, Thrombus, Mortality.

## INTRODUCTION

Influenza a (H1N1) has become world-wide now, since its initial spread from Mexico in 2009[1]. Various studies had reported that the most common population affected by H1N1 is young population, and the most common cause of death is pneumonia, ARDS with rapidly developing hypoxic respiratory failure [2-4].

Influenza A infection has been found to be associated with disseminated intravascular coagulation (DIC) and pulmonary micro embolism [5,6]. Similarly, in cases of H1N1 influenza ("swine flu"), both thrombotic and haemorrhagic complications are noticed, including deep venous thrombosis, pulmonary embolism, and pulmonary haemorrhage [6-16].

The hall mark of H1N1 Pneumonia-ARDS is widespread inflammation of lung parenchyma. It may be postulated that this wide-spread lung inflammation damages the endothelial cells, and the affected endothelial cells becomes activated, and therefore, synthesize and secretes tissue plasminogen activator and other mediators, which are responsible for micro-thrombus formation in lungs, leading to ARDS and respiratory failure [17-19].

This study was carried out to assess marker of thrombus formation (FDP, D-dimer levels) in H1N1 patients and their association with morbidity (hypoxia) and mortality.

**MATERIALS AND METHODS**

This study is an ongoing, analytical, case-control study, being conducted at a tertiary care Medical College hospital among H1N1 infected patients, after due approval from institutional ethics committee. The preliminary data of only 20 H1N1 infected patients are being reported here. The presented data are of only three month duration. H1N1 infected patient having radiographic evidence of pneumonia, having age >18 years and less than 60 years were included in this study, after taking informed consent (the case). Twenty age and sex matched were also included in this study that had bilateral pneumonia, but were H1N1 negative (the control).

The patients who had heart disease, cerebrovascular diseases, haemorrhagic disorder, coagulation disorder, diabetes, hypertension, received injection recently, hepatic disorder, malignancy, recent surgery or infections other than H1N1 were excluded. Pregnant females were also excluded from this study.

The nasopharyngeal-swab specimens were collected from each study participants at the time of hospitalization, and the collected specimens were transported to the institutional laboratory within 6 hours, in a transport medium, keeping 2-4°C temperature. The specimens were analysed by of a real-time reverse-transcriptase-polymerase- chain-reaction (RT-PCR) assay.

The venous blood samples were collected from left antecubital vein for complete blood count, random blood sugar, renal function test, and liver function test,

FDP, D-dimer, PT-INR and LDH from all study participants at the time of hospitalization. Arterial blood gas analysis (ABG) was also performed at the same time.

**STATISTICAL ANALYSIS**

Microsoft Excel® and SPSS® 17.0 for Windows® were used for data storage and analysis. Continuous variables were expressed as mean ± standard deviation. Student’s t test and Chi-Square test were used to determine statistical difference between variables. Statistical significance was set at P value ≤ 0.05.

**RESULTS**

The male: female ratio in case group was 1:1, while in control group, it was 2:3. The age of cases was 42±11.06 years (range 23-60 years), and controls was 43.85±10.41years (22-60 years). The cases and controls were age-sex matched (P>0.05).Among the cases, 13/20 were FDP positive, and 5/20 controls were FDP positive (P<0.05). Hypoxia was higher in cases (17/20) as compared to controls (7/20) (P<0.05). The mean levels of LDH and PT-INR were higher in H1N1 positive cases, while mean SpO2 was lower. (P<0.05 for each). (Table No.1)

FDP positivity was associated with significantly higher frequency of hypoxia (15/20) and high mortality (10/20) (P<0.05 for each). (Table No.2)

D-dimer positivity was associated with significantly higher frequency of hypoxia (15/20) and high mortality (10/20) (P<0.05 for each). (Table No.3).

**Table-1: Characteristics of study participants**

	H1N1 Positive (n 20)	H1N1 Negative (n 20)	p	Sig
M:F	10 :10	8:12	0.751	NS
Age (Years)	42±11.06	43.85±10.41	0.589	NS
FDP positivity (n)	13	5	0.025	Sig
D-dimer positivity (n)	13	5	0.025	Sig
Hypoxia (n)	17	7	0.003	Sig
Mortality(n)	12	2	0.002	Sig
SpO2 (mean±sd)	73.60±14.28	93.10±06.47	0.001	Sig
LDH (mean±sd)	875.3±377.2	450.3±211.2	0.001	Sig
PT-INR (mean±sd)	1.9± 1.744	1.1±1.309	>0.05	Sig

**Table-2: FDP and morbidity/mortality among study participants**

	FDP positive	FDP negative	P	Sig
Hypoxia	15	9	0.01	Sig
Mortality	10	4	0.039	Sig

**Table-3: D-dimer and morbidity/mortality among study participants**

	D-dimer positive	D-dimer negative	P	Sig
Hypoxia	15	9	0.01	Sig
Mortality	10	4	0.039	Sig

## DISCUSSION

The preliminary results of an ongoing study are being presented in the article. In this study, we found higher mortality in H1N1 positive cases as compared to H1N1 negative controls of bilateral pneumonia with ARDS.

The FDP positivity and hypoxia were observed in significantly higher number in H1N1 positive cases, indicating role of H1N1 pneumonia in hypoxia and FDP d-Dimer positivity. LDH levels were also raised in H1N1 positive cases with is in echo with a previous report [20].

D-dimer and FDP positivity was associated with significantly higher frequency of hypoxia (15/20) and high mortality (10/20). A study from Mexico also revealed higher d-Dimer/FDP positivity among H1N1 cases who died[21]. In a study, there were 10/12 deaths caused by H1N1 which had higher D-dimer levels, which is similar to our study. So it can be stated that the disease course is indirectly determined by the increased D-dimer via its effect of hypoxia (SpO<sub>2</sub>)[1].

The findings of hypoxia along with prolong PT-INR and positive FDP/D-dimer raise the possibility that disseminated intravascular coagulation and/or pulmonary embolism may have played a role in the pathogenesis. The same observations were also made in a previous study[20].

The negative correlation between oxygenation index and D-dimer of H1N1 positive patients was found in one study, indicating the importance of D-dimer in predicting respiratory failure[1]. The possible explanation of association between D-dimer positivity and respiratory failure (hypoxia) may be formation of pulmonary microthrombus[1].

The mechanism of thrombus formation is a complex phenomenon, consisting of three chief elements, namely primary haemostasis, secondary haemostasis/coagulation, and fibrinolysis.<sup>22</sup> The fibrinolysis is initiated by tissue plasminogen activator, along with other mediators after their synthesis, and release from endothelial cells. The tissue plasminogen activator, along with other mediators, collectively converts plasminogen to plasmin, which hydrolyses polymerized fibrin strands into soluble fibrin degradation products and degrades the fibrin clot, which results in formation of fibrin degradation products (FDP)[23].

In this study all the possible causes of raised D-dimer were excluded such as heart disease, cerebrovascular diseases, haemorrhagic disorder, infections other than H1N1, coagulation disorder, diabetes, hypertension, any recent injection, hepatic disorder, malignancy, recent surgery or pregnancy. Thus, the only possibility of raised D-dimer and FDP is thrombus

formation. In Mexican studies, pulmonary embolism was found in patients of H1N1 positive pneumonia [24-25]. The pulmonary thrombi also explain the hypoxia and respiratory failure. There are various studies supporting this notion and evaluating acute infection as a risk factor for thrombosis [26-28]. Various infection are documented as a risk factor for thrombosis [17-19, 29].

## LIMITATIONS

Our study had some limitations. We included patients with radiographic evidence of bilateral Pneumonia only, and not included H1N1 positive patient without radiographic evidence of Pneumonia. So whether our findings can be extrapolated to those H1N1 positive cases without pneumonia is debatable. We have not estimated levels of FDP and D-dimer quantitatively, and thus, have not measured correlation of these with hypoxia. This study was done at a tertiary care centre, and recruited admitted patients only, resulting in a limited sample size, thus the nature of the investigation and the results do not imply a general case, and further studies with a larger sample size are needed.

## CONCLUSION

This study showed that H1N1 positivity and D-dimer/FDP positivity was associated with significantly higher frequency of hypoxia and high mortality.

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