MAJOR ARTICLE

Risk Factors for Severe Illness with 2009 Pandemic Influenza A (H1N1) Virus Infection in China

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Background. Data on risk factors for severe outcomes from 2009 pandemic influenza A (H1N1) virus infection are limited outside of developed countries.

Methods. We reviewed medical charts to collect data from patients hospitalized with laboratory-confirmed 2009 H1N1 infection who were identified across China during the period from September 2009 through February 2010, and we analyzed potential risk factors associated with severe illness (defined as illness requiring intensive care unit admission or resulting in death).

Results. Among 9966 case patients, the prevalence of chronic medical conditions (33% vs 14%), pregnancy (15% vs 7%), or obesity (19% vs 14%) was significantly higher in those patients with severe illness than it was in those with less severe disease. In multivariable analyses, among nonpregnant case patients aged ⩾2 years, having a chronic medical condition significantly increased the risk of severe outcome among all age groups, and obesity was a risk factor among those <60 years of age. The risk of severe illness among pregnant case patients was significantly higher for those in the second and third trimesters. The risk of severe illness was increased when oseltamivir treatment was initiated ⩾5 days after illness onset (odds ratio, 1.42; 95% confidence interval, 1.20–1.67). For persons <60 years of age, the prevalence of obesity among case patients with severe illness was significantly greater than it was among those without severe illness or among the general population.

Conclusions. Risk factors for severe 2009 H1N1 illness in China were similar to those observed in developed countries, but there was a lower prevalence of chronic medical conditions and a lower prevalence of obesity. Obesity was a risk factor among case patients <60 years of age. Early initiation of oseltamivir treatment was most beneficial, and there was an increased risk of severe disease when treatment was started ⩾5 days after illness onset.

The global epidemiology of human infection with 2009 pandemic influenza A (H1N1) virus indicates that the age distribution of rates of hospitalization and mortality [1–5] is different than that for seasonal influenza, which occurs predominantly among elderly persons [6]. Risk factors for severe 2009 H1N1 disease [4, 5, 7–15] have been reported to be similar to those identified for complications from seasonal influenza [6]. A higher risk of severe complications from 2009 H1N1 virus infection has also been reported in obese individuals [5, 7, 16–18] and among indigenous populations [9, 18, 19]; whether they are independent risk factors is unknown [20].

Nationwide 2009 H1N1 surveillance was established in China on 30 April 2009. Most Chinese cases identified during the early containment phase of the pandemic were clinically mild [21, 22]. In this report, we describe the epidemiological and clinical characteristics of identified case patients who were hospitalized with

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laboratory-confirmed 2009 H1N1 infection across China from September 2009 through February 2010, and we analyze potential risk factors associated with severe illness.

METHODS

Case Patients

Beginning on 30 April 2009, all laboratory-confirmed cases of 2009 H1N1 infection were required to be reported to the Chinese Center for Disease Control and Prevention (China CDC). During the first 4 months of the pandemic, all confirmed case patients, regardless of the clinical severity of their illness, were admitted to the hospital and placed in isolation at designated hospitals for containment purposes [22]. By approximately mid-August 2009, as 2009 H1N1 activity expanded, containment strategies were stopped and the clinical management policy was changed by the Chinese Ministry of Health (MoH), such that only confirmed case patients who required medical treatment for complications, based on clinical judgment, were admitted to hospitals.

A confirmed case patient was defined as a patient who was hospitalized for at least 24 h with an acute influenza-like illness (temperature $\geq$38 °C with either cough or sore throat) and 2009 H1N1 virus infection detected by real-time reverse-transcription polymerase chain reaction testing of respiratory specimens. Details on laboratory testing and confirmation of case patients are published elsewhere [22]. Confirmed case patients were classified as having severe illness if they were admitted to an intensive care unit (ICU) or died, and they were classified as having nonsevere illness if they were alive and had not been admitted to an ICU by the end of the study period.

Data Collection

Each confirmed case patient with individual data on sex, age, and location, was required to be reported from all admitting hospitals nationwide to the China CDC. Under the coordination of the MoH, all admitting hospitals were asked to retrospectively collect detailed epidemiological and clinical data from a sample of confirmed case patients on a voluntary basis as part of public health response. Case patients were selected by physicians for medical chart review and data abstraction to reflect the monthly distribution of case patients per hospital. Data extraction was performed by physicians using a standardized form to collect data about demographic characteristics, underlying chronic medical conditions, height and weight, pregnancy status, treatment, and outcomes, and all data were reported electronically to the China CDC. We included confirmed case patients reported to the China CDC during the period from 1 September 2009 through 28 February 2010 for final analysis, and we censored data collection by 7 March 2010.

Medical conditions associated with a high risk for influenza complications were defined on the basis of those listed by the United States Advisory Committee on Immunization Practices [6]. Body mass index (BMI; defined as the weight in kilograms divided by the square of height in meters) was calculated for case patients with available height and weight data to assess obesity using both Chinese and US criteria (Supplementary Information). BMI was not calculated in young children aged $<$2 years or for pregnant women. We defined pregnancy to include pregnant women of any gestational age up to 2 weeks postpartum (including after pregnancy loss), per previous reports [12, 13]. We estimated 11,607,818 pregnant women in China using census data [23] (Supplementary Information).

Statistical Analysis

Three subsets of the study population were analyzed separately to assess risk factors associated with severe illness using multivariable logistic regression (Supplementary Information): (1) nonpregnant patients $\geq$2 years of age, to assess chronic medical conditions and obesity; (2) female patients of reproductive age, to assess pregnancy; and (3) pregnant patients, to assess gestational age at illness onset. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Hospitalization and mortality rates and death-hospitalization ratios were calculated (Supplementary Information). We compared the prevalence of obesity and pregnancy among case patients with nonsevere illness and those with severe illness and among the general population. We also compared outcomes for case patients who received early antiviral treatment ($\leq$2 days after illness onset) with outcomes for those treated later.

Statistical analysis was performed using SAS, version 9.2 (SAS Institute). For all analyses, probabilities were 2-tailed, and a P value of $<$.05 was considered to be statistically significant.

RESULTS

From September 2009 through February 2010, a total of 31,562 confirmed case patients were hospitalized throughout China and were reported to the China CDC, including 793 (2.5%) who died and 24,268 (77%) who were discharged from the hospital. Of these patients, 9966 (32%), including 783 (8%) who died and 8491 (85%) who were discharged from the hospital, had complete chart abstractions and were included in analyses of risk factors. These represented 35% of all discharged patients (8491 of 24,268 patients) and 99% of deaths (783 of 793 deaths) reported from 30 of 31 provinces (Supplementary Figure 1). Illness onsets of included case patients peaked in late November and decreased after early December 2009 (Figure 1). The characteristics of included case patients and reported case patients without chart abstractions are shown in Supplementary Table 1; details of case patients' enrollments are provided in Supplementary Figure 2.

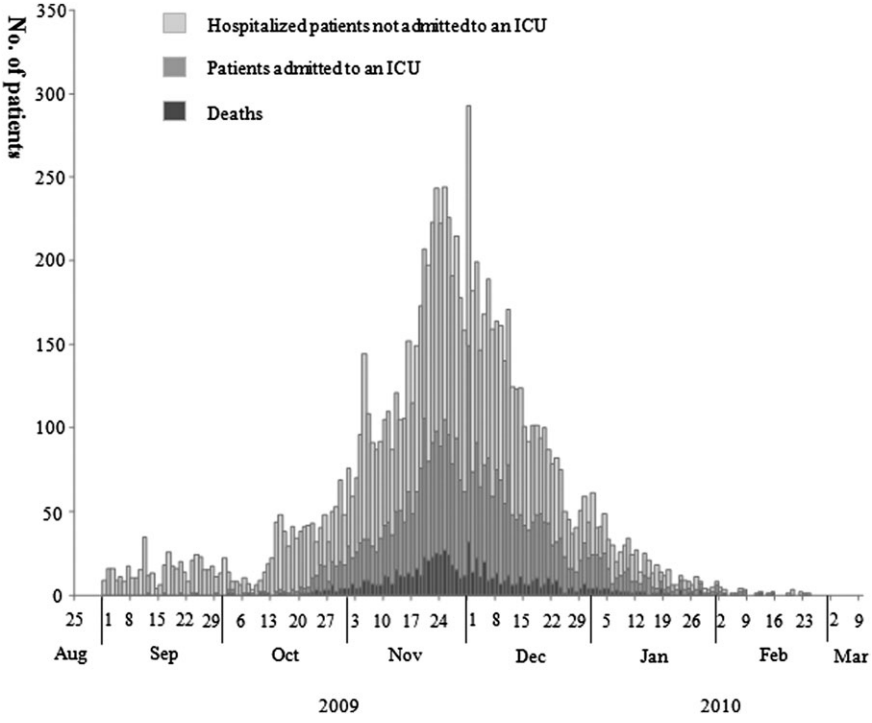

Figure 1. Case patients hospitalized with 2009 pandemic influenza A (H1N1) virus infection ($n = 9966$) with chart review data, by date of illness onset, China, September 2009–February 2010. ICU, intensive care unit.

A total of 31,562 reported hospitalized case patients, including 793 patients who died, were used to calculate hospitalization and mortality rates, as well as death-hospitalization ratios. The overall hospitalization and mortality rates during the 6-month study period were 2.4 hospitalizations per 100,000 population and 0.6 deaths per 1,000,000 population. Hospitalization rates ranged from 6.1 hospitalizations per 100,000 population among children 5–14 years of age to 0.6 hospitalizations per 100,000 population among persons ⩾65 years of age. Mortality rates ranged from 1.2 deaths per 1,000,000 population in children <5 years of age to 0.3 deaths per 1,000,000 population in children 5–14 years of age (Figure 2A). Death-hospitalization ratios were highest among those ⩾65 years of age (0.115) and lowest among children 5–14 years of age (0.007) (Figure 2B).

Demographic Characteristics and Underlying Risk Conditions

The median age of the 9966 case patients was 22 years (range, 1 day–93 years), 58% were <25 years of age, and 56% were male (Table 1). The median age of case patients increased with increasing disease severity, from 18 years for those without ICU admission, to 27 years for those with ICU admission, to 30 years for those with fatal outcomes. Of 9503 case patients with known information, 21% had at least 1 high-risk chronic medical condition; high-risk conditions were uncommon among those <25 years of age (found in <10% of such patients). The prevalence of chronic medical conditions among hospitalized case patients increased with increasing disease severity, from 14% among those without ICU admission, to 31% among those with ICU admission, to 38% among those with fatal outcome.

A total of 1014 case patients (10%) were considered to be pregnant, including 19 postpartum women who had delivered within 2 weeks after illness onset. Of these, most (95%) were <35 years of age, and only 63 (7%) had chronic high-risk medical conditions. Of 563 pregnant women (56%) who required ICU admission, 156 (15%) died. Of 968 pregnant case patients with known gestational age, 63% were in the 3rd and 29% were in the 2nd trimester.

Of the 8456 nonpregnant case patients ⩾2 years of age with known BMI, 1002 (12%) or 1336 (16%) were obese, based on US criteria and Chinese criteria, respectively; only 33 (0.7%) of the adults were morbidly obese (BMI ⩾40). Of the 1336 case patients who were obese according to Chinese criteria, 559 (42%) required ICU admission, and 91 (7%) died. Twenty-four percent of obese case patients (311 of 1287) also had chronic high-risk medical conditions. Among obese case patients, 62% of patients with nonsevere illness were <15 years of age, whereas 68% of deaths were in those ⩾25 years of age.

Treatment and Outcomes

Case patients were admitted to the hospital a median of 3 days (interquartile range [IQR], 1–5 days) after illness onset (Table 2). During hospitalization, 7266 case patients (76%),

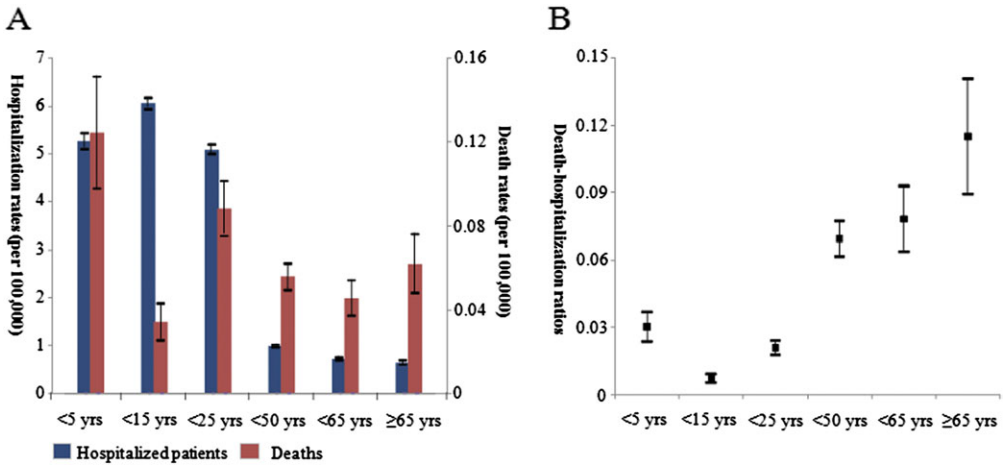

Figure 2. Hospitalization and mortality rates and death-hospitalization ratios by age group. *A*, Hospitalization rates ($n = 31,562$) and mortality rates ($n = 793$) per 100,000 population. *B*, Death-hospitalization ratios. Error bars indicates 95% confidence intervals. Yrs, years.

including 2683 (90%) of the case patients with ICU admission and 622 (83%) of those with fatal outcomes, were treated with neuraminidase inhibitors; all received oseltamivir, except 2 patients who only received inhaled zanamivir. Oseltamivir treatment was started within 2 days after symptom onset for 1155 case patients (17%), on days 3–4 after symptom onset in 1703 (26%), and ⩾5 days after symptom onset in 3807 (57%).

The median time from illness onset to initiation of oseltamivir treatment was significantly shorter for case patients with nonsevere illness, compared with those who had severe illness, among nonpregnant case patients ⩾2 years of age ($P < .001$; Supplementary Table 2); this was also observed for female case patients of reproductive age and for those who were pregnant (Supplementary Tables 3–4). In multivariable analyses of the effectiveness of early oseltamivir treatment (initiated within 2 days after illness onset) among nonpregnant case patients ⩾2 years of age (Table 3), later initiation (3–4 days after onset) was associated with a trend toward an increased risk of severe illness, and initiating oseltamivir treatment ⩾5 days after illness onset was associated with a statistically significant risk of severe illness (OR, 1.42; 95% CI, 1.20–1.67); this observation was consistent for female case patients of reproductive age and for those who were pregnant (data not shown).

Of the 9966 case patients, 3797 (38%), including 783 patients with fatal outcome, were admitted to an ICU for a median of 5 days (IQR, 2–10 days), and 1961 (52%) of case patients admitted to the ICU required mechanical ventilation. Of the 9966 hospitalized patients, 8491 (85%) were discharged from the hospital; 783 (8%) died after a median of 11 days (IQR, 6–19 days) after illness onset.

Risk Factors Associated with Severe Illness

The proportion of case patients with at least 1 high-risk chronic medical condition (33% vs 14%; $P < .001$), pregnancy (15% vs 7%; $P < .001$), or obesity by Chinese criteria (19% vs 14%; $P < .001$) were all significantly higher among case patients with severe illness than they were among case patients with nonsevere illness (Table 1). The proportion of case patients with severe illness who had any of these 3 risk factors was significantly higher than the proportion of case patients with nonsevere illness who had any of these 3 risk factors (54% vs 31%; $P < .001$).

In multivariable analyses (Table 3), male sex (OR, 1.19; 95% CI, 1.07–1.31) and delayed time to hospital admission (OR, 1.27; 95% CI, 1.13–1.42) were significantly associated with severe illness among nonpregnant patients ⩾2 years of age. In a multivariable "main effects" model that did not account for any interactions, obesity (OR, 1.54; 95% CI, 1.35–1.76) and having a chronic disease (OR, 2.72; 95% CI, 2.41–3.08) were independent risk factors for severe illness among all ages of nonpregnant case patients (data not shown). Although age was a modifier of the effect of both chronic medical conditions and obesity on severe illness, results of the multivariable model that accounted for interactions between age, chronic medical conditions, and obesity indicated that having a chronic medical condition significantly increased the risk of severe outcomes with increasing age >18 years; the highest risk was observed among patients ⩾60 years of age and those with chronic medical conditions (OR, 6.88; 95% CI, 5.54–8.55), compared with patients without chronic medical conditions. When obese patients were compared with nonobese patients, multivariable analyses indicated that obesity significantly increased the risk of severe outcomes among those 2–17 years of age (OR, 1.34; 95% CI, 1.10–1.63) and 18–59 years of age (OR, 1.91; 95% CI, 1.57–2.31) but not in persons ⩾60 years of age.

Age ⩾35 years (OR, 1.40; 95% CI, 1.10–1.77) and delayed time to hospital admission (OR, 1.80; 95% CI, 1.47–2.19) were independent risk factors for severe illness among female case patients of reproductive age (15–49 years of age) in

Table 1. Demographic Characteristics and Underlying Conditions of Case Patients Hospitalized with 2009 Pandemic Influenza A (H1N1)

Characteristic	All case patients (n = 9966)	Patients with nonsevere cases(n= 6169)	Patients with severe illness		
			Subtotal(n= 3797)	Admitted to an ICU(n = 3014)	Death(n = 783)
Male sex	5558 (56)	3470 (56)	2088 (55)	1688 (56)	400 (51)
Age, median years (IQR)	22 (11–39)	18 (10–31)	28 (14–47)	27 (12–46)	30 (20–49)
At least 1 chronic medical condition[a]	1999 (21)	833 (14)	1166 (33)	896 (31)	270 (38)
Chronic respiratory disease	609 (6)	246 (4)	363 (10)	291 (10)	72 (10)
Asthma	204 (2)	113 (2)	91 (3)	80 (3)	11 (2)
Chronic cardiovascular disease	422 (4)	127 (2)	295 (8)	226 (8)	69 (10)
Type 1 or 2 diabetes	380 (4)	129 (2)	251 (7)	184 (6)	67 (9)
Chronic liver disease	340 (4)	154 (3)	186 (5)	151 (5)	35 (5)
Chronic renal disease	286 (3)	104 (2)	182 (5)	134 (5)	48 (7)
Immunosuppression	191 (2)	67 (1)	124 (3)	80 (3)	44 (6)
Neurological disease	194 (2)	71 (1)	123 (3)	85 (3)	38 (5)
Pregnancy	1014 (10)	451 (7)	563 (15)	407 (14)	156 (20)
Gestational weeks					
0–13	77 (8)	64 (15)	13 (2)	11 (3)	2 (1)
14–28	278 (29)	124 (29)	154 (28)	100 (26)	54 (36)
⩾29	613 (63)	238 (56)	375 (69)	281 (72)	94 (63)
Gravidity					
1	576 (63)	280 (69)	296 (58)	206 (57)	90 (63)
⩾2	334 (37)	124 (31)	210 (42)	158 (43)	52 (37)
Obesity					
US criteria	1002 (12)	610 (11)	392 (13)	330 (14)	62 (11)
BMI ⩾40	33 (.7)	16 (.6)	17 (1)	15 (1)	2 (.4)
China criteria	1336 (16)	777 (14)	559 (19)	468 (19)	91 (16)
Influenza vaccination during 2008–2009 season	178 (2)	115 (2)	63 (2)	54 (2)	9 (2)
H1N1 vaccination	22 (.2)	15 (.3)	7 (.2)	5 (.2)	2 (.3)

NOTE. Data are no. (%) of patients, unless otherwise indicated. Percentages may not total 100 because of rounding. All patients who died had been admitted to an ICU. BMI, body mass index, defined as the weight in kilograms divided by the square of height in meters; ICU, intensive care unit; IQR, interquartile range.

[a] Chronic medical conditions listed are not mutually exclusive.

multivariable analyses. Chronic medical conditions modified the effect of pregnancy on severe illness. Compared with previously healthy nonpregnant female case patients, pregnant women with chronic medical conditions had the highest risk for severe illness (OR, 3.69; 95% CI, 2.15–6.31) in multivariable analyses (Table 3). The risk of severe illness was markedly higher in the second (OR, 6.10; 95% CI, 3.12–11.94) or third trimester (OR, 7.62; 95% CI, 3.99–14.55) among pregnant case patients; the risk of severe illness appeared higher in the third trimester than in the second trimester (OR, 1.25; 95% CI, 0.92–1.70) but was not significantly different (P = .152). Pregnant multigravida case patients had a higher risk of severe illness than did primgravida case patients (OR, 1.56; 95% CI, 1.16–2.08).

The proportion of pregnant women among case patients with nonsevere illness was higher than that among the general Chinese population of reproductive-age women (31% vs 3%; OR, 13.20; 95% CI, 11.82–14.75); a higher proportion of pregnant women experienced severe illness than experienced nonsevere illness (51% vs 31%; OR, 2.39; 95% CI, 2.03–2.81) (Table 4).

Except for those case patients ⩾60 years of age, the proportion of individuals with obesity was higher among patients with nonsevere illness than it was among the general population, including those 2–17 years of age (18% vs 2%; OR, 10.45; 95% CI, 9.49–11.52) and those 18–59 years of age (11% vs 8%; OR, 1.35; 95% CI, 1.18–1.54); the proportion of individuals with obesity was also significantly higher among case patients with severe illness than among case patients with nonsevere illness (Table 4).

DISCUSSION

In this large series of case patients hospitalized with 2009 H1N1 virus infection, children and young adults <25 years of age had the highest rates of hospitalization. Although case patients ⩾65 years of age had the highest death-hospitalization ratios, children <5 years of age had the highest mortality rate. Risk factors for

Table 2. Treatment, Complications, and Clinical Course of Case Patients Hospitalized with 2009 Pandemic Influenza A (H1N1)

Characteristic	All case patients (n = 9966)	Patients with nonsevere cases(n= 6169)	Patients with severe illness		
			Subtotal(n= 3797)	Admitted to an ICU(n = 3014)	Death(n = 783)
Antiviral treatment	7266 (76)	3961 (67)	3305 (89)	2683 (90)	622 (83)
Antiviral initiation time					
Median days (IQR)	4 (2–6)	4 (2–6)	5 (2–7)	4 (2–7)	5 (3–7)
Started on symptom day 1–2	1155 (17)	671 (19)	484 (16)	401 (16)	83 (14)
Started on symptom day 3–4	1703 (26)	1006 (28)	697 (22)	574 (23)	123 (21)
Started on symptom day ⩾5	3807 (57)	1883 (53)	1924 (62)	1532 (61)	392 (66)
Duration of oseltamivir treatment					
Median days (IQR)	5 (3–6)	5 (3–5)	5 (2–7)	5 (3–7)	3 (2–7)
1–4 days	2296 (36)	1158 (34)	1138 (39)	818 (35)	320 (56)
5 days	2038 (32)	1413 (41)	625 (21)	567 (24)	58 (10)
⩾6 days	2018 (32)	842 (25)	1176 (40)	985 (42)	191 (34)
Mechanical ventilation	1961 (20)	0 (0)	1961 (52)	1326 (44)	635 (82)
Complications					
Pneumonia	6682 (70)	3198 (54)	3484 (94)	2761 (93)	723 (97)
Respiratory failure	2429 (25)	0 (0)	2429 (65)	1724 (58)	705 (93)
Acute respiratory distress syndrome	1574 (17)	0 (0)	1574 (43)	994 (34)	580 (79)
Hepatic dysfunction	1002 (11)	184 (3)	818 (23)	511 (18)	307 (43)
Cardiac failure	892 (9)	0 (0)	892 (24)	503 (17)	389 (53)
Renal dysfunction	590 (6)	60 (1)	530 (15)	243 (8)	287 (39)
Toxic shock syndrome	430 (4)	0 (0)	430 (12)	177 (6)	253 (35)
Neurologic disorders	393 (4)	88 (1)	305 (8)	174 (6)	131 (19)
Disseminated intravascular coagulation	105 (1)	3 (.1)	102 (3)	33 (1)	69 (10)
Clinical course, median days (IQR)					
From illness onset to hospital admission	3 (1–5)	3 (1–5)	4 (1–6)	4 (1–6)	4 (2–6)
Length of stay in ICU	5 (2–10)	–	5 (2–10)	6 (2–10)	4 (2–11)
Length of stay in hospital	8 (6–13)	7 (5–10)	13 (8–19)	13 (9–20)	8 (2–15)
From illness onset to discharge or death	12 (8–18)	10 (7–15)	16 (10–24)	17 (12–25)	11 (6–19)

NOTE. Data are no. (%) of patients, unless otherwise indicated. Percentages may not total 100 because of rounding. All case patients who died had been admitted to an ICU. ICU, intensive care unit; IQR, interquartile range.

severe 2009 H1N1 disease were similar to those observed in developed countries [4, 5, 7–15] but with a lower prevalence of underlying chronic medical conditions and a lower prevalence of obesity among hospitalized patients and those with severe illness. Notably, obesity was identified as a risk factor for severe illness among case patients <60 years of age, and multigravida pregnancy was a risk factor among pregnant case patients. The risk of severe disease increased when oseltamivir treatment was started >2 days after illness onset, and initiation of treatment >4 days after onset was associated with a significant risk of severe disease.

Obesity has not been identified as a risk factor for severe complications from seasonal influenza. A high prevalence of obesity has been reported among case patients hospitalized with 2009 H1N1 virus infection [5, 7, 16–18], although co-existing chronic medical conditions are often present. A small observational study from the United States suggested that morbid obesity was significantly associated with hospitalization among adults [20]. However, the prevalence of obesity among children and adolescents (2.1%), and among adults (7.1%) is much lower in China [24] than in the United States (16.9% and 33.8%, respectively) [25, 26]. Nearly half of obese Chinese case patients required ICU admission or died, but only 24% also had chronic medical conditions, although the overall prevalence of obesity was lower than in previous reports [5, 6, 16–18]. The age-specific prevalence of obesity among those with severe illness was much higher than the prevalence among patients with nonsevere illness and among the general Chinese population for persons <60 years of age. The absence of increased risk of severe outcomes associated with obesity in patients aged ⩾60 years may be attributable to the small numbers of obese patients in that age group or attributable to a ''survivor'' effect, whereby obesity-related mortality among the elderly population may have already occurred before the pandemic, leaving more-resilient

Table 3. Multivariable Analyses of Risk Factors associated with Severe Illness due to 2009 Pandemic Influenza A (H1N1) Virus Infection

Characteristic	OR (95% CI)	P^a
Risk factors associated with severe 2009 H1N1 illness		
Among nonpregnant patients ⩾ 2 years of age		
Male sex (vs female sex)	1.19 (1.07–1.31)	.001
Delayed hospital admission (on symptom day ⩾3 vs day <3)	1.27 (1.13–1.42)	<.001
Age and chronic medical conditions[b]		
2–17 years of age and without chronic medical conditions	Ref	Ref
18–59 years of age and without chronic medical conditions	2.12 (1.86–2.41)	<.001
⩾ 60 years of age and without chronic medical conditions	3.49 (2.51–4.85)	<.001
2–17 years of age and with chronic medical conditions	3.93 (3.03–5.08)	<.001
18–59 years of age and with chronic medical conditions	5.37 (4.55–6.34)	<.001
⩾ 60 years of age and with chronic medical conditions	6.88 (5.54–8.55)	<.001
Age and obesity[b]		
2–17 years of age		
Not obese	Ref	Ref
Obese	1.34 (1.10–1.63)	.004
18–59 years of age		
Not obese	Ref	Ref
Obese	1.91 (1.57–2.31)	<.001
⩾ 60 years of age		
Not obese	Ref	Ref
Obese	0.68 (.37–1.25)	.211
Among female patients of reproductive age (15–49 years of age)		
Age ⩾35 years (vs 15–34 years)	1.40 (1.10–1.77)	.006
Delayed hospital admission (on symptom day ⩾3 vs day <3)	1.80 (1.47–2.19)	<.001
Chronic medical conditions and pregnancy[b]		
Without chronic medical conditions and nonpregnant	Ref	Ref
With chronic medical conditions and nonpregnant	3.62 (2.65–4.94)	<.001
Without chronic medical conditions but pregnant	3.30 (2.72–4.00)	<.001
With chronic medical conditions and pregnant	3.69 (2.15–6.31)	<.001
Effectiveness of early antiviral treatment on severe 2009 H1N1 illness among nonpregnant patients ⩾ 2 years of age[c]		
Started on symptom day 1–2	Ref	Ref
Started on symptom day 3–4	1.01 (.84–1.22)	.885
Started on symptom day ⩾5	1.42 (1.20–1.67)	<.001

NOTE. CI, confidence interval; OR, odds ratio; Ref, reference.

[a] Multivariable logistic regression analyses were performed. Age, obesity, pregnancy, and chronic medical conditions were not highly correlated with each other (Spearman's rank correlation coefficients were calculated; r<.38 for all), which indicated little evidence for taking account of collinearity in multivariate analyses.

[b] Chunkwise likelihood ratio tests suggested that there are statistical 2-way interactions between age and chronic medical conditions ($P = .003$), between age and obesity ($P = .001$), and between chronic medical conditions and pregnancy ($P < .001$) but no 2-way statistical interaction between chronic medical conditions and obesity ($P = .073$). Three-way interaction among age, chronic medical conditions, and obesity was evaluated as part of a model containing all possible 2-way interactions but was not statistically significant ($P = .489$). The final model was used to estimate OR within strata defined by interactions between age and chronic diseases and between age and obesity. Stratum-specific ORs equal e^{β}, where e denotes the base of natural logarithms and β denotes regression efficient. ORs were calculated as follows: eg, compared with reference group (those 2–17 years of age without chronic medical conditions), for those with chronic medical conditions and ⩾ 60 years of age, β=β (⩾ 60 years of age) + β (chronic medical conditions) + β (interaction term); here, the latter 3 β values were obtained from the multivariable logistic regression model.

[c] Only patients who received antivirus treatment and have had clinical outcome defined as discharged from the hospital or died during study period were included in the analysis.

individuals. Overall, our study provides robust evidence to suggest that obesity is an independent risk factor associated with severe illness from 2009 H1N1 virus infection for persons <60 years of age in China.

\Compared with the age distribution in the United States, younger age categories account for a much larger proportion of the general Chinese population [23], which may account for the observed lower median age of hospitalized case patients in China (22 years), compared with that in the United States (27 years) [5]. In addition, the lower prevalence of chronic high-risk conditions among hospitalized Chinese case patients, compared with that reported in the United States

Table 4. Comparison of Prevalence of Pregnancy and Obesity between Case Patients with Nonsevere and Severe 2009 Pandemic Influenza A (H1N1) Illness and the General Chinese Population

Variable	No. (%) of patients (or persons) with obesity or pregnancy			Odds ratios (95% confidence interval), *P*	
	Severe illness	Nonsevere illness	General population	Severe illness vs Nonsevere illness	Nonsevere illness vs general population
Pregnancy[a]	562 (51)	450 (31)	11,607,818 (3)	2.39 (2.03–2.81), <.001	13.20 (11.82–14.75), <.001
Obesity[b]	559 (19)	777 (14)	88,303,356 (7)	1.36 (1.21–1.53), <.001	2.26 (2.09–2.44), <.001
2–17 years of age	198 (24)	498 (18)	5,714,358 (2)	1.40 (1.17–1.69), <.001	10.45 (9.49–11.52), <.001
18–59 years of age	335 (19)	251 (11)	66,542,622 (8)	1.99 (1.66–2.37), <.001	1.35 (1.18–1.54), <.001
⩾60 years of age	26 (6)	28 (9)	16,046,376 (9)	0.66 (.38–1.15), .142	1.02 (.69–1.51), .906

[a] Prevalence of pregnancy was expressed as the percentage of pregnant women among women of reproductive age (15–49 years of age).

[b] Children <2 years of age and pregnant women were excluded.

[5, 7] and Canada [9], may be partially explained by unrecognized underlying chronic medical conditions among Chinese case patients and a lower prevalence of chronic diseases among the general Chinese population [27]. Multivariable analyses also suggested that chronic medical conditions significantly increased the risk of severe outcomes from 2009 H1N1 virus infection, although age modified the effect of chronic medical conditions.

Similar to previous studies [12–15], our study found that 2009 H1N1 has had a major impact upon pregnant women in China. Twenty percent of 2009 H1N1–related deaths in China were in pregnant women, but only 7% of pregnant case patients had chronic medical conditions. Similar to other studies [12–15], and consistent with past pandemics [28–30], we found that pregnancy significantly increased the risk of severe outcomes from 2009 H1N1 virus infection, and later gestational age at illness onset was associated with a trend toward severe illness, with the highest risk in the third trimester. Additionally, we found that multigravida pregnancy was associated with an increased risk of severe 2009 H1N1 illness.

Our findings support those from other observational studies that suggest early initiation of oseltamivir treatment of hospitalized patients may reduce subsequent radiographic pneumonia [22], disease severity, and mortality for both 2009 H1N1 virus infection [7, 15, 17] and seasonal influenza [31–33]. Our multivariable analyses suggested that delayed initiation of oseltamivir treatment was associated with severe 2009 H1N1 illness, with a trend toward an increased risk from initiation of ⩽2 days after illness onset to initiation 3–4 days after illness onset and a significant risk of severe illness when treatment was started ⩾5 days after illness onset. Consistent with observational treatment studies involving hospitalized patients with seasonal influenza [33, 34], these data suggest that some benefit might be achieved even if initiation of oseltamivir treatment occurs up to 4 days after symptom onset.

A limitation of this retrospective study is that the included case patients with completed chart abstractions accounted for 32% of all hospitalized patients with confirmed cases reported to the China CDC. Case patients with data available for risk factor analyses were older and were hospitalized more often in late 2009, compared with those patients without chart review. Chart abstractions were performed voluntarily, rather than systematically, and possibly reflect the willingness and capacity of physicians to perform chart abstraction at admitting hospitals during the pandemic response. This highlights the challenges of collecting nationally representative data for assessment and monitoring of severity and risk factors during an evolving pandemic in the setting of a very large middle-income, but resource-limited, country. We censored data collection by 1 week after the end of the study period, which may have introduced incomplete data collection on clinical outcomes and antiviral treatment, although 93% of included case patients had been discharged from hospitals or died. To avoid selection bias, we compared risk factors for patients admitted to an ICU and patients with fatal cases with risk factors among patients with nonsevere illness, instead of comparing patients with fatal cases to patients with nonfatal cases. Although the large number of case patients allowed statistical power to assess potential independent risk factors associated with severe 2009 H1N1 illness, our findings should be interpreted with caution because of the retrospective study design and selection bias.

Our findings reinforce current recommendations for previously recognized high-risk populations [15], which include 2009 H1N1 vaccination [35] and empirical oseltamivir treatment of all hospitalized patients with suspected influenza as soon as possible [36]. In addition, obese persons <60 years of age in China should also be considered a high-risk group and targeted for influenza prevention and control interventions, including influenza vaccination [37].

Supplementary Material

Supplementary materials are available at Clinical Infectious Diseases online (http://www.oxfordjournals.org/our_journals/cid/).

Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted

materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

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