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Predictors of Death in Patients with H1N1 Influenza: A Retrospective Analytical Study

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ABSTRACT

Aims: Influenza A virus subtype H1N1, known as H1N1 influenza virus, could cause moderate to severe swine influenza in humans. H1N1 influenza is associated with high mortality rate. Effective symptom management could significantly reduce the mortality rate. This study aimed to determine the clinical manifestations, outcomes, and predictors of mortality in patients with H1N1 influenza, admitted to hospitals during January to September 2016.
Materials & Methods: This retrospective descriptive-analytical study was conducted during January to September 2016 in eight hospitals located in Razavi Khorasan province, northeastern Iran. The medical records of 65 patients were retrieved, and the necessary data were extracted from the records using a demographic questionnaire and a clinical manifestations checklist. The SPSS software Version 23.0 was used to analyze the data via the measures of descriptive statistics and the logistic regression analysis with odds ratio.
findings: The most common clinical manifestations of H1N1 influenza were headache (70.8%), numbness in the extremities (63.1%), myalgia (60%), cough (58.5%), fever and shivering (53.8%), and nausea (53.8%). In total, 14 (21.53%) patients had died due to H1N1 influenza. The significant predictors of death were dyspnea (OR: 13.91, *p*: .032), myalgia (OR: 0.04. *p*: .010), and age (OR: 1.05, *p*: .024) so that dyspnea and myalgia were associated with 13.9 and 0.04 times higher odds of death, respectively. Moreover, each one year increase in age was associated with 5% increase in the odds of experiencing death.
Conclusions: In the case of H1N1 influenza epidemics, care services need to be allocated more to patients who have higher age and suffer from myalgia and dyspnea.

Keywords: Influenza A virus; H1N1 subtype; Risk factors; Mortality

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Introduction

Influenza A virus subtype H1N1, simply known as H1N1 influenza virus, was first discovered in the United States in 1918. H1N1 influenza re-emerged in 2009 in South California as swine flu with distinct shape and virulence. Immediately, countries such as Mexico, Canada, and European countries reported H1N1 influenza cases [1]. H1N1 influenza virus causes moderate to severe H1N1 influenza among humans and affects all age groups [2].

Estimations show that influenza caused 20–50 million deaths during 1918-1920, while plague caused this number of deaths in four years [3]. The Center for Disease Control and Prevention (CDC) reported that in 2009, there were 89 million H1N1influenza cases in the United States, of whom 403000 cases were hospitalized, and 18300 cases died [4]. Since 2009, more than 30000 H1N1 influenza cases were reported in more than seventy countries. In 2015, the prevalence of H1N1 influenza drastically increased compared to the 2010–2014 five-year period. For example, the number of H1N1 influenza cases in 2015 in India reached 10000 with 774 mortality rate [2]. In Iran, 162 cases were diagnosed with H1N1 influenza in Yazd city from April 21, 2009 to March 26, 2010; however, the resulting mortality rate remained unknown [5]. According to the World Health Organization (WHO) and the Center for Disease Control and Prevention, H1N1 influenza is currently in its pandemic phase, affecting all countries around the world [6]. Therefore, any indifference towards its hazards could cause catastrophic consequences for humans [7].

Appropriate triage and provision of early healthcare services are key factors for effective H1N1 influenza management. However, most studies conducted on H1N1 influenza were focused on the awareness of healthcare students or general population about its transmission and prevention. Also, a limited number of studies were conducted on patients with H1N1 influenza in the post-pandemic period. Most of the studies on swine flu were pivoted around pandemic years during 2009-2010. Thus, through this retrospective study, the authors were able to look at the clinical manifestations, outcomes, and predictors of mortality in patients with H1N1 influenza, admitted to hospitals from January to September 2016.

Material and methods

Study design: This retrospective descriptive-analytical study was conducted during January to September 2016.

Patients and setting: Participants were 65 patients with H1N1 influenza, who had been hospitalized in hospitals of Razavi Khorasan, Iran. Hospitals included Imam Reza, Ghaem, and Hasheminejad in Mashhad; Hakim and 22 Bahman in Neyshaboor; 22 Bahman in Gonabad; Abolfazl in Kashmar; and 9 Dey in Torbat-e-Heydarieh. Sampling was done through the census method.

Data collection instruments: Data collection instruments were a demographic questionnaire and a clinical manifestations checklist. The demographic questionnaire included six items, namely age, gender, educational status, pregnancy, foreign travel, and direct contact with animals. The clinical manifestations checklist also included nine items on dyspnea, fever and shivering, headache, cough, myalgia, sore throat, diarrhea, nausea, and numbness in the extremities. The content validity of this checklist was approved by ten infectious diseases specialists, general physicians, and head nurses of emergency department and infectious diseases wards. For data collection, the first author referred to the study setting, retrieved the medical records of eligible patients (patients whose Real Time PCR results were positive for nasopharyngeal

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secretions), extracted the necessary data from the records, and recorded the final outcomes (death or recovery) of patients. **Statistical analysis**: The SPSS software Version 23.0 (IBM SPSS Statistics, IBMCorp., New York) was used to analyze data via the measures of descriptive statistics and the logistic regression analysis with odds ratio. The logistic regression analysis was used to evaluate the effects of clinical manifestations on death. The results of logistic regression analysis with the enter method showed that none of the clinical manifestations of H1N1 influenza were significant predictors of death. Thus, the logistic regression analysis was repeated using the forward method. The level of significance was established at less than 0.05.

Findings

Descriptive analysis: In this study, the participants were 65 patients with H1N1 influenza (patients whose Real Time PCR results were positive for nasopharyngeal secretions) with the age ranges from 3–92 years. Of whom 53.8% were male, 35.4% had secondary education, and 30.8% aged more than fifty years. The most common clinical manifestations experienced by the participants with H1N1 influenza were headache (70.8%), numbness in the extremities (63.1%), myalgia (60%), cough (58.5%), fever and shivering (53.8%), and nausea (53.8%). Other manifestations were dyspnea (44.6%), diarrhea (24.6%), and sore throat (13.8%). Table 1 shows participants' demographic and clinical characteristics. The number of patients who had died due to H1N1 influenza was fourteen (21.53%).

Evaluating the effects of clinical manifestations on death: The forward method of logistic regression illustrated that the significant predictors of death among the patients with H1N1 were dyspnea (p = .032), myalgia (p = .010), and age (p = .024). Accordingly, the odds of experiencing death in patients with dyspnea was 13.9 times higher than in patients without dyspnea (odds ratio: 13.91). Moreover, patients with myalgia were 0.04 times more likely to experience death compared to those without myalgia (odds ratio: 0.04). In addition, each one year increase in age was associated with 5% increase in the odds of experiencing death (odds ratio: 1.05) (Table 2).

Discussion

This study aimed to determine the predictors of death in the patients with H1N1 influenza. Findings revealed that the most common manifestations of H1N1 influenza were headache (70.8%), numbness in the extremities (63.1%), myalgia (60%), cough (58.5%), fever and shivering (53.8%), nausea (53.8%), dyspnea (44.6%), diarrhea (24.6%), and sore throat (13.8%), respectively.

In line with this study findings, a study in Taiwan reported that H1N1 influenza was mostly associated with the manifestations such as fever, myalgia, cough, sore throat, rhinorrhea, and diarrhea [8]. Cytokines were reported to be responsible for muscle ache. In their study, myalgia was found in 57.1% of cases and as the only significant symptom differentiating H1N1 influenza cases from the non-H1N1 group [8]. Also, in another study, the main H1N1 influenza manifestations were reported as fever and dyspnea [9]. In another study in India, headache was the most common manifestation (92.9%) among the 141 patients affected by H1N1 influenza, while manifestation of dyspnea was about 54.6% [10]. The present study findings indicated that headache was the most common H1N1 influenza manifestation (70.8%).

Moreover, a study in the United States showed that the most common manifestations of H1N1 influenza were cough and dyspnea

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Table 1) The outcome of H1N1 influenza based on patients' demographic and clinical characteristics

Characteristics \ Outcome		Recovery		Death		Total	
		N	%	N	%	N	%
Gender	Male	24	47.1	11	78.6	35	53.8
	Female	27	52.9	3	21.4	30	46.2
Age (Years)	< 20	12	23.5	0	0.0	12	18.5
	20–30	11	21.6	0	0.0	11	16.9
	30–40	11	21.6	3	21.4	14	21.5
	40–50	3	5.9	5	35.7	8	12.3
	> 50	14	27.5	6	42.9	20	30.8
Educational status	Illiterate	15	29.4	3	21.4	18	27.7
	Elementary	16	31.4	6	42.9	22	33.8
	Secondary	18	35.3	5	35.7	23	35.4
	University	2	3.9	0	0.0	2	3.1
Dyspnea	Yes	28	54.9	1	7.1	29	44.6
	No	23	45.1	13	92.9	36	55.4
Headache	Yes	33	64.7	13	92.9	46	70.8
	No	18	35.3	1	7.1	19	29.2
Myalgia	Yes	26	51.0	13	92.9	39	60.0
	No	25	49.0	1	7.1	26	40.0
Numbness in the extremities	Yes	36	70.6	5	35.7	41	63.1
	No	15	29.4	9	64.3	24	36.9
Fever and shivering	Yes	27	52.9	8	57.1	35	53.8
	No	24	47.1	6	42.9	30	46.2
Cough	Yes	29	56.9	9	64.3	38	58.5
	No	22	43.1	5	35.7	27	41.5
Sore throat	Yes	9	17.6	0	0	9	13.8
	No	42	82.4	14	100.0	56	86.2
Diarrhea	Yes	14	27.5	2	14.3	16	24.6
	No	37	72.5	12	85.7	49	75.4
Contact with animals (Tau, Sheep, Bird)	Yes	15	29.4	2	14.3	17	26.2
	No	36	70.6	12	85.7	48	73.8
Pregnancy	Yes	5	9.8	2	14.3	7	10.8
	No	46	90.2	12	85.7	58	89.2
Foreign travel	Yes	10	19.6	0	0.0	10	15.4
	No	41	80.4	14	100.0	55	84.6

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Table 2) The logistic regression analysis with the forward method to determine the predictors of death in H1N1 influenza

Factor	B	S.E.	Wald	df	P value	OR	95% CI	
							Lower	Upper
Dyspnea	2.63	1.23	4.58	1	.032	13.91	1.25	155.26
Myalgia	–3.20	1.24	6.71	1	.010	0.04	0.00	0.46
Age	0.04	0.02	5.06	1	.024	1.05	1.01	1.09
Constant	–4.47	1.56	8.22	1	.004	0.01		

B: B test, S.E: Standard Error, Wald: Wald test, OR: Odds ratio, CI: Confidence interval

[11]. Another study in Taiwan found fever, cough, and runny nose as the most common manifestations [8].

Similarly, a review study which assessed the studies on 642 patients with H1N1 influenza indicated that the most common manifestations of this illness were fever, cough, sore throat, and diarrhea [12]. However, in contradiction with the present study findings, a study in Taiwan reported that none of the patients had experienced gastrointestinal problems such as diarrhea, nausea, and vomiting [8]. Moreover, in another study in 2009, numbness in the extremities and dyspnea which were reported as the manifestations of H1N1 influenza in the present study, were not reported as H1N1 influenza manifestations [12]. These contradictions could be attributed to the differences among the studies respecting their samples and data collection methods.

Around 15.4% of the participants had had a foreign travel 7–8 days before the onset of H1N1 influenza manifestations. The studies in Taiwan and India also reported a high rate of foreign travel among the afflicted patients 7–8 days before the manifestations onset [8,13]. These findings denote that foreign travel could be an important risk factor for H1N1 influenza. This study findings also revealed that the number of male patients was almost the same as the number of female patients (53.8% vs. 46.2%). Similarly, an earlier study reported no significant difference between the male and female patients regarding the prevalence of H1N1 influenza [8], while in other studies, male gender was considered as a risk factor for swine influenza and the cause of death [14-15].

Findings also indicated that 26.2% of participants had had direct contact with animals (such as cow, sheep, dog, or birds) before affliction with H1N1 influenza. Around 14.3% of these patients had experienced death. Similarly, a study reported that H1N1 influenza virus was transmitted from swine to humans and caused death; this risk became even greater if the virus did not kill swine hosts and if new susceptible animals were frequently introduced to the farm, sustaining the transmission route [16]. This study findings suggest that H1N1 influenza virus may also be transmitted to humans by animals other than swine (Table 1). Of course, this hypothesis deserves further investigations in future studies.

In this study, it was also found that H1N1 influenza affected almost all age groups from three-year-old children to 92-yeal-old elderly people. This finding is in line with the findings of the previous studies which reported that the age distribution of H1N1 influenza was different from that of the seasonal influenza [17-20]. Moreover, age was found to be as a significant predictor of death among the patients with H1N1

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influenza so that each one year increase in age was associated with 5% increase in the odds of death. Accordingly, around 42.9% of the patients who had died due to the disease aged 50–99 years. Similarly, a global pooled analysis on the risk factors of H1N1 influenza severe outcomes showed higher mortality rate among the patients with H1N1 influenza and the age ranges more than sixty years [21]. The greater likelihood of death among older patients could be due to different age-related problems such as comorbidities, impaired immunity, and decreased physiological capacities [22].

Dyspnea was another significant predictor of death in H1N1 influenza so that the patients with dyspnea were 13.9% more likely to experience death. Similarly, another study showed that dyspnea in H1N1 influenza significantly increased the likelihood of death [21]. Another significant predictor of death in the present study was myalgia. An explanation for the significant contribution of dyspnea and myalgia to death in H1N1 influenza may be the greater severity of H1N1 influenza among the patients with these two symptoms [23]. Moreover, dyspnea may be a preliminary symptom of serious respiratory problems such as respiratory distress and chronic lung diseases, which could eventually result in death [24].

Limitations: This study failed to assess patients' past medical history and their comorbid conditions; hence, it was not possible to assess the relationship between comorbid conditions and death outcome. Moreover, there was no credible information in patients' medical records about the time interval between the onset of clinical manifestations and the first attendance at healthcare settings for receiving care services. Consequently, it was not possible to assess the effects of this time interval on H1N1 influenza severity and outcomes.

Conclusion

This study showed that the clinical manifestations of H1N1 influenza were headache, numbness in the extremities, myalgia, cough, fever and shivering, nausea, dyspnea, diarrhea, and sore throat. The significant predictors of death among the patients with H1N1 influenza were myalgia, dyspnea, and age. In other words, the patients with myalgia, dyspnea, and higher age were significantly more at risk of death. Healthcare professionals could reduce the rate of mortality due to H1N1 influenza through identifying patients with myalgia, dyspnea, and higher age and providing them with more intensive care. Moreover, the findings of the present study suggest that in case of H1N1 influenza epidemics, care services need to be allocated more to patients who have higher age and suffer from myalgia and dyspnea.

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Ethical Permissions: This study was approved by the Research Administration of Mashhad University of Medical Sciences, Mashhad, Iran (approval code: IR.MUMS.REC.1395.138). All data collected from the patients' records were recorded anonymously.

Conflict of interests: None is declared.

Authors' Contribution: MSNA and MR: Main researcher and writing the article, AS: Data Analyzer, AEZ: Collaborate on the writing of introduction and discussion.

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