Mortality in H1N1: A comparison of patient attributes in outbreaks due to *A/California/7/2009* and *A/Michigan/45/2015* strains

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Abstract

Introduction: The resurgence of epidemic of Influenza A (H1N1) pdm 09 was phenomenal in 2015 and has become an annual phenomenon. Antigenic drift and reassortment is the rule rather than exception, conferring survival benefit to the virus. As this disease has high mortality, we compared the clinico-epidemiological profile of patients expired in the year 2015 due to "A/California/7/2009" strain with those of expired in the year 2018 due to "A/Michigan/45/2015" strain.

Material and Method: We collected data of all expired patients in our institute in the year 2015 from 1st January to 30th may as well as 2018 in the same time period. The data of 116 patients who expired in 2015 due to "A/California/7/2009" H1N1 strain were compared with similar data of 30 patients expired in 2018 due to "A/Michigan/45/2015" strain of H1N1. Patients of pneumonia, having age >18 years, positive for H1N1by real-time reverse-transcriptase–polymerase- chain-reaction (RT-PCR) and died in our hospital were included in this study. Clinical features and laboratory data were obtained from the hospital records of the patients. Data analysis was done using SPSS software.

Result: In 2015 total number of hospitalized patients due to "A/California/7/2009" strain were 571 and 116(20.31%) out of them died, in 2018 those due to "A/Michigan/45/2015" total admission were 177 and 30(16.94%) out of them died (p-0.032). Though it was not statistically significant but it is lesser than in 2015 despite the fact that more patients with co morbidities were affected in 2018.

Duration in ICU was significantly longer in 2018(MS) group [5(1-7)] compared to 2015 (CS) group [3(1-17)] with p value of 0.017 (i.e. < 0.05). But both groups were not different in terms of duration on mechanical ventilator. (p-0.257).

The 2015 (CS) group had 74.1% with other co-morbidities versus 96.7% of those in 2018 (MS) group (p- 0.015). This implies that the mortality with "A/Michigan/45/2015" infection was mainly seen in the patients who already had one or more co-morbidities unlike "A/California/7/2009" infection.

The 2018 (MS) group had significantly higher proportion (60%) of patients with acute kidney injury compared to 34.5% in 2015(CS) (p-0.019). 50% of dead patients in 2018(MS) had anemia compared to 11.2% in 2015(CS) (p<0.001). Deranged liver function test was seen in 46.7% patients in 2018(MS) compared to only 15.5% patients in 2014(CS) (p<0.001).

The only reverse trend was shown in case of diabetes, A/California/7/2009 strain affected 27% diabetics compared with 6.7% affected by A/Michigan/45/2015 strain (p=0.030) (Table 5).

Conclusion: The study showed that though "A/Michigan/45/2015" affected higher number of patients with co morbidities compared to "A/California/7/2009" but had slightly lesser mortality.

Introduction

The year 2009 witnessed a sudden upsurge in the Influenza A (H1N1) case which started in Mexico in 2009[2] and managed to spread across most part of the world within short span of time leading to significant mortality and morbidity over the years. A similar outbreak occurred in 2015 in western parts of India due to Influenza A(H1N1) Pdm09 ,claiming many lives.

After a quiescence of 2-3 years, in 2018 there was again a rise in H1N1 cases. Meanwhile, the Indian Council of Medical Research (ICMR) bulletin[3] has stated that a new strain of novel human influenza virus (H1N1) "A/Michigan/45/2015" also called Michigan strain(MS) was circulating in India since September 2016. As compared to the previous strain "A/California/7/2009" (CS) which was in circulation since 2009.[3]

As India is the most densely populated country of the world, it is notorious for its reputation for rapid spread of various communicable diseases. The double whammy being the new strain of H1N1 "A/Michigan/45/2015" is reported to be active in summer season also unlike the previous one "A/California/7/2009".[3] As Indian climate ranges from tropical in the southern part to temperate in north and alpine in Himalayas, we get prolonged heat wave and summer season, this was previously considered season of quiescence for influenza virus related illnesses. Many studies have confirmed that the most common population affected by H1N1 was young people, and the cause of death in majority of them was pneumonia, ARDS along with rapidly developing hypoxic respiratory failure.[4-5]

This study was carried out to compare the clinico epidemiological profile of patients expired in 2015(CS) with those of 2018(MS), in a tertiary care hospital of north India i.e. Sawai Mansingh Hospital, Jaipur.

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Table 1: Factors associated with swine flu deaths during 2015 and 2018

Variable	Subgroup	2015	2018	P value
Age (years)	Mean ± SD	42.38 ± 15.03	44.17 ± 17.07	0.606
Gender	Female	68 (58.6%)	11 (36.7%)	0.052
	Male	48 (41.4%)	19 (63.3%)	
Time lag between symptoms onset and hospitalization	Median (range) days	5 (1 – 30)	6.5 (6.5 – 30)	0.244
Time lag between symptoms onset and oseltamivir	Median (range) days	5 (0 – 30)	6.5 (2 – 30)	0.156
Duration of Hospitalization	Median (range) days	4 (<1 – 22)	6 (<1 – 18)	0.126
Duration of ICU stay	Median (range) days	3 (0 – 21)	5 (1 – 17)	0.017 (S)
Duration on ventilator	Median (range) days	2 (<1 – 16)	3 (<1 – 12)	0.257
Pregnancy/ postpartum/ IUD	N (%)	22 (19%)	8 (26.7%)	0.498
ARDS	N (%)	65 (56%)	10 (33.3%)	0.092
Lung involvement (%)	Median (range) days	60 (10 – 100%)	50 (20 – 70%)	0.198

Material and Methods

This cross sectional and analytical study was conducted at a tertiary care Medical College Hospital among swine influenza H1N1 positive patients. We collected exhaustive data of all expired patients in our institute in the year 2015 from 1st January to 30th may as well as 2018 in the same time period. The data of 116 patients who expired in 2015 due to "A/California/7/2009" H1N1 strain were compared with similar data of 30 patients expired in 2018 due to "A/Michigan/45/2015" strain of H1N1. The presented data was collected over four year duration. All patients with radiographic evidence of pneumonia, having age >18 years, positive for H1N1by RT-PCR and died in our hospital were included in this study.

During the H1N1 outbreak the nasopharyngeal-swab samples were collected from all study subjects at the time of hospitalization and were subjected to analysis by RT-PCR assay.

Radiography, hematology and routine biochemistry serum examination were performed in all the patients. Other specific investigation e.g. ABG, serum sodium, 2-D echocardiography, abdominal ultrasound were performed as indicated on the discretion of the clinician. Incomplete record was excluded from the study.

Statistical Analysis

Microsoft Excel® and SPSS® 17.0 for Windows® was used for data storage and analysis. The continuous variables were expressed as mean ± standard deviation. Student's t test and chi-Square test were applied to determine statistical difference between variables. Statistical significance was set at P value ≤ 0.05. P value of ≤ 0.005 was labeled as highly significant

Results

The patients died during 2015 epidemic were assigned 2015 (CS) group while the patients died during 2018 were assigned 2018(MS) group.

The age distribution of the expired patients were similar 42.34 ± 15.03 in 2015 (CS) group± and 44.17± 17.7 in 2018 (MS) group with p value of 0.606. Gender distribution was also similar with 58.6% females in 2015(CS) versus 36.7% in 2018(MS) (Table 1).

In 2015 total number of hospitalized patients due to H1N1were 571 and 116(20.31%) out of them died, likewise in 2018 total admission were 177 and 30(16.94%) out of them died (p=0.032). Though it was not statistically significant but it is lesser than in 2015 despite the fact that more patients with co morbidities were affected in 2018.

Time lag between onset of symptoms and hospitalization had median and range of 5 days (1-30) in 2015(CS) versus 6.5 days (6.5-30) in 2018(MS) group. Its P value was non-significant (0.244) (Table 1).

Time lag between onset of symptom and initiation of Oseltamivir was also similar in both the groups (p=0.156) (Table 1).

Duration in ICU was significantly longer in MS group [5(1-7)] compared to CS group [3(1-17)] with p value of 0.017 (i.e. < 0.05). But both groups were not different in terms of duration on mechanical ventilator which had p=0.257 (Table 1).

Pregnancy and post-partum patents presented in comparable number in both CS and MS group (p=0.498).[10]

ARDS was present in 65 (56%) patients in 2015 (CS) group compared to 10 (33.3%) patients in 2018 (MS) group.

Table 2: Severity at presentation among H1N1 deaths

Severity at presentation*	2015		2018	
	N	%	N	%
Category B	5	4.3	0	100
Category C	109	94.0	30	0
Total	116	100	30	100

Chi-square = 0.369 with 1 degree of freedom; P = 0.544 (S); *None of the deaths had Category A at presentation

This was not significant statistically. (p=0.092). Lung involvement was also similar in both the groups (p=0.198) (Table 1).

Time lag between hospitalization and death i.e. duration of hospitalization was also comparable between both the groups (Table 1).

Severity of disease as per Ministry of Health and Family Welfare, clinical categorization [6] at presentation among patients who died was similar illness in 2015(CS) (cat-B 4.3%, cat-C 94.0%) and 2018(MS) (cat-B 5%, cat-C 100%) with p value 0.544(NS). None of the expired patients in either group had category A clinical status on presentation (Table.2). This may be due to the fact that we studied hospitalized patients only and category A patients don't require hospitalization.

It was observed that 83.6% patients were admitted in ICU at the time of death in 2015(CS) compared to 100% in 2018 (MS) which is statically significant with P value of <0.05 % (Table 3).

The 2015(CS) group had 74.1% with other co-morbidities versus 96.7% of those in 2018(MS) group which was statistically significant with p value of 0.015. This implies that the mortality with "A/Michigan/45/2015" infection was mainly seen in the patients who already had one or more co-morbidities unlike "A/California/7/2009" which fatally infected the relatively healthy population (Table 4).

Another significant observation was that A/California/7/2009 affected 27% diabetics compared with 6.7% affected by A/Michigan/45/2015(p=0.030) (Table 5).

The 2018 (MS) group had significantly higher proportion (60%) of patients with acute kidney injury compared to 34.5% in 2015 (CS) p=0.019. 50% of dead patients in 2018 (MS) had anemia compared to 11.2% in 2015 (CS). This was highly significant (p<0.001). Deranged liver function test was seen in 46.7% patients in 2018 (MS) compared

Table 3: ICU admission among study subjects

ICU admission	2015		2018	
	N	%	N	%
Yes	97	83.6	30	100
No	19	16.4	0	0
Total	116	100	30	100

Chi-square = 4.295 with 1 degree of freedom; P = 0.038 (S)

to only 15.5% patients in 2014 (CS) (p<0.001).

The most common complications and causes of death among the expired patients were septicemia, acute respiratory distress syndrome (ARDS) and shock (Figure 1). The latter two were not different among both the groups but septicemia was found in 56% of 2015(CS) group compared to 33.3% in 2018 (MS) group. P=0.044 (Table 4).

Discussion

The result of the cross sectional analytical study is being presented in this study. From 2009 till early 2016 the strain of H1N1 that was circulating all over the world was "A/California/7/2009" strain[4,5,7], since the CDC confirmed the first case of "A/Michigan/45/2015",[8] there are confirmation from various bodies regarding the change in strain of H1N1.[9] Diversity of antigenic mutations of influenza A(H1N1)pdm09 is confirmed in various studies.[11]

We did a head to head comparison of demographic, clinical and laboratory data of patients who have expired in 2015 outbreak (1st January to 30th May) in our institute probably due to "A/California/7/2009" strain (number of patients expired in 2015 -116) with those expired in 2018(1st January to 30th May) presumably due to "A/Michigan/45/2015" strain (number of patients expired in 2018-30). The preliminary results of this study are presented here.

We found the study subjects had similar age and gender distribution implying that both outbreaks affected similar population.

Time lag between onset of symptoms and hospitalization as well as between hospitalization and death was also comparable in both the groups, suggesting similar behavior of both strains of virus. The time lag between onset of symptoms and start of antiviral Oseltamivir was similar in both CS and MS group. Though the duration of ICU stay was found to be more in MS group (p<0.05), but the duration of patient on ventilator was akin. This may be explained as 2015(CS) patients were more sick and died early after admission to ICU.

Table 4: Co-morbidities among H1N1 subjects

Co-morbidities	2015 (N=116)		2018 (N=30)		P value
	N	%	N	%	
Hypothyroidism	3	2.6	1	3.3	0.686
CAD	5	4.3	1	3.3	0.783
RHD	2	1.7	1	3.3	0.866
SABE	2	1.7	0	0.0	0.875
CCF	7	6.0	3	10.0	0.718
Hypertension	12	10.3	4	13.3	0.889
Diabetes	32	27.6	2	6.7	0.030 (S)
Asthma	0	0.0	1	3.3	0.465
COPD	12	10.3	5	16.7	0.520
K chest	11	9.5	4	13.3	0.778
ILD	1	0.9	1	3.3	0.875
Liver disease	1	0.9	0	0.0	0.465
Deranged LFT	18	15.5	14	46.7	<0.001 (S)
CKD	9	7.8	0	0.0	0.280
AKI	40	34.5	18	60.0	0.019 (S)
Pregnancy/ Postpartum/IUD	22	19.0	8	26.7	0.498
Obesity	2	1.7	1	3.3	0.866
Anaemia	13	11.2	15	50.0	<0.001 (S)
Any one or more co-morbidity	86	74.1	29	96.7	0.015 (S)

It was observed that the case fatality characteristics were similar in respect to severity of disease as most of expired patients were of category C (94.0% in 2015 and 100% in 2018) and some were of category B (4.3% in 2015 and 5% in 2018).

It was observed that none of the dead patients had category A on presentation reinforcing the previous conviction that category A patients can be managed at home to prevent them from spreading the disease as much as possible.[6]

Lesser percentage (83.6%) of patients expired in ICU in 2015 compared to 2018 (100%) with p value <0.05%, implying ICU care could not be offered to some seriously ill patients. This happened as overwhelmingly large population of patients were affected with H1N1 pneumonia in 2015 causing large scale influx of patient in our hospital.

Table 5: Complications among H1N1 deaths

Complication	2015 (N=116)		2018 (N=30)		P value
	N	%	N	%	
Septicemia	65	56.0	10	33.3	0.044
ARDS	83	71.6	16	53.3	0.092
Shock	36	31.0	11	36.7	0.712

The most interesting observation of this study was that the patients expired in 2015(CS) had lesser co morbidities compared to those of 2018(MS), (p= 0.015). This means that the "A/California/7/2009" attacked healthier population causing greater devastation compared to "A/Michigan/45/2015".

Talking of individual complication, 60% of 2018(MS) group had acute kidney injury compared to 34.5% 2015 (CS) group (p value-0.019). This implies that newer stains has higher affinity to renal tissue. However the type of renal injury could not be established due to lack of autopsy data.

50% of expired patients of 2018 (MS) group had anemia compared to only 11.2% of 2015(CS) group, (ph-<0.001), so were deranged liver function i.e. 46.7% in 2018 versus 15.5% in 2015.

Type 2 diabetes mellitus was the only co morbidity showing significant inverse trend, 2015(CS) group had 27.6% versus only 6.7% in 2018 (MS) (p-0.03).

Septicemia, ARDS and shock were overall the most common cause of death, but septicemia was more prevalent (56%) in 2015 (CS) group compared to (33.3%) 2018(MS) group.

During literature search the authors could not find any other study where head to head comparison between the clinical virulence of two strains of swine flu was done. This could be considered as a first of its kind study.

Limitations

Our study had some limitations. As the study was done at a tertiary care centre and we recruited only admitted patients. Thus the nature of the comparison and the results may not reflect the trends in general population. As this was a cross sectional study temporality could not be established between some parameters like LFT and AKI.

Another limitation was that due to lack of resources to isolate the virus the

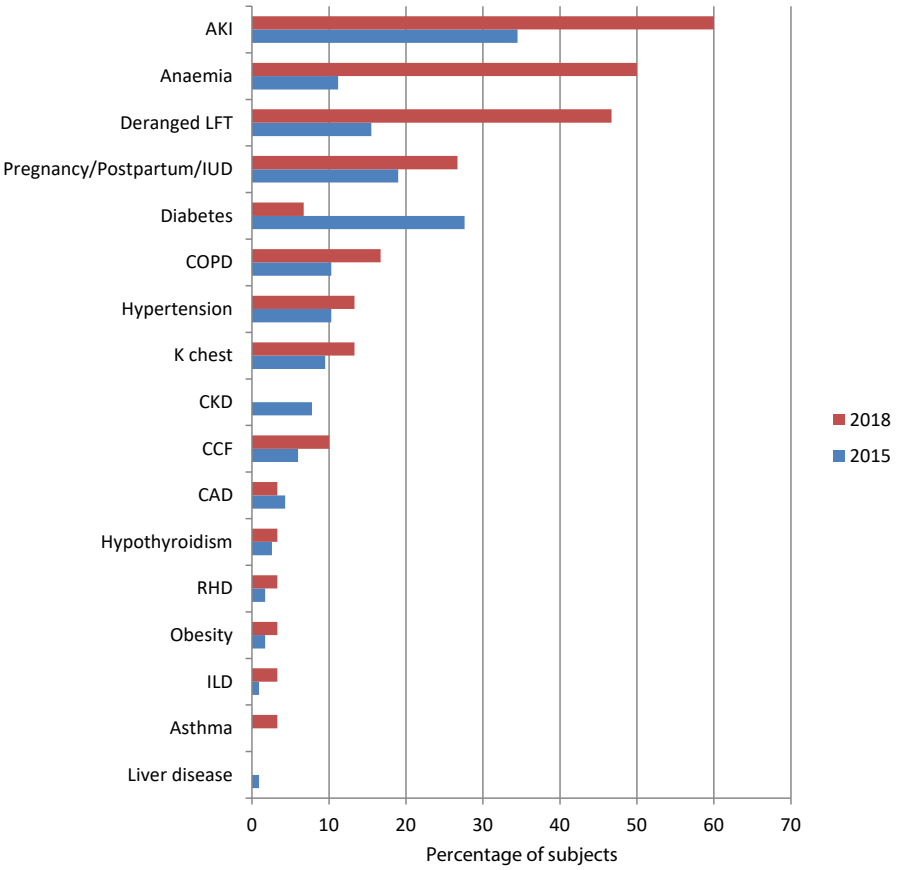

Fig. 1: Complications among patients who expired due to H1N1 infection

presence of Michigan stain could not be established specifically in our patients. The presence of Michigan stain was presumed as it was demonstrated from other samples from across the country in reference laboratory.

Conclusion

The study showed that though "A/Michigan/45/2015" affected higher number of patients with co morbidities compared to "A/California/7/2009" but had slightly lesser mortality.

References

1. The 2009 H1N1 Pandemic: Summary Highlights, April 2009-April 2010: update june 16, 2010. CDC guidelines.
2. Wang ZF1, Su F, Lin XJ, Dai B, Kong LF, Zhao HW, Kang J. Serum D-dimer changes and prognostic implication in 2009 novel influenza A (H1N1). *Thromb Res* 2011; 127:198-201.
3. Dr. Soumya Swaminathan Director-General, ICMR and Secretary, DHR Ministry of Health and Family Welfare, Government of India By Supervisory Editor: ICMR Bulletin vol.48 No. 4—6 Apr- June 2017 ISSN 2456-0014.
4. CDC. Updated CDC estimates of 2009 H1N1 influenza cases, hospitalizations, and deaths in the United States, April 2009--April 10, 2010. Atlanta, GA: US Department of Health and Human Services, CDC; 2010. Available at http://www.cdc.gov/h1n1flu/estimates_2009_h1n1.htm. Accessed July 23, 2010.
5. Bal Ram AdhikariEmail author,; Geeta Shakya,; Bishnu Prasad Upadhyay,; Khagendra Prakash KC. *https://virologyj.biomedcentral.com/articles/10.1186/1743-422X-8-133* Outbreak of pandemic influenza A/H1N1 2009 in Nepal.
6. Ministry of Health and Family Welfare, India. Guidelines on categorization of Seasonal Influenza A H1N1 cases during screening for home isolation, testing, treatment and hospitalization (Revised on 11.02.2015). https://mohfw.gov.in/sites/default/files/394697031477913837_3.pdf. Published 2015. Accessed August 28, 2018
7. Friedman N, Drori Y, Pando R, Glatman-Freedman A, Sefty H, Bassal R, Stein Y, Shohat T, Mendelson E, Hindiyeh M, Mandelboim M. A(H1N1)pdm09 influenza infection: vaccine inefficiency. *Oncotarget* 2017; 8:32856-32863.
8. Joint Information Center 888-EMD-TODAY (888-363-8632) SOM - CDC Confirms First Michigan Case of Influenza A (H1N1) https://www.michigan.gov/som/0,4669,7-192-34773-213792--,00.html
9. www.cidrap.umn.edu/.../who-swaps-h1n1-2017-18-flu-vaccine-recommends-2-new-h...Mar 2, 2017 - The new H1N1 vaccine strain, called A/Michigan/45/2015, replaces A/California/7/2009,
10. Agarwal A, Agarwal S, et al. A study of influenz A (H1N1) pdm09 outbreak in pregnant women in Rajasthan, India. *Int J Gynaecol Obstet* 2016.
11. Yasuhara A, et al. Diversity of antigenic mutants of influenza A(H1N1) pdm09 virus escaped from human monoclonal antibodies. www.nature.com/scientificreports.