SURVIVAL ANALYSIS AND RISK FACTORS FOR DEATH IN HOSPITALIZED INFLUENZA PATIENTS

INFECTED WITH PANDEMIC (H1N1) 2009 IN CANADA

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To obtain additional information, please contact:

Public Health Agency of Canada
Address Locator 0900C2
Ottawa, ON K1A 0K9
Tel.: 613-957-2991
Toll free: 1-866-225-0709
Fax: 613-941-5366
TTY: 1-800-465-7735
E-mail: publications@hc-sc.gc.ca

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BACKGROUND

On April 26, 2009, the first six cases of pandemic (H1N1) influenza were reported in Canada: four in Nova Scotia[1] and two in British Columbia.[2] The community-based transmission occurred rapidly and the virus rapidly spread across Canada. By the end of May 2009, more than 1,000 laboratory-confirmed cases of pandemic (H1N1) influenza had been reported in Canada and the virus had spread in 12 of the 13 provinces and territories. As of April 3, 2010, Canada had experienced two defined waves of the pandemic, one in the spring and the second in early fall 2009 with a total of 8,678 laboratory-confirmed hospitalized cases (including patients admitted to the intensive care unit (ICU)).[2]

An extensive amount of work has been done on the pandemic databases throughout the world as well as in Canada including two reports[2,3] by the Centre for Immunization and Respiratory Infectious Diseases (CIRID), Public Health Agency of Canada (PHAC). Helferty et al.[2] looked at the demographic and clinical characteristics as well as severe outcomes (defined as admission to ICU or death) of all laboratory confirmed cases of pandemic (H1N1) influenza admitted to hospital in all provinces and territories of Canada from April 12, 2009 to April 3, 2010. Their findings showed differences in epidemiologic features of the first and second waves of the 2009 pandemic with second wave substantially larger but only a smaller portion of older population had severe outcome. Campbell et al.[3] provided a detailed review of the disease characteristics and outcomes, including risk factors for admission to ICU and death of patients admitted to hospital in Canada during the first five months of the pandemic. Donaldson et al.[4] looked at the mortality from pandemic (H1N1) 2009 influenza in England. They found that age-specific case fatality rate was lowest for children age (5–14) and highest for seniors (age $\geq$ 65). They concluded that mortality in this pandemic compared favourably with other 20th century influenza pandemics and recommended priority vaccination for high risk groups and of timely availability of antiviral treatment to reduce deaths. Louie et al.[5] looked into the clinical and epidemiological features of pandemic (H1N1) 2009 influenza leading to hospitalization or death in the first 16 weeks of pandemic in California. Their findings showed that infants had highest hospitalization rates whereas the older persons (age $\geq$ 50) years had the highest mortality rates once hospitalized. They noticed that the median age of hospitalized infected cases was younger than that of seasonal influenza. Nickel et al.[6] evaluated the risk factors for ICU admission or death among pandemic (H1N1) 2009 influenza infected hospitalized patients in Washington State. They found that older age and delayed time to hospitalization each independently affected the progression to ICU admission or death among hospitalized pandemic patients. Yu et al.[7] explored the association between age, obesity, pregnancy and chronic medical conditions with the severe illness (ICU admission or death) in patients affected with pandemic (H1N1) 2009 virus infection in lab-confirmed, hospitalized patients in China. They found that risk factors for severe illness were similar to those observed in developed countries, but admitted that Chinese population had lower prevalence of chronic medical conditions and obesity compared to developed countries.

In this report, we looked at the survival probability of all laboratory-confirmed hospitalized cases of pandemic (H1N1) 2009 influenza in Canada, for both waves combined to assess the impact of age, sex, presence or absence of underlying medical conditions and ICU admission on the survival of pandemic patients. Subgroup analyses were performed for aboriginal

population and cohort of seniors (age ≥ 65). An overall Kaplan-Meier (KM) curve was plotted for all pandemic patients to see the overall pattern of survival. Then separate KM curves were plotted for each of the above risk factors to compare the survival probability among different levels of each risk factor. Then employing Cox-proportional regression, the hazard ratios (HR) and their 95% confidence intervals (CIs) were estimated for each risk factor individually and adjusted hazard ratio (aHR) and their 95% CIs were obtained for each risk factor by including all the risk factors (covariates) in the model.

MATERIALS AND METHODS

DATA COLLECTION

The study sample consisted of all hospitalized, laboratory-confirmed pandemic (H1N1) 2009 cases (included patients admitted to intensive care unit (ICU)) and fatal cases (including fatal cases from institutions) from all provinces and territories in Canada, which were reported on a weekly basis to the PHAC from April 12, 2009 to April 3, 2010. The data collection methods have been described in more detail in previous publications.[2,3]

Because Ontario (ON) and Nova Scotia (NS) did not report on aboriginal status, the data from these provinces was excluded for aboriginal-specific calculations. Missing and unknown observations were not included in the calculation of percentages. For the underlying medical conditions, except for ON and Manitoba (MB), where it was assumed that missing values reflected no underlying condition, missing and unknown information was removed from the calculations. Pregnancy was ascertained only in women of child-bearing age (15–44) years. Missing and unknown values were not included in the calculation of percentages for this variable as well as for ICU admission and Ventilation Status. Canada has 13 distinct provinces and territories and in pandemic (H1N1) database, some provinces and territories (P/T) have sparse data. Therefore, four Atlantic Provinces (New Brunswick, NS, Prince Edward Island (PE), and Newfoundland and Labrador (NL)) and three territories (Nunavut (NU), Northwest Territories (NWT), and Yukon (YK)) were grouped together for the descriptive statistics.

Fig. 1 illustrates the flow chart of the patients included in the analysis. From April 12, 2009 to April 3, 2010, a total of 8,678 laboratory confirmed cases of pandemic (H1N1) 2009 influenza requiring admission to hospital (including 1,473 ICU admissions) and 428 deaths related to pandemic (H1N1) influenza were reported. Core data was unavailable for 375 cases; hence they were excluded from the survival analysis cohort. For the remaining 8,301 cases, the dates of symptom onset or specimen collection were not available for 181 patients and hence these cases were also excluded from the cohort. For 13 cases, there was no date of death listed in the database; therefore they were removed from the analysis cohort. The final analysis cohort included 8,107 patients for whom the survival times could be calculated. The survival time was defined as time-to-death, which was ascertained as the difference between the date of "symptom onset (if not available, then used the date of specimen collection)" and the date of death for pandemic (H1N1) affected patients during both waves of pandemic (H1N1) 2009 in Canada. The survival times for the patients who survived by the end of pandemic or who were lost to follow up were censored.

STATISTICAL ANALYSIS

An overall Kaplan-Meier survival curve was plotted for the full analysis cohort (8,107 patients) to see the overall survival pattern of the pandemic (H1N1) 2009 cohort, and separate KM survival curves were produced for each risk factor (Fig. 2). The Cox-regression was used for analysis to identify the significant risk factors for pandemic death. From these univariate analyses, variables with p-values < 0.05 were entered into multivariate Cox-regression model (stepwise selection) and the analysis was performed to with age, sex, underlying medical conditions and ICU admission in the model (sex was not significant in the univariate analysis, but was retained in the model for the sake of completeness since excluding it didn't make any difference in the results). An adjusted hazard ratio < 1 indicated a lower chance of death compared to its reference group for each risk factor adjusting for all other risk factors in the multivariate analysis. Ventilation status was aliased with the ICU admission (all patients on ventilation were among the ICU patients), therefore this variable was not included in the model. Since pregnancy status was only ascertained in the women of child-bearing age, it was also excluded from the multivariate analysis. All these analyses were conducted for combined data from all P/T since (H1N1) 2009 database only included data from hospitalized pandemic patients and data from outside hospitals is not available. In this work, we looked at predictors of death for the pandemic data combined for both waves.

SUBGROUP ANALYSES

To evaluate the risk factors affecting the survival of seniors (age ≥ 65) years and for aboriginal status a subgroup analysis was performed for both of these cohorts separately.

In all the above analyses, a p-value of < 0.05 was considered to indicate the statistical significance. All probabilities were two-tailed. Statistical analysis was performed using SAS EG v. 4.2.

RESULTS

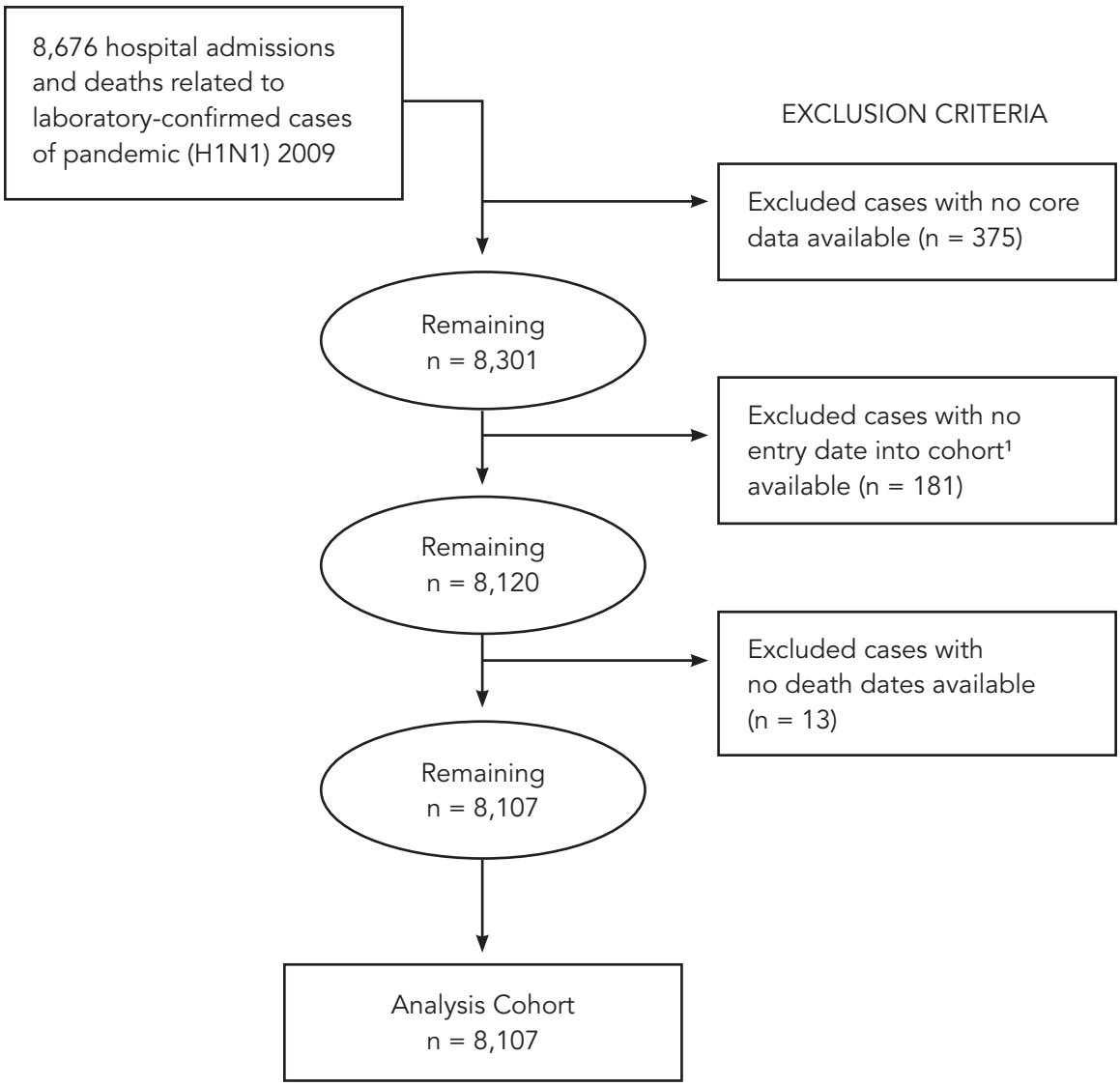
CLINICAL DESCRIPTION OF COHORT

Table 1 presents the descriptive statistics for combined and by wave pandemic data by age, sex, pregnancy status, aboriginal status, presence or absence of underlying medical conditions, ventilation status, ICU admission, and province/territory of residence. Case-fatality rates are reported only for combined data. Following is the description of combined (both waves) pandemic data, by waves data is included in the Table 1 only for illustration and has not been discussed in this report.

The median age for p(H1N1) 2009 cohort was 29 (interquartile range (IQR) 6–52) years. Median age for seniors (age ≥ 65) years was 74 (IQR 69–79) years. Age-specific case-fatality rates are 0.9%, 5%, 8.4%, and 13.4% for (0–19), (20–44), (45–64), and (age ≥ 65) age groups, showing highest case-fatality rate for seniors and lowest rate for (0–19) age group. Female patients comprise 49.8% of both; pandemic cohort and pandemic deaths and have the same case-fatality rate as for men. Among hospitalized patients, 30% were aboriginal patients and accounted for 19% of pandemic deaths with 4.9% case-fatality rate. There were 45.4% patients with underlying medical conditions and 73.7% of deaths occurred among them with a case-fatality rate of 11.2%. 30.7% of women of reproductive age (15–44) were pregnant and

only 4 (12.9%) deaths occurred among them (case-fatality rate 1.5%). 22% of hospitalized patients were admitted to ICU and accounted for 72% of pandemic deaths (case-fatality rate 16.6%).among the P/T, SK showed the highest case-fatality rate (22%) and MB showed the lowest (2.9%).

FIGURE 1: Flow chart of patients included in the analysis



1 Date of symptom onset or specimen collection

TABLE 1: Characteristics of 8,107 hospital admissions and 406 deaths during the first wave (Apr. 12 to Aug. 29, 2009) and the second wave (Aug. 30, 2009 to Apr. 3, 2010) of the 2009 pandemic (H1N1) in Canada

CHARACTERISTIC	NO. (%) OF PATIENTS						CASE-FATALITY RATES (%) FOR COMBINED DATA‡
	FIRST WAVE		SECOND WAVE AND POST-PEAK PERIOD		COMBINED		
	HOSPITAL ADMISSIONS N = 1447	DEATHS N = 67	HOSPITAL ADMISSIONS N = 6660	DEATHS N = 339	HOSPITAL ADMISSIONS N = 8107	DEATHS N = 406	
AGE, YR	**n = 1443**	**n = 67**	**n = 6659**	**n = 339**	**n = 8102**	**n = 406**	
0–19	669 (46.4)	8 (11.9)	2653 (39.8)	21 (6.2)	3322 (41)	29 (7.1)	0.9
20–44	366 (25.4)	18 (26.9)	1482 (22.3)	74 (21.8)	1848 (22.8)	92 (22.7)	5
45–64	293 (20.3)	24 (35.8)	1846 (27.7)	155 (45.7)	2139 (26.4)	179 (44.1)	8.4
≥ 65	115 (8)	17 (25.4)	678 (10.2)	89 (26.3)	793 (9.8)	106 (26.1)	13.4
Unknown	4	-	1	-	5	-	
SEX	**n = 1446**	**n = 67**	**n = 6654**	**n = 339**	**n = 8100**	**n = 406**	
females	741 (51.2)	41 (61.2)	3290 (49.4)	161 (47.5)	4031 (49.8)	202 (49.8)	5
males	705 (48.8)	26 (38.8)	3364 (50.6)	178 (52.5)	4069 (50.2)	204 (50.2)	5
Unknown	1	-	6	-	7	-	
ABORIGINAL[a]	**n = 366**	**n = 15**	**n = 1703**	**n = 140**	**n = 2069**	**n = 155**	
Yes	299 (81.7)	9 (60)	315 (18.5)	21 (15)	614 (29.7)	30 (19.4)	4.9
No	67 (18.3)	6 (40)	1388 (81.5)	119 (85)	1455 (70.3)	125 (80.6)	8.6
Unknown	680	26	3324	94	4004	120	

CHARACTERISTIC	NO. (%) OF PATIENTS						CASE-FATALITY RATES (%) FOR COMBINED DATA‡
	FIRST WAVE		SECOND WAVE AND POST-PEAK PERIOD		COMBINED		
	HOSPITAL ADMISSIONS N = 1447	DEATHS N = 67	HOSPITAL ADMISSIONS N = 6660	DEATHS N = 339	HOSPITAL ADMISSIONS N = 8107	DEATHS N = 406	
UNDERLYING MEDICAL CONDITION[b]	**n = 1361**	**n = 66**	**N = 4393**	**n = 330**	**n = 5754**	**n = 396**	
Yes	641 (47.1)	48 (72.7)	1969 (44.8)	244 (73.9)	2610 (45.4)	292 (73.7)	11.2
No	720 (52.9)	18 (27.3)	2424 (55.2)	86 (26.1)	3144 (54.6)	104 (26.3)	3.3
Unknown	86	-	2267	-	2353	-	
PREGNANT[c]	**n = 158**	**n = 8**	**n = 695**	**n = 23**	**n = 853**	**n = 31**	
Yes	73 (46.2)	4 (50)	189 (27.2)	0	262 (30.7)	4 (12.9)	1.5
No	85 (53.8)	4 (50)	506 (72.8)	23 (100)	591 (69.3)	27 (87.1)	4.6
Unknown	104	5	311	13	415	18	
VENTILATION	**n = 961**	**n = 39**	**n = 2970**	**n = 214**	**n = 3931**	**n = 253**	
Yes	145 (15)	30 (77)	526 (17.7)	124 (58)	671 (17.1)	154 (60.9)	23
No	816 (85)	9 (23)	2444 (82.3)	90 (42)	3260 (82.9)	99 (39.1)	3
Unknown	486	28	3690	125	4176	153	
ICU	**n = 1074**	**n = 57**	**n = 5393**	**n = 271**	**n = 6467**	**n = 328**	
Yes	279 (26)	49 (86)	1145 (21.2)	187 (69)	1424 (22)	236 (72)	16.6
No	795 (74)	8 (14)	4248 (78.8)	84 (31)	5043 (78)	92 (28)	1.8
Unknown	373	10	1267	68	1640	78	

CHARACTERISTIC	NO. (%) OF PATIENTS						CASE-FATALITY RATES (%) FOR COMBINED DATA‡
	FIRST WAVE		SECOND WAVE AND POST-PEAK PERIOD		COMBINED		
	HOSPITAL ADMISSIONS N = 1447	DEATHS N = 67	HOSPITAL ADMISSIONS N = 6660	DEATHS N = 339	HOSPITAL ADMISSIONS N = 8107	DEATHS N = 406	
PROVINCE/ TERRITORIES	**n = 1447**	**n = 67**	**n = 6660**	**n = 339**	**n = 8107**	**n = 406**	
Alberta	130 (9)	7 (10.5)	1154 (17.3)	63 (18.6)	1284 (15.8)	70 (17.2)	5.5
NB, NS, PE, and NL	7 (0.5)	1 (1.4)	723 (10.9)	31 (9.1)	730 (9)	32 (7.9)	4.4
British Columbia	48 (3.3)	4 (6)	572 (8.6)	46 (13.6)	620 (7.7)	50 (12.3)	8
Manitoba	213 (14.7)	7 (10.4)	167 (2.5)	4 (1.2)	380 (4.7)	11 (2.7)	2.9
Ontario	400 (27.6)	25 (37.3)	1424 (21.4)	99 (29.2)	1824 (22.5)	124 (30.6)	6.8
Quebec	544 (37.6)	18 (26.9)	2505 (37.6)	81 (23.9)	3049 (37.6)	99 (24.4)	3.2
Saskatchewan	23 (1.6)	4 (6)	45 (0.7)	11 (3.2)	68 (0.8)	15 (3.7)	22
NU, NWT, and YK	82 (5.7)	1 (1.5)	70 (1.0)	4 (1.2)	152 (1.9)	5 (1.2)	3.3

‡ Case-fatality rate was defined as the number of death due to the pandemic (H1N1) 2009 divided by the total number of pandemic cases in each group;

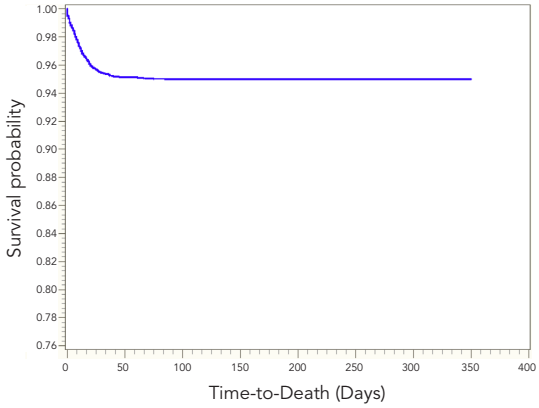
[a] Excluding ON and NS;

[b] Includes lung disease, asthma, diabetes and other metabolic disorders, pre-existing heart disease, renal disease, immunosuppression, anemia, liver disease, neurologic disorder, or other chronic medical condition predisposing to complications of influenza;[4,5]

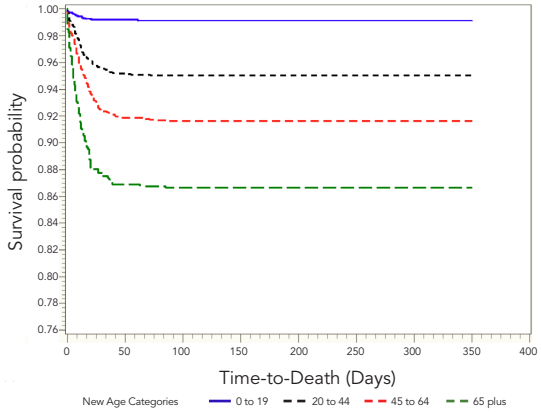
[c] Among women of child-bearing age (15–44) years; Unknown includes missing and unknown observations.

FIGURE 2: Kaplan-Meier Survival Curves for pandemic (H1N1) 2009 Patients

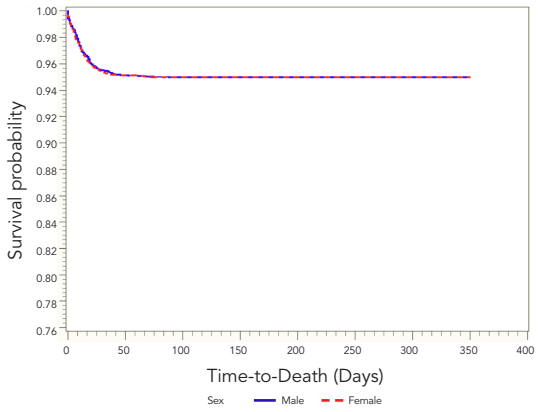
Overall Kaplan-Meier Survival Curve



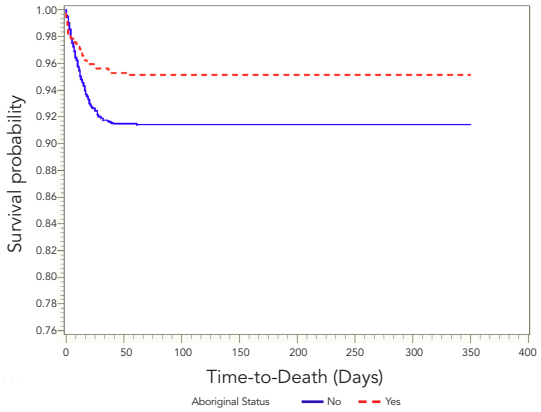
Kaplan-Meier Survival Curve by Age



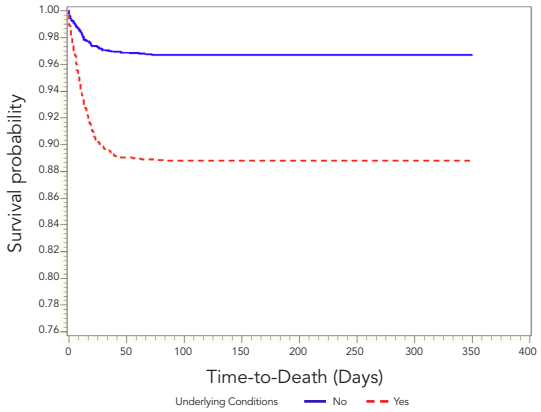
Kaplan-Meier Survival Curve by Sex



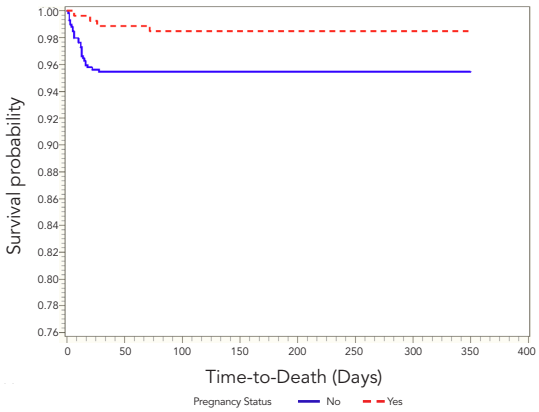
Kaplan-Meier Survival Curve by Aboriginal Status



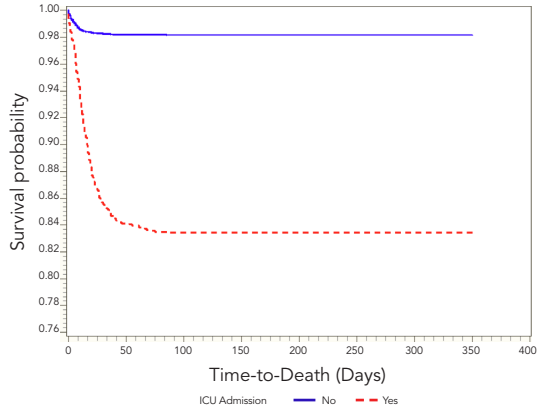
Kaplan-Meier Survival Curve by Underlying Medical Conditions



Kaplan-Meier Survival Curve by Pregnancy Status



Kaplan-Meier Survival Curve by ICU Admission



Kaplan-Meier Survival Curve by P/T

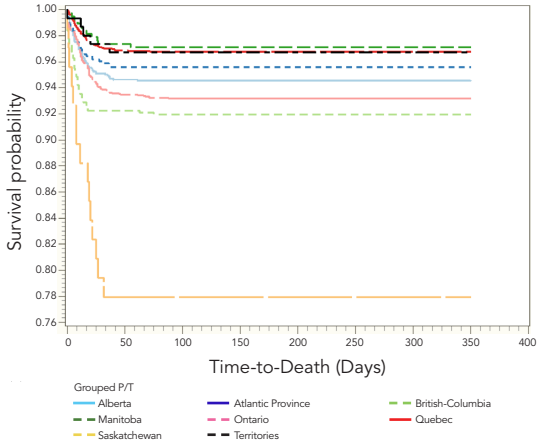


TABLE 2: Hazard Ratios and 95% confidence intervals for individual risk factors using Cox proportional hazards regression model

RISK FACTORS	HR (95% CI)	P-VALUE
Age		
20 ≤ age ≤ 44	Ref	Ref
0 ≤ age < 19	0.17 (0.113, 0.261)	< 0.0001
45 ≤ age ≤ 64	1.71 (1.327, 2.195)	< 0.0001
65 ≤ age	2.82 (2.134, 3.731)	< 0.0001
Sex		
Male	Ref	Ref
Female	1.000 (0.823, 1.215)	1.000
Underlying Medical Conditions		
No	Ref	Ref
Yes	3.52 (2.82, 4.41)	< 0.0001
ICU Admissions		
No	Ref	Ref
Yes	9.67 (7.59, 12.302)	< 0.0001
Ventilation Status		
No	Ref	Ref
Yes	8.248 (6.407, 10.619)	< 0.0001

HR = hazards ratio; CI = confidence interval; Ref = reference group

TABLE 3: Adjusted Hazard Ratios and 95% confidence intervals from multiple Cox proportional hazards regression model for various risk factors

RISK FACTORS	AHR (95% CI)	P-VALUE
Age		
20 ≤ age ≤ 44	Ref	Ref
0 ≤ age < 19	0.32 (0.182, 0.503)	< 0.0001
45 ≤ age ≤ 64	1.386 (1.038, 1.850)	0.0269
65 ≤ age	2.695 (1.946, 3.732)	< 0.0001
Sex		
Male	Ref	Ref
Female	0.988 (0.792, 1.232)	0.9144
Underlying Medical Conditions		
No	Ref	Ref
Yes	1.766 (1.344, 2.321)	< 0.0001
ICU Admissions		
No	Ref	Ref
Yes	4.689 (3.651, 6.023)	< 0.0001

AHR = Adjusted hazards ratio; CI = confidence interval; Ref = reference group

TABLE 4: Adjusted Hazard Ratios and 95% confidence intervals from multiple Cox proportional hazards regression model for subgroup analysis for seniors

RISK FACTORS	AHR (95% CI)	P-VALUE
Sex		
Male	Ref	Ref
Female	0.861 (0.559, 1.327)	0.4980
Underlying Medical Conditions		
No	Ref	Ref
Yes	1.633 (0.816, 3.267)	< 0.1660
ICU Admissions		
No	Ref	Ref
Yes	2.564 (1.649, 3.988)	< 0.0001

AHR = Adjusted hazards ratio; CI = confidence interval; Ref = reference group

TABLE 5: Adjusted Hazard Ratios and 95% confidence intervals from multiple Cox proportional hazards regression model for subgroup analysis for aboriginals

RISK FACTORS	AHR (95% CI)	P-VALUE
Age		
20 ≤ age ≤ 44	Ref	Ref
0 ≤ age < 19	0.267 (0.151, 0.470)	< 0.0001
45 ≤ age ≤ 64	1.237 (0.897, 1.706)	0.1951
65 ≤ age	2.532 (1.766, 3.629)	< 0.0001
Sex		
Male	Ref	Ref
Female	0.962 (0.751, 1.232)	0.7564
Underlying Medical Conditions		
No	Ref	Ref
Yes	1.703 (1.201, 2.414)	< 0.0028
ICU Admissions		
No	Ref	Ref
Yes	4.032 (3.089, 5.263)	< 0.0001

AHR = Adjusted hazards ratio; CI = confidence interval; Ref = reference group

DISCUSSION

The overall KM survival curve (Fig. 2) showed a decline in survival over time with all 406 deaths occurred by Day 88 (different from calendar days), and then there is a plateau after that. KM curves by age group showed the highest survival for age group (0–19) years while the seniors (age ≥ 65) had the worst survival. The KM curves by sex are superimposed indicating no difference in the survival probability for men and women during the pandemic (H1N1) 2009. The KM curves from the limited aboriginal data showed the better survival for aboriginal patients compared to non-aboriginals. Since the aboriginal data has not been captured for all provinces (ON and NS didn't collect the data on this variable), these plots may not be representative of all aboriginals affected by the pandemic. The KM curves by underlying medical conditions showed better survival for people with no comorbidities. The KM curves by pregnancy status for women of child bearing age (15–44) years indicated better survival for pregnant women (there were only 4 deaths (case fatality rate 8.2%) for pregnant women in this age cohort). This could be due to the fact that pregnant women were well taken care of compared to other women in this cohort. The KM curves by ICU admission showed a huge difference in survival experience between ICU and non-ICU patients, this may be due to the fact that ICU patients were sicker than non-ICU patients. Provincial comparisons showed that the best survival rates were for Atlantic province and worst for Saskatchewan. But, this may not be representing the true picture of pandemic deaths and survival by P/T because pandemic database was limited to only hospitals and have not captured the pandemic data outside the hospitals, and not all the pandemic patients were admitted to the hospitals. The median survival times could not be estimated for any of the risk factors because more than 50% observations were censored for these risk factors in the pandemic database as well as the largest observations were censored.

The results of the Cox regression analysis for individual risk factors are presented in Table 2. The (20–44) age group has been used as reference group. The HR for (0–19) age group indicated 83% better survival compared to the reference group. The HR for seniors (age ≥ 65) years is 2.82 indicating about 3-fold increased risk of death for seniors compared to the reference group. There is no difference in the survival experience of men and women, with a HR of 1.00. The pandemic patients with underlying medical conditions have a HR = 3.52 compared to patients with no underlying conditions indicating 3.5-fold increased risk of death for this group. Since all ICU patients were very sick, they have about 10-fold increased risk of death, HR = 9.67, compared to rest of the pandemic patients. The risk factor "ventilation" showed an HR = 8.24, a greater risk of death in patients on ventilation. Pregnancy status showed a protected effect and HR = 0.33 showed 67% better survival among pregnant women (within the cohort of child-bearing age). All the risk factors, except variable sex, showed statistically significance (p-value < 0.0001) better survival compared to their respective reference groups in the univariate analysis.

Table 3 presents the adjusted hazard ratios and their 95% confidence intervals from the multivariate Cox regression analysis with risk factors age, sex, underlying medical conditions, and ICU admission. The variable sex was not significant in the univariate analysis but was retained in the model for the sake of completion. The results in Table 3 are in the same direction as those of Table 2 and showed the adjusted hazard ratios for each predictor in the model similar to unadjusted hazard ratios. Adjusted HR for age group (0–19) is 0.32 indicating 68% better survival for this group compared to reference group (20–44), and seniors have about 3-fold increase in hazard of death compared to the reference group. Adjusted HR for sex is 1 showing no difference in risk of death among males and females. But aHRs for underlying medical conditions and ICU admission reduced from 3.5 to 1.7 and 9.7 to 4.7 respectively, when adjusted for other predictors, but still showed increased risk of pandemic death compared to their reference groups.

Results of subgroup analysis for seniors (age ≥ 65) using Cox regression with sex, underlying medical conditions and ICU status in the model showed 14% better survival, though not statistically significant for women compared to men during pandemic (H1N1) 2009 (aHR 0.86) (Table 4). The aHR for underlying conditions is the same as in the full cohort analysis, showing about 2-fold increased risk of death for seniors with comorbidities. For ICU admitted seniors, the risk of death is 2.5-fold compared to non-ICU seniors when adjusted for other predictors.

Aboriginal pandemic cohort was analyzed with age, sex, underlying medical conditions and ICU status in the model with aHR for each predictor very similar to those obtained for the full cohort (Table 5). As mentioned earlier, the database had limited aboriginal representation and therefore the results may not be generalizable to all Aboriginals.

CONCLUSIONS

Results of our study showed that age, presence of underlying medical conditions and ICU admission significantly affected the survival of pandemic (H1N1) 2009 patients in Canada. These results were expected. The case-fatality rate was highest for seniors (age ≥ 65) and lowest for (0–19) age group. Our findings match with those of others,[4–7] the pandemic hit the seniors hardest with highest case-fatality rate (our results showed the 3-fold increased risk of death for seniors).

LIMITATIONS

The pandemic (H1N1) 2009 database included only laboratory-confirmed hospitalized cases and may only be representative of the most severe cases of pandemic (H1N1). Also, there is no information on pandemic deaths outside hospitals (and institutions). The database did not collect the information on the status of vaccination for H1N1 virus; therefore no comments could be made on the effectiveness of the vaccination in pandemic patients from this database.

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Authors: Shagufta. Ahmed Sultan (PhD),[a,b] Samina Aziz (MSc)[a,c]

[a] Surveillance and Outbreak Response Division, Center for Immunization and Respiratory Infectious Diseases, Public Health Agency of Canada, Ottawa, Canada[§]

[b] Office of Science, Therapeutic Products Directorate, Health Products and Food Branch, Health Canada

[c] Therapeutic Effectiveness and Epidemiology Section, Therapeutic Effectiveness and Policy Bureau, Marketed Health Products Directorate, Health Products and Food Branch, Health Canada

[§] At the time this work was developed, both authors were affiliated to SORD, CIRID, PHAC with first author working on a secondment to Public Health Agency of Canada.