ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 12, Issue, 06, pp.12108-12113, June, 2020

DOI: https://doi.org/10.24941/ijcr.38950.06.2020

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

INFLUENZA A (H1N1) VIRUS INFECTIONS IN HOSPITALISED CANCER PATIENTS: OBSERVATION STUDY AT A REGIONAL CANCER INSTITUTE IN WESTERN INDIA

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ARTICLE INFO

Article History:
Received 20th March, 2020
Received in revised form
19h April, 2020
Accepted 17th May, 2020
Published online 30th June, 2020

Key Words:

Haematological malignancies
Solid tumours
Patients on chemotherapy
Clinical manifestation

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ABSTRACT

Background: During initial months of 2015 an epidemic of novel Influenza A (H1N1) virus emerged in the western part of India especially in Ahmedabad, Gujarat and parts of Rajasthan. A similar surge in influenza cases were again noticed during the initial months of 2019. We are describing the clinical characteristics and mortality indicators of hospitalised cancer patients in our institute. **Methods:** We reviewed the case records retrospectively, of our patients who were hospitalized during the 2015 epidemic period and during the initial months of 2019. Patients with cancer and a microbiologically confirmed diagnosis of Seasonal Influenza A (H1N1) were evaluated. The demography, clinical parameters, laboratory reports and outcome data were collected, analyzed and presented here. A total of 24 and 22 hospitalized cancer patients, during 2015 and 2019 respectively, with confirmed H1N1 Influenza infection were studied. One patient was infected twice during the 2019 season. None of our patients were previously immunised with influenza vaccine. In the year 2015 out of the 24 patients 17(70.8%) were male and 7 (29.2%) were females, and that in 2019 12 (54.5%) were male and 10 (45.5%) were female. Haematological malignancies were present in 19 (79.2%) during 2015 epidemic, and in 19 (86.4%) patients in 2019. Number of patients with solid malignancies were 5 (20.8%) and 3 (13.6%) in 2015 and 2019 respectively. During both the episodes pneumonia was the most common manifestation in the hospitalized patients, bilateral being more common than a unilateral presentation. Oseltamavir was started within 48 hours of suspicion of influenza in 17 (58.3%) patients in the previous epidemic of 2015, and in 9 (39.2%) patients in the current year of 2019. Co-morbidities were present in 6(25%) and 6 (27.3%) patients in the two episodes respectively. Associated infections were present in 8 (33.33%) and 5 (21.7%) patients. Absolute lymphocyte count of less than or equal to 1000/microL was observed in 14 (58.3%) and 15 (65.2%) patients in 2015 and 2019 respectively. Altered biochemical parameters in the form of deranged LFT was found in 9 (37.5%) and altered RFT in 5 (20.8%) in the cohort of 2015, and the same were found in 5 (21.8%) and 4 (17.4%) patients observed during the 2019 study period. During the 2015 study, 13 (54.2%) and during 2019, 17 (74%) patients required intensive care. The overall hospital mortality in our cohort was 8 (33%) patients in 2015 and it increased to 15 (65.2%) patients in 2019. Adverse outcome in the patients was closely related to factors like presentation in the form of bilateral pneumonia, development of ARDS, time of commencement of oseltamavir (neuraminidase inhibitor), associated co-morbidities and infections, underlying malignancy and ongoing chemotherapy, absolute lymphocyte count of less than 1000 and multi organ failure. Presence of hypoxemia, bilateral pneumonia, and CURB 65 score more than equal to 3, timing of starting Neuraminidase inhibitors beyond 48 hours of presentation and lymphopenia were predictors of requirement of mechanical ventilation and death. **Conclusion:** Seasonal Influenza A infection in patients with cancer can cause severe illness, resulting in bilateral pneumonia, ARDS and death. Hypoxemia, bilateral pneumonia, CURB 65 score of more than equal to 3, timing of starting Neuraminidase inhibitors following symptoms, and lymphopenia were predictors of adverse outcome. Cancer patients are prone to develop more severe disease and require longer course of therapy with Neuraminidase inhibitors than the general population. Therefore, a larger study is needed to identify predictors for early suspicion and unfavourable evolution of influenza infection in these patients.

Citation: ***Dr. Harsha P Panchal and Dr. Roshni Dasgupta,*** **2020.** "Influenza A (H1N1) Virus Infections in Hospitalised Cancer Patients: Observation Study at a regional cancer institute in western India.", *International Journal of Current Research*, 12, (06), 12108-12113.

INTRODUCTION

During the initial months of 2015 an epidemic of novel Influenza A (H1N1) virus emerged in the western part of India including states like Gujarat, Rajasthan, Maharashtra and Delhi. The country's Ministry of Health estimated there to be 42,592 cases of swine flu across India, resulting in 2990 deaths (https://ncdc.gov.in/showfile.php?lid=275).

These figures surpass the country's H1N1 numbers from the 2009 pandemic, in which 27,236 cases and 981 deaths were reported. As per National Centre for Disease Control, till March 2019, 19,385 cases and 605 deaths have been reported (https://scroll.in/pulse/916491/india-is-ignoring-other-types-of-influenza-with-its-focus-on-swine-flu). Repeated outbreak and significant increase in the number of cases and deaths suggests a more virulent mutated strain might have developed over the years, however a complete genome analysis conducted by National Institute of Virology, Pune, on six virus strains from the 2015 outbreak indicated that the virus has not undergone any genetic changes that could have affected H1N1 virulence or resistance to oseltamivir (Chemaly *et al*., 2012). We have described clinical characteristics and possible Mortality Indicators of cancer patients hospitalized at our regional centre. Patients with malignancies are more susceptible for acquisition of infections than the general population and are likely to develop more sever disease and complications. Due to disruptions in both innate and acquired immunity, either as result of the underlying malignancy or due to chemotherapy induced immunosupressed state, even organisms with low virulence are can cause significant morbidity and mortality in cancer patients. A myriad of conditions in patients of cancer may present with overlapping symptoms including fever, pneumonia, bilateral lung infiltration on chest imaging and cytopenias as result of the cancer itself or as an after effect of chemotherapy induced myelosupression, making the threshold for suspecting influenza in such patients very high, and thus resulting in delay of specific treatment. Till date, there are very few reports describing clinical characteristics of cancer patients with severe forms of influenza. These patients represent a more vulnerable population, which requires rapid identification, diagnostic work up and intensive management in specialized units. Therefore, it is important to report the clinical characteristics of cancer patients with severe forms of H1N1 infection.

PATIENTS AND METHODS

We performed a retrospective single centre observational study in hospitalized cancer patients in Gujarat Cancer and Research Institute (GCRI), Ahmedabad, Gujarat, India during the epidemic of 2015 and outbreak in 2018-19. Adults as well as paediatric cancer patients requiring hospitalization due to clinical symptoms suggestive of influenza infection were subjected to nasopharyngeal swab testing for Seasonal Influenza A (H1N1) infection. Laboratory diagnosis was confirmed by means of polymerase chain reaction analysis of nasopharyngeal swab specimens. Patients who tested positive for Seasonal influenza A (H1N1) were included in the study and detailed information regarding their clinical status, clinical profile including associated co-morbidities, radiological findings, associated infections, haematological and biochemical parameters and ventilatory support requirement and mortality data were obtained. The main outcome measure in this study were mortality indicators in fatal cases of H1N1 infection in hospitalized cancer patients.

RESULTS

A total of 24 and 22 cancer patients in 2015 and 2019 respectively, with confirmed Seasonal influenza A (H1N1) infection were studied, out of these one patient developed infection twice in 2019, making the incidence count as 23 instead of 22. None of the patients were immunised with influenza vaccine. As shown in Table-1, in the year 2015, 17(70.8%) were male and 7(29.2%) were female, 8(33.3%) were paediatric and 16(66.7%) were adult patients. Hematological malignancies were present in 19(79.2%) which includes Acute Promyelocytic Leukemia(APML) (2), Lymphoma (3), Myelodysplastic Syndrome(MDS) (2), Acute Myeloid Leukemia(AML) (2),Chronic Lymphoid Leukemia(CLL) (1),Chronic Myeloid Leukemia(CML) (1), Plasmacytoma (1),Acute Lymphoblastic Leukemia (ALL)(7) . Solid malignancies were present in 5(20.8%) patients: (Ca Lung (1), Ca Breast (1), Head and neck squamous cell ca (HNSCC) (3).Out of these patients 16(66.7%) were on chemotherapy at the time of diagnosis of H1N1 infection. Co-morbidities were present in 6(25%) patients. Associated infections were present in 8(33.33%) patients. While in the current year of 2019, out of the 22 patients, 12 (54.4%) were male and 10 (45.5%) were female, 3 (13.6%) were paediatric and 19 (86.4%) were adult patients. Haematological malignancies were present in 18 (81.8%) patients, which included APML (1), Lymphoma (3), ALL (7), MM (2), AML (4) and CML (1). Solid malignancies were present in 4 (18.2%) patients including Ca Lung (1), Metastatic Breast Ca (2) and Ca ovary (1). Out of these patients 17 (74%) were on chemotherapy at the time of diagnosis of H1N1 infection. Co-morbidities were present in 6 (27.3%) patients. Associated infection were present in 5 (21.7%) patients.

Pneumonia was common manifestation in hospitalized cancer patients with unilateral in 6(25%), bilateral in 14(58.3%) and URTI in 4(16.7%) patients. Oseltamivir was started within 48 hours of symptoms of Influenza in 17(70.8%) patients. Absolute lymphocyte count was less than 1000 in 14(58.3%) patients. Altered LFT was found in 9(37.5%), altered RFT was found in 5(20.8%) and dyselectrolytemia in the form of hyponatremia or hypokalemia was found in 10 (41.6%) patients. In the current study period of 2019, pneumonia was observed in all the patients, with unilateral infiltration on chest imaging in 1 (4.4%) and bilateral in 22 (95.6%), none of the patients presented with URTI. Oseltamavir was started within 48 hours of symptoms in 9 (39.2%) patients. ALC was less than equal to 1000/microL in 15 (65.2%) patients. Altered LFT was observed in 5 (21.8%), altered RFT in 4 (17.4%) and dyselectrolytemia in 9 (39.1%) patients. In 2015, out of the 24 patients, 13 (54.2%) of them required intensive care. The overall hospital mortality in our cohort was 8 patients (33%) as shown in Table-2. Profiling of these 8 expired patients showed, that 7(87.5%) of them were male, 6(75%) were adult and 2(25%) were paediatric patients. Haematological malignancies were present in 6(75%) expired cancer patients (APML, DLBCL, HD, NHL, MDS, AML one of each of the diseases). Solid malignancies were present in 2(25%), one Ca Buccal mucosa and other Ca Maxilla. Out of theses 7(87.5%) patients were on chemotherapy at the time of diagnosis or had received chemotherapy within 21 days of contracting influenza. In 2019, out of the 23 incidences of H1N1 infection in cancer patients, 17 (74%) required intensive care. Mortality in this year occurred in 15 (65.2%) patients. Out of the 15 expired patients 8 (53.4%) were male, 13 (86.7%) were adult and 2 (13.3%) were paediatric patients. Haematological malignancies were present in the majority, 13 (86.7%) patients {Lymphoma (2), ALL (6), AML (3), APML (1), Multiple myeloma (1)}. Solid malignancies were present in 2 (13.3%) patients; both of them had metastatic breast carcinoma. Of the expired cohort, 13 (86.7%) patients were either on chemotherapy or had received chemotherapy within 21 days of presentation.

Table 1. Patient Characteristics and Laboratory Parameters

Total Patients:	24 (Year 2015)	22 (Year 2019)
Sex		
Male	17(70.8%)	12(54.5%)
Female	07(29.2%)	10(45.5%)
Type of cancer		
Haematological malignancies	19(79.2%)	18(81.8%)
Solid tumours	05(20.8%)	4(18.2%)
Patients on chemotherapy *		
Yes	16(66.7%)	17(74%)
No	08(33.3%)	6(26%)
Co- morbidities		
Present	06(25%)	6(27.3%)
Absent	18(75%)	16(72.7%)
Associated infections *		
Present	08(33.3%)	5(21.7%)
Absent	16(66.7%)	18(78.3%)
Clinical manifestation *		
Pneumonia	B/L=14(58.3%) U/L=06(28.6%)	B/L=22(95.6%) U/L=1(4.4%)
Upper respiratory tract infection	04(19%)	0
Oseltamivir started within 48 hrs of onset of symptoms *		
Yes	17(70.8%)	9(39.2%)
No	07(29.2%)	14(60.8%)
Alc(absolute lymphocyte count) *		
</=1000	14(58.3%)	15(65.2%)
>1000	10(41.7%)	8(34.8%)
Biochemical parameters *		
Altered s. Creatinine	05(20.8%)	4(17.4%)
Altered LFT	09(37.5%)	5(21.8%)
Dyselectrolytemia	10(41.6%)	9(39.1%)
Icu care required *		
Yes	13(54.2%)	17(74%)
No	11(45.8%)	6(26%)

*Out of the 22 patients in 2019, one of them developed influenza infection twice, so in these cases the incidence is taken as 23 and percentage is calculated out 23 incidents of influenza infection.

Table -2. Clinical Characteristics of Expired Patients

Total patients:	08 (Year 2015)	15 (Year 2019)
Sex		
Male	07(87.5%)	8(53.4%)
Female	01(12.5%)	7(46.6%)
Type of cancer		
Hematological malignancies	06(75%)	13(86.7%)
Solid tumours	02(25%)	2(13.3%)
Patients on chemotherapy		
Yes	07(87.5%)	13(86.7%)
No	01(12.5%)	2(13.3%)
Co-morbidities		
Present	03(37.5%)	4(26.7%)
Absent	05(62.5%)	11(73.3%)
Associated infections		
Present	04(50%)	5(33.4%)
Absent	04(50%)	10(73.3%)
Clinical manifestation		
Pneumonia	B/L= 07 (87.5%) U/L =01(12.5%)	B/L= 15(100%) U/L= 0
Urti	-	-
Neuraminidase inhibitors started within 48 hrs of onset of symptoms		
Yes	02(25%)	4(26.7%)
No	06(75.6%)	11(73.3%)
ALC(Absolute lymphocyte count)		
</=1000	06(75%)	11(73.4%)
>1000	02(25%)	4(26.6%)
Biochemical parameters		
Altered S. creatinine	03(37.5%)	2(13.4%)
Altered LFT	05(62.5%)	5(33.4%)
Dyselectrolytemia	4(50%)	6(40%)
Ventilatory support required		
Yes	08(100%)	15(100%)
No	-	-

Table 3. Comparison of Variables at the time of admission, between Patients who Survived and those who Expired

Variable At Admission	Patients Who Survived		Patients Who Expired*	
	Year 2015	Year 2019	Year 2015	Year 2019
1)Age				
Median	24		43	
Range	4-64	8-76	7-45	4-73
2)Male sex	10(62.5%)	5(63.5%)	7(87.5%)	8(53.4%)
3)Hypotension that does not resolve after fluid administration	-		6(75%)	11(73.4%)
4)Endotracheal intubation required in first 24 hours	-		6(75%)	11(73.4%)
5)Co-existing conditions	3(18.8%)	2(25%)	3(42.9%)	9(60%)
6)Associated infections	4(25%)	0	4(50%)	5(33.4%)
7)Absolute Lymphocyte Count(</=1000/dl)	7(43.8%)	4(50%)	6(75%)	11(73.4%)
8)Hypoxia (pao2/Fio2)	5(31.3%)	2(25%)	8(100%)	15(100%)
9)ARDS	-	-	8(100%)	15(100%)
10)Renal failure	2(12.5%)	2(25%)	3(37.5%)	2(13.4%)
11)Opacity in 3 / 4 Lung fields	4(25%)	2(25%)	7(87.5%)	11(73.4%)
12)CURB 65 SCORE for Pneumonia				
Median	1	1	3	3
Range	0-2	0-2	3-4	3-4
13) Neuraminidase started within 48 hours of onset of symptoms	15(93.8%)	5(62.5%)	2(25%)	4(26.7%)

The clinical status observed in the expired patients in 2015, showed that all the 8 (100%) and in 2019 all the 15 (100%) patients developed pneumonia and hypoxemia. Majority of the patients, 7 (87.5%) and 15 (100%) in the two study periods respectively, had bilateral extensive infiltration on chest imaging at the time of diagnosis. All the patients were started on Oseltamavir on clinical suspicion of influenza, but on further probing into the history it was found that only 2 (25%) (in 2015) and 4 (26.7%) (in 2019) patients received it within 48 hours of onset of clinical symptoms. During both the years, it was observed that in the expired cohort of patients the ALC was less than or equal to 1000/microL in majority of them; 6 (75%) patients in 2015 and 11 (73.4%) in 2019. Altered biochemical profile, as in altered LFT was recorded in 5 (62.5%) and 5 (33.4%) patients, altered RFT in 3 (37.5%) and 2 (13.4%) and dyselectrolytemia in 4 (50%) and 6 (40%) patients in 2015 and 2019 study periods respectively. All the patients developed ARDS and needed ventilator support for variable periods of time before they succumbed to death.

Clinical characteristics of the expired patients showed that co-morbidities, other than malignancy, like diabetes mellitus and hypertension was present in 3 (47.5%) and 4 (26.7%) patients during the study period of 2015 and 2019 respectively. Associated bacterial infection was present in 4 (50%) and 2 (13.4%) patients, during the two different study periods respectively. Associated bacterial infection was present in 4 (50%) and 5 (33.4%) patients in each of the study periods in 2015 and 2019 respectively. On comparing the clinical characteristics between patients who survived and those who expired, certain variables could be identifies as predictors of adverse outcome (Table 3)

This study shows that the variables at admission associated with death were hypotension despite fluid challenge, endotracheal intubation requirement in the first 24 hours of presentation, co-existing conditions like diabetes, hypertension, and associated infections. It is also observed that hypoxia, ARDS, CURB 65 score of more than equal to 3 and bilateral chest infiltration and lymphopenia (ALC less than equal to 1000) were present in majority of the patients who expired. The timing of starting of neuraminidase inhibitors within 48 hours essentially played a role in the outcome, with adverse outcome being more commonly observed in patients who received it after 48 hours of onset of symptoms.

DISCUSSION

H1N1 Virus, also referred as the 'Swine Flu' is major health concern for most of people, especially it is known to have serious manifestations and can be fatal in immunocompromised people, which includes cancer patients among many others. So the importance of preventive measures and low threshold for suspicion in such patients during flu season is highly recommended. Our study shows the clinical course of the infection by epidemic Seasonal Influenza A (H1N1) virus in single tertiary cancer care centre from western part of India during the outbreaks of 2015 and 2019. Overall we found a high rate of pneumonia (83.4% in 2015 and 100% in 2019) and mortality (33.4% in 2015 and 65.2% in 2019) among the hospitalised cancer patients with confirmed cases of H1N1 infection, during both the study periods. The clinical course was less severe in those who presented with an URTI in contrast to those who had presented with pneumonia and hypoxemia. We also found that the best predictors of death were hypoxemia, development of ARDS and requirement of invasive ventilator support within 24 hours of presentation.

Immunosuppressed state either due to the underlying malignancy or due to myelosupression resulting from chemotherapy was a common underlying risk factor for mortality. In our study among the patients who expired, 75% (2015) and 86.7% (2019) of them had an underlying haematological malignancy; and 87.5% (2015) and 86.7% (2019) of them were either on chemotherapy during or had received chemotherapy within 21 days of symptom onset. Among the patients with microbiologically confirmed Seasonal Influenza A (H1N1) infection, associated infection contributed to significant morbidity in 8 (33.3%) and 5 (21.7%) patients, in 2015 and 2019 study period respectively. In the outbreak of 2015, in our study cohort 13 (54.2%) patients required ICU care, while in 2019, 17 (74%) patients required ICU admission. Of these patients admitted in ICU, 8(61.5%) and 15 (88.2%) in the year 2015 and 2019 respectively succumbed to death. Mortality had a positive correlation with refractory hypoxemia (Estenssoro, 2010) and CURB 65 score 3 or more, and all the patients who expired had developed ARDS during the clinical course. All the patients who expired had developed ARDS during the clinical course. These values are comparable to those reported in the same type of population (Choi *et al*., 2011; Espinosa-Aguilar *et al*., 2011; Ljungman *et al*., 2011;

Casper, 2010; Dignani *et al*., 2014), but are higher than those reported in other populations, which ranged from 0–24% (Jain *et al*., 2009; Cao *et al*., 2009; Dominguez-Cherit *et al*., 2009; Louie *et al*., 2009; Rello, 2009). Study of pathogenesis shows that Influenza-mediated damage of the airway, alveolar epithelium and alveolar endothelium results from a combination of: 1) intrinsic viral pathogenicity, attributable to its tropism for host airway and alveolar epithelial cells; and 2) a robust host innate immune response, which, while contributing to viral clearance, can worsen the severity of lung injury (Susanne Herold, 2015). The course of IAV infection when considered in three stages, it is found that at first is the viral infection of the alveolar epithelium and its replication in these cells, during which Neuraminidase inhibitors can limit viral entry and can prevent or attenuate the severity of the infection (Shinya, 2006; Zhang, 2013; Rossman, 2011). The second is the innate followed by the adaptive immune response to the virus, which is important for viral clearance but also induces damage to the alveolar epithelium and endothelium (Teijaro , 2014; Braciale , 2012). A number of agents with potential immunomodulating effects, including immunoglobulins, N-acetylcysteine, macrolides, peroxisome proliferator-activated receptors agonists, celecoxib and mesalazine, have been suggested for clinical use[27], but only a few of them reached clinical trials. The third is the development of long-term immunity and resolution of infiltrates and regeneration of damaged lung tissue, during which there is an increased susceptibility to secondary bacterial infection (Hogan, 2014; Sun, 2013).

Lymphocytopenia has been described as a risk factor for progression from upper to lower viral respiratory tract infection in cancer patients (Chemaly *et al*., 2012; Casper, 2010) and profound lymphopenia (<100 cell/μL) was reported as a significant risk factor for requirement of mechanical ventilation and death in patients with influenza virus (Dignani, 2009; Boudreault, 2011). In our study, ALC of less than equal to 1000/μL at presentation was observed in 50% (2015) and 75% (2019) of the patients who expired and was a predictor for the need for mechanical ventilation and mortality. Neuraminidase inhibitor therapy (Oseltamivir) appears to be effective in preventing progression to LRTI (Boudreault, 2011; Chemaly, 2007) and hypoxemia (Boudreault, 2011) when instituted early after onset of symptoms. It has been reported that delaying therapy in cancer patients with the *Influenza A* H1N1 virus infection was significantly associated with death (Chemaly, 2012). Early initiation of antiviral therapy in these patients may attenuate the severity of disease (Jain, 2009; Dominguez-Cherit, 2009). In our study we found that among patients who expired in 2016, 6(75%) and in 2019, 11 (73.4%) patients had not received this therapy within 48 hours; while among survivors 93.8% and 62.5% of the patients had received Oseltamavir within 48 hours of symptom onset. In our study none of the patients were vaccinated against seasonal influenza.

In this study, we found that 24 patients in 2015 and 22 patients, one of them admitted twice during the same season, in the year 2019 required hospitalization with a high number of them, 13(54.2%) in 2015 and 17 (74%) in 2019, requiring admission to ICU, among whom again, respiratory support was required by 8(61.5%) and 15 (74%) patients. Interestingly among the patients who expired, 7 (87.5%) and 15 (100%) patients in the both the years presented with bilateral pneumonia.

The dismal outcome seen in these patients despite treatment with oseltamivir probably indicates that this high-risk group needs to be treated differently from patients with isolated URTI. Some authors have suggested an initial treatment with high dose of oseltamivir and/or combination therapy approaches in the case of respiratory failure (Rello *et al*., 2009). Higher doses could also be considered in a setting of profound lymphocytopenia (Boudreault *et al*., 2011). All our patients received standard dose of oseltamivir (75 mg PO twice a day) for a minimum of 10 days based on data on slower viral clearance (Boudreault, 2011) along with broad spectrum antibiotics. Two of ICU admissions were given trial of intravenous immunoglobulin and both (100%) recovered completely, in 2015 (Casper, 2010). It was also noted that in the cohort of 2019 patients, 7 patients developed clinical manifestations other than fever and pneumonia in the form of encephalopathy, cardiomyopathy, acute kidney injury and hepatitis. Involvement of other organs has also been contributory to morbidity and mortality signifying the importance of multimodality treatment with intensive supportive care required for this cohort of patients.

In conclusion, we have reported a series of cancer patients with the Seasonal Influenza A (H1N1) infection with a high incidence of hospitalization, severe pneumonia, ICU admission and requiring mechanical ventilation, and high mortality. In our study hypoxemia, bilateral pneumonia, and CURB 65 score for pneumonia more than or equal to 3, development of ARDS, timing of starting Neuraminidase inhibitors more than 48 hours of symptom onset, and lymphopenia were predictors of requirement of ICU care including mechanical ventilation and death. Our study also highlights the fact that cancer patients can have similar presentation for a myriad of other causes, including sepsis, bacterial and fungal pneumonia, leukemic infiltration of the lung, differentiation syndrome in APML patients, and bilateral pulmonary metastasis in solid malignancies, creating a diagnostic dilemma and therefore provoking further delay of identification of influenza infection and treatment of the same in such patients. Thus, a larger study is needed to identify predictors of unfavourable evolution of this potentially treatable disease among cancer patients.

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