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Medical Risk Factors for Severe West Nile Virus Disease, United States, 2008–2010

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Abstract. We conducted enhanced surveillance to identify medical risk factors for severe illness (i.e., hospitalization or death) and neuroinvasive disease (i.e., encephalitis or meningitis) among all West Nile virus disease cases reported from selected states from 2008 to 2010. Of the 1,090 case-patients included in the analysis, 708 (65%) case-patients were hospitalized, 641 (59%) case-patients had neuroinvasive disease, and 55 (5%) case-patients died. Chronic renal disease (adjusted odds ratio [aOR] = 4.1; 95% confidence interval [CI] = 1.4–12.1), history of cancer (aOR = 3.7; 95% CI = 1.8–7.5), history of alcohol abuse (aOR = 3.0; 95% CI = 1.3–6.7), diabetes (aOR = 2.2; 95% CI = 1.4–3.4), and hypertension (aOR = 1.5; 95% CI = 1.1–2.1) were independently associated with severe illness on multivariable analysis. Although the same medical conditions were independently associated with encephalitis, only hypertension was associated with meningitis. The only condition independently associated with death was immune suppression. Prevention messages should be targeted to persons with these conditions.

INTRODUCTION

Since it was first detected in the Western hemisphere, West Nile virus (WNV) has become the leading cause of arboviral disease in the contiguous United States, with more than 12,000 cases of neuroinvasive disease (i.e., encephalitis, meningitis, or acute flaccid paralysis) and more than 1,100 deaths reported from 1999 to 2010.[1–4] The risk of WNV neuroinvasive disease increases with age and is highest among older adults.[1,3,5–7] Among patients with neuroinvasive disease, patients aged ≥ 50 years have substantially higher case fatality rates and are more likely to be reported as cases of encephalitis compared with younger patients.[8] With the exception of increased age, risk factors for poor outcomes among persons infected with WNV have not been clearly defined. Persons acquiring WNV infection through organ transplant from a WNV-infected donor seem to be at high risk of developing severe disease.[9] Solid organ transplant recipients infected through bites of infected mosquitoes may be at increased risk for severe disease, but previous studies have reported conflicting results.[10,11] Severe WNV disease has been described in persons with malignancies,[12] but the relative risk for poor outcomes among persons with these conditions or other immunocompromising conditions remains unclear. Hypertension, cerebrovascular disease, renal disease, and diabetes also have been identified as possible risk factors for severe WNV disease.[1,5–7,13–16] However, findings have been inconsistent between previous studies, and many of these studies were performed on cohorts of hospitalized patients with relatively small sample sizes.

Identifying people at highest risk for poor outcomes after WNV infection would allow for better targeted public health prevention messages, inform healthcare providers about potential clinical course and outcomes, and help focus future immunization strategies should a human WNV vaccine become available. We conducted enhanced population-based surveillance to identify risk factors for severe illness (i.e., hospitalization or death) and development of neuroinvasive disease (i.e., encephalitis or meningitis) among all cases of WNV disease reported from selected states from 2008 to 2010.

METHODS

Data collection. State and local health departments routinely report WNV data to the Centers for Disease Control and Prevention (CDC) through ArboNET, a national electronic surveillance system for arboviral disease.[3] Variables routinely collected in ArboNET include patient demographics (i.e., age, sex, race, ethnicity, and state and county of residence), date of illness onset, clinical syndrome (i.e., encephalitis, meningitis, acute flaccid paralysis, and uncomplicated fever), and outcome (i.e., hospitalization and death). For this enhanced surveillance project, an optional ArboNET module was developed to collect information on pre-existing medical conditions and medication use. All state and local health departments were invited to participate in the project. The 19 jurisdictions choosing to participate (Arkansas, California, Colorado, Georgia, Iowa, Minnesota, Mississippi, North Dakota, New Mexico, Nevada, New York City, Ohio, Oklahoma, Oregon, Tennessee, Texas, Washington, Wisconsin, and Wyoming) obtained medical history information on all reported WNV disease case-patients using a standard set of questions. Not all jurisdictions participated in all years. Medical history information was collected from patients, surrogate respondents, medical records, and/or healthcare providers. If data were collected from multiple sources and there were discrepancies, the patient's self-reported data were entered into ArboNET.

Case definitions. For the purpose of this project, a case-patient was defined as a resident of a participating state meeting the national case definition for laboratory-confirmed or probable WNV disease[17] from 2008 to 2010. Because only about 5% of all reported WNV cases occur in children[8] and many of the medical risk factors of interest are not common in children, case-patients aged < 18 years were excluded. A severe illness case was defined as a case-patient who was reported to have died or been hospitalized as a result of WNV disease. Case-patients were classified as having neuroinvasive disease if they were reported to ArboNET as having encephalitis, meningitis, and/or acute flaccid paralysis. Cases of acute flaccid paralysis can occur in persons with

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TABLE 1

Characteristics of reported WNV disease case-patients aged ≥ 18 years by inclusion status (2008–2010)

Patient characteristics	Included case-patients (N = 1,090)		Not included case-patients* (N = 1,873)		
	Number	Percent	Number	Percent	P value†
Age group (years)					0.28
18–59	647	59	1,110	59	
60–69	209	19	324	17	
≥ 70	234	21	439	23	
Male sex	615	56	1,092	58	0.32
Race other than white non-Hispanic	257	24	341	18	< 0.01
Illness outcomes					
Hospitalization	708	65	1,205	64	0.73
Neuroinvasive disease‡	641	59	999	53	< 0.01
Fatality	55	5	78	4	0.26

*Includes 1,796 case-patients from states that did not participate and 77 case-patients from participating states that did not have medical history information available.
†χ^2 test.
‡Encephalitis, meningitis, and/or acute flaccid paralysis.

or without concurrent encephalitis or meningitis. For this analysis, any case reported to have encephalitis, with or without acute flaccid paralysis, was classified as encephalitis; similarly, any case reported to have meningitis, with or without acute flaccid paralysis, was classified as meningitis. Age was categorized into three groups (18–59, 60–69, and ≥ 70 years), and the youngest age group was used as the reference category. These cut points were chosen after examination of estimated logistic regression coefficients for 10-year age groups. Unknown and missing responses for pre-existing medical conditions were considered negative responses. Pre-existing hypertension was defined as previous diagnosis of hypertension by a physician, and it included persons being treated for hypertension. Any history of coronary artery disease, heart attack, stroke, or congestive heart failure was collapsed into a single cardiovascular disease variable. Similarly, some conditions and medication use were collapsed into a single immune suppression variable, which included human immunodeficiency virus (HIV) infection, previous organ transplantation, current antirejection medication use, current cancer or chemotherapy, oral or injected corticosteroid use, other immunosuppressive medication use, and some unspecified immune suppressive conditions.

Data analysis. For each outcome of interest, univariate odds ratios (OR) and 95% confidence intervals (CI) were calculated using logistic regression. Variables associated with the outcome in univariate analysis ($P < 0.20$) were entered in a logistic regression model. Variables with $P > 0.05$ were excluded using a purposeful backward approach. If exclusion of a variable resulted in a > 10% change in the adjusted OR (aOR) for any of the variables remaining in the model, that variable was considered a significant confounder and was retained. The PROC REG procedure in SAS version 9.2 (SAS Institute Inc., Cary, NC) was used to assess potential colinearity by examining tolerance levels; there was no evidence of colinearity of any variables in the final models. Population attributable risk was calculated for pre-existing medical conditions found to be independently significant in multivariable analyses. Population attributable risk was calculated as $P_{exp} \times [(aOR - 1)/aOR]$, where P_{exp} is the proportion of case-patients with the risk factor.[18] Statistical analyses were conducted using SAS.

RESULTS

Nationally, 2,963 WNV disease cases in persons aged ≥ 18 years were reported from 2008 to 2010. Of those cases, 1,167 (39%) cases were reported from states participating in the enhanced surveillance project, and medical history data were collected for 1,090 (93%) of these case-patients. Characteristics of the case-patients included in this analysis were similar to those characteristics not included (those characteristics from non-participating states and participating states that were missing data), with the exception of race and development of neuroinvasive disease (Table 1). Included case-patients

TABLE 2

Risk factors for severe illness among WNV disease case-patients

Patient characteristics	Severe* (N = 708)		Non-severe (N = 382)		Univariate analysis			Multivariable analysis		
	Number	Percent	Number	Percent	OR	95% CI	P value	aOR	95% CI	P value
Demographics										
Age group (years)										
18–59	340	48	307	80	Ref.			Ref.		
60–69	156	22	53	14	2.7	1.9–3.8	< 0.01	2.0	1.4–3.0	< 0.01
≥ 70	212	30	22	6	8.7	5.5–13.9	< 0.01	6.5	3.9–10.7	< 0.01
Male sex	428	60	187	49	1.6	1.2–2.0	< 0.01	1.4	1.0–1.8	0.04
Race other than white non-Hispanic	208	29	49	13	2.8	2.0–4.0	< 0.01	2.9	2.0–4.2	< 0.01
Pre-existing medical conditions										
Hypertension	384	54	96	25	3.5	2.7–4.6	< 0.01	1.5	1.1–2.1	0.01
Diabetes	217	31	31	8	5.0	3.4–7.5	< 0.01	2.2	1.4–3.4	< 0.01
Cardiovascular disease†	154	22	24	6	4.1	2.6–6.5	< 0.01	–	–	–
Immune suppression‡	80	11	28	7	1.6	1.0–2.5	0.04	–	–	–
Any history of cancer§	79	11	10	3	4.7	2.4–9.1	< 0.01	3.7	1.8–7.5	< 0.01
Chronic renal disease	62	9	4	1	9.1	3.3–25.1	< 0.01	4.1	1.4–12.1	0.01
History of alcohol abuse	45	6	8	2	3.2	1.5–6.8	< 0.01	3.0	1.3–6.7	0.01
Chronic obstructive pulmonary disease	34	5	7	2	2.7	1.2–6.2	0.02	–	–	–
Chronic liver disease	19	3	1	< 1	10.5	1.4–78.7	0.02	–	–	–
Solid organ transplant	15	2	3	1	2.7	0.8–9.5	0.11	–	–	–

*Hospitalization and/or death.
†Including history of coronary artery disease, congestive heart failure, heart attack, or stroke.
‡Including HIV infection, previous organ transplantation, current antirejection medication use, current cancer or chemotherapy, oral or injected corticosteroid use, other immunosuppressive medication use, and some unspecified immune suppressive conditions.
§Excluding basal cell carcinoma.
aOR = adjusted odds ratio; CI = confidence interval; OR = odds ratio; Ref. = reference group.

were more likely to be classified as neuroinvasive disease than case-patients not included in the analysis.

Risk factors for severe illness. Overall, 708 (65%) case-patients were classified as having severe illness; all had been hospitalized, and 55 (8%) case-patients died. The majority (607; 86%) of case-patients with severe illness were also classified as having neuroinvasive disease. All demographic variables and medical conditions evaluated, with the exception of history of solid organ transplant, were significantly associated with developing severe illness in univariate analysis (Table 2). The highest univariate ORs were for chronic liver disease and chronic renal disease, but CIs were wide in both instances. Of the 708 case-patients with severe illness, 217 (31%) case-patients had diabetes compared with only 31 (8%) of 382 case-patients with non-severe illness. Hypertension was reported in 384 (54%) case-patients with severe disease versus 96 (25%) case-patients with non-severe disease. In multivariable analysis, age, sex, race/ethnicity, chronic renal disease, history of cancer, history of alcohol abuse, diabetes, and hypertension were identified as independent risk factors for severe illness (Table 2). Taking into account the OR and prevalence of underlying medical conditions among case-patients, the highest population attributable risk was estimated for hypertension (15%) followed by diabetes (13%), history of cancer (7%), chronic renal disease (5%), and history of alcohol abuse (3%).

Risk factors for neuroinvasive disease. A total of 641 (59%) case-patients had neuroinvasive disease; all but 34 (5%) case-patients were hospitalized. Of 641 neuroinvasive disease case-patients, 386 (60%) case-patients had encephalitis (including 411 case-patients with concurrent acute flaccid paralysis), and 245 (38%) case-patients had meningitis (including 12 case-patients with acute flaccid paralysis). Only 10 (2%) case-patients had acute flaccid paralysis without encephalitis or meningitis; these cases were not further analyzed.

Case-patients with encephalitis or meningitis were each compared with case-patients with non-neuroinvasive disease. With the exception of immune suppression and chronic liver disease, all the same variables associated with severe illness in univariate analysis were also associated with developing encephalitis (Table 3). In multivariable analysis, older age and male sex were identified as independent risk factors for encephalitis. In addition, history of alcohol abuse, chronic renal disease, history of cancer, diabetes, and hypertension were found to be independent risk factors for encephalitis after adjusting for age, sex, and race/ethnicity. These risk factors were the same medical risk factors independently associated with severe illness.

In univariate analysis, sex, race/ethnicity, diabetes, and hypertension were associated with meningitis (Table 4). Male sex and race other than white non-Hispanic were identified as independent risk factors for meningitis in multivariable analysis. Age was not significantly associated in either univariate or multivariable analysis. After adjustment for age, sex, and race/ethnicity, the only medical condition associated with meningitis was hypertension.

Risk factors for death. Overall, 55 (5%) case-patients died, including 48 (12%) encephalitis case-patients, 5 (2%) meningitis case-patients, and 2 (< 1%) case-patients without neuroinvasive disease. Significant risk factors for death identified in univariate analysis included older age, cardiovascular disease, hypertension, history of cancer, chronic obstructive pulmonary disease, chronic renal disease, diabetes, history of alcohol abuse, and immune suppression (Table 5). Of all medical conditions evaluated, only immune suppression was significantly associated with death after adjustment for age.

DISCUSSION

To our knowledge, this is the largest study ever conducted to evaluate medical risk factors for severe WNV disease. Chronic renal disease, history of cancer, history of alcohol abuse, diabetes, and hypertension were independently associated with the development of severe illness and encephalitis among patients with WNV disease; only hypertension was independently associated with the development of meningitis.

TABLE 3
Risk factors for encephalitis among WNV disease case-patients

	Encephalitis ($N = 386$)		Non-neuroinvasive ($N = 449$)		Univariate analysis			Multivariable analysis		
Patient characteristics	Number	Percent	Number	Percent	OR	95% CI	*P* value	aOR	95% CI	*P* value
Demographics										
Age group (years)										
18–59	139	36	334	74	Ref.			Ref.		
60–69	89	23	70	16	3.1	2.1–4.4	< 0.01	2.1	1.4–3.2	< 0.01
≥ 70	158	41	45	10	8.4	5.7–12.4	< 0.01	5.8	3.8–8.9	< 0.01
Male sex	227	59	226	50	1.4	1.1–1.8	0.02	1.2	0.9–1.6	0.28
Race other than white non-Hispanic	90	23	67	15	1.7	1.2–2.5	< 0.01	1.5	0.9–2.2	0.08
Pre-existing medical conditions										
Hypertension	245	63	130	29	4.3	3.2–5.7	< 0.01	1.8	1.3–2.6	< 0.01
Diabetes	133	34	52	12	4.0	2.8–5.7	< 0.01	1.8	1.1–2.7	0.01
Cardiovascular disease*	110	28	41	9	4.0	2.7–5.9	< 0.01	–	–	–
Immune suppression†	47	12	38	8	1.5	0.9–2.4	0.08	–	–	–
Any history of cancer‡	55	14	18	4	4.0	2.3–6.9	< 0.01	2.7	1.5–5.1	< 0.01
Chronic renal disease	46	12	10	2	5.9	3.0–11.9	< 0.01	2.9	1.3–6.3	0.01
History of alcohol abuse	30	8	12	3	3.1	1.5–6.1	< 0.01	3.3	1.6–7.0	< 0.01
Chronic obstructive pulmonary disease	26	7	10	2	3.2	1.5–6.7	< 0.01	–	–	–
Chronic liver disease	9	2	3	1	3.5	0.9–13.2	0.06	–	–	–
Solid organ transplant	8	2	5	1	1.9	0.6–5.8	0.27	–	–	–

* Including history of coronary artery disease, congestive heart failure, heart attack, or stroke.
† Including HIV infection, previous organ transplantation, current antirejection medication use, current cancer or chemotherapy, oral or injected corticosteroid use, other immunosuppressive medication use, and some unspecified immune suppressive conditions.
‡ Excluding basal cell carcinoma.
aOR = adjusted odds ratio; CI = confidence interval; OR = odds ratio; Ref. = reference group.

TABLE 4
Risk factors for meningitis among WNV disease case-patients

Patient characteristics	Meningitis (*N* = 245)		Non-neuroinvasive (*N* = 449)		Univariate analysis			Multivariable analysis		
	Number	Percent	Number	Percent	OR	95% CI	*P* value	aOR	95% CI	*P* value
Demographics										
Age group (years)										
18–59	170	69	334	74	Ref.			Ref.		
≥ 60	75	30	115	26	1.3	0.9–1.8	0.16	1.2	0.8–1.7	0.38
Male sex	155	63	226	50	1.7	1.2–2.3	< 0.01	1.5	1.1–2.1	0.02
Race other than white non-Hispanic	98	40	67	15	3.8	2.6–5.5	< 0.01	3.6	2.5–5.2	< 0.01
Pre-existing medical conditions										
Hypertension	101	41	130	29	1.7	1.2–2.4	< 0.01	1.6	1.1–2.3	0.01
Diabetes	60	24	52	12	2.5	1.6–3.7	< 0.01	–	–	–
Cardiovascular disease*	25	10	41	9	1.1	0.7–1.9	0.65	–	–	–
Immune suppression†	23	9	38	8	1.1	0.7–1.9	0.68	–	–	–
Any history of cancer‡	15	6	18	4	1.6	0.8–3.2	0.21	–	–	–
Chronic renal disease	9	4	10	2	1.7	0.7–4.2	0.27	–	–	–
History of alcohol abuse	9	4	12	3	1.4	0.6–4.2	0.46	–	–	–
Chronic obstructive pulmonary disease	5	2	10	2	0.9	0.3–2.7	0.87	–	–	–
Chronic liver disease	6	2	3	1	3.7	0.9–15.0	0.06	–	–	–
Solid organ transplant	5	2	5	1	1.9	0.5–6.5	0.33	–	–	–

*Including history of coronary artery disease, congestive heart failure, heart attack, or stroke.
†Including HIV infection, previous organ transplantation, current antirejection medication use, current cancer or chemotherapy, oral or injected corticosteroid use, other immunosuppressive medication use, and some unspecified immune suppressive conditions.
‡Excluding basal cell carcinoma.
aOR = adjusted odds ratio; CI = confidence interval; OR = odds ratio; Ref. = reference group.

Immune suppression was not associated with severe illness or neuroinvasive disease, but it was associated with a fatal outcome. Although the highest aORs were estimated for chronic renal disease, history of cancer, and history of alcohol abuse, population-attributable risk estimates suggest that as much as one-quarter of all severe WNV disease might be attributable to hypertension and diabetes.

Our results corroborated findings from previous studies that older age is associated with more severe WNV disease, particularly hospitalization and development of encephalitis.[1,3,5–8] In our study, the risk of severe illness increased with increasing age above 60 years. Although we found an increased risk of severe illness among males, sex was not associated with development of encephalitis or meningitis. Race/ethnicity was significantly associated with severe illness and development of meningitis but not encephalitis. It is unknown if this association is related to underreporting of less severe disease related to decreased access to healthcare among some minority groups or some other factor not accounted for in our analysis.

The literature is somewhat inconsistent regarding the association between underlying medical conditions and severe WNV disease. Many of the previously conducted studies examined factors associated with the most severe outcomes (e.g., encephalitis with muscle weakness and death) among cohorts of hospitalized patients.[1,7,14–16] These studies generally included small numbers of patients, limiting power to detect associations. Two previous studies evaluated risk factors

TABLE 5
Risk factors for death among WNV disease case-patients

Variable	Fatal (*N* = 55)		Non-fatal (*N* = 1,035)		Univariate analysis			Multivariable analysis		
	Number	Percent	Number	Percent	OR	95% CI	*P* value	aOR	95% CI	*P* value
Demographics										
Age group (years)										
18–59	4	7	643	62	Ref.			Ref.		
60–69	14	25	195	19	11.5	3.8–35.5	< 0.01	11.9	3.9–36.6	< 0.01
≥ 70	37	67	197	19	30.2	10.6–85.7	< 0.01	31.2	10.9–88.9	< 0.01
Male sex	35	64	580	56	1.4	0.8–2.4	0.27	–	–	–
Race other than white non-Hispanic	6	11	251	24	0.4	0.2–0.9	0.03	–	–	–
Pre-existing medical conditions										
Hypertension	41	75	439	42	4.0	2.1–7.4	< 0.01	–	–	–
Diabetes	22	40	226	22	2.4	1.4–4.2	< 0.01	–	–	–
Cardiovascular disease*	23	42	155	15	4.1	2.3–7.2	< 0.01	–	–	–
Immune suppression†	11	20	97	9	2.4	1.2–4.8	0.01	2.8	1.3–5.9	< 0.01
Any history of cancer‡	13	24	76	7	3.9	2.0–7.6	< 0.01	–	–	–
Chronic renal disease	9	16	57	6	3.4	1.6–7.2	< 0.01	–	–	–
History of alcohol abuse	4	7	49	5	1.6	0.5–4.5	0.40	–	–	–
Chronic obstructive pulmonary disease	6	11	35	3	3.5	1.4–8.7	< 0.01	–	–	–
Liver disease	1	2	19	2	1.0	0.1–7.5	0.99	–	–	–
Solid organ transplant	1	2	17	2	1.1	0.1–8.5	0.92	–	–	–

*Including history of coronary artery disease, congestive heart failure, heart attack, or stroke.
†Including HIV infection, previous organ transplantation, current antirejection medication use, current cancer or chemotherapy, oral or injected corticosteroid use, other immunosuppressive medication use, and some unspecified immune suppressive conditions.
‡Excluding basal cell carcinoma.
aOR = adjusted odds ratio; CI = confidence interval; OR = odds ratio; Ref. = reference group.

for neuroinvasive disease among all WNV disease cases reported to state health departments.[5,6] The first of these studies described risk factors for development of WNV encephalitis and meningitis (separately) among 656 cases reported in Colorado in 2003.[5] However, because of relatively small numbers of patients with the outcomes of interest and low prevalence of medical conditions being studied, age and sex aORs were calculated, but multivariable modeling was not conducted. Similar to our study, several medical conditions, such as renal disease, diabetes, hypertension, cancer, and undergoing chemotherapy, were found to be associated with the development of encephalitis after adjusting for age and sex. Only cancer and undergoing chemotherapy were associated with meningitis. A second study described risk factors for neuroinvasive disease among 880 patients with WNV disease reported in California in 2005.[6] Standardized data were only collected for two pre-existing medical conditions (hypertension and diabetes); information about other underlying conditions was collected through an open-ended question about past medical history. This work noted that age > 64 years, male sex, and diabetes were identified as independent risk factors for neuroinvasive disease.[6]

Despite the use of different methodologies and different outcome measures, several studies have identified hypertension and/or diabetes as risk factors for progression to WNV neuroinvasive disease or death.[1,5–7,14] It has been suggested that these conditions could increase the permeability of the blood–brain barrier to allow greater viral entry, leading to increased susceptibility of the patient to neuroinvasive disease.[14,19] Chronic renal disease and history of alcohol abuse have also previously been associated with development of encephalitis and death, despite the low prevalence of these conditions.[5,7,14] The results of our analysis further support these associations.

Most pre-existing medical conditions do not seem to increase risk of meningitis after infection with WNV. In our study, only hypertension was independently associated; the only other study that looked at medical conditions associated with meningitis reported associations with cancer and chemotherapy.[5] Although outcomes among patients with WNV meningitis are generally favorable compared with patients with encephalitis, meningitis patients frequently require hospitalization for pain control for severe headache or other supportive care.[20]

Although solid organ transplantation has been identified as a potential risk for more severe disease,[9,10] we did not find an association. This finding might have been caused by the limited power to detect an association because of the small number of case-patients with history of solid organ transplant, or perhaps, it is related to additional factors that were not accounted for in this analysis, such as time since transplantation and type of post-transplant immunosuppressive therapy. Our findings are consistent with a recent study conducted in a university organ transplant center that estimated that naturally acquired asymptomatic WNV infection occurred with equal prevalence among transplant recipients and non-immunocompromised controls.[11] In that study, no documented WNV neuroinvasive disease was detected during retrospective review of medical charts of transplant recipients.

Although many of the conditions that have been associated with severe WNV disease are also associated with immune suppression (e.g., solid organ transplant, diabetes, alcohol abuse, and cancer), immune suppression, as defined in this study, was not independently associated with severe illness or neuroinvasive disease. Neither of the two previous studies that built multivariable models found immune suppression to be independently associated with development of encephalitis among hospitalized patients.[7,14] However, as in this study, both of those studies reported an association between immune suppression and death. Additional research to better define the role of different immune suppressive conditions in the development of severe WNV disease and death would be useful.

There are several limitations of this study. Case-patients were identified through routine passive public health surveillance and may not be representative of all WNV disease cases that occur. Patients with more severe illness are more likely to seek medical attention and therefore, are more likely to be captured by passive surveillance systems. Case-patients included in the analysis differed from case-patients not included regarding race and development of neuroinvasive disease; the differences were driven by case-patients from non-participating states. Because of these differences, the results of this analysis may not be generalizable to all WNV disease cases occurring in the United States. Additionally, because ArboNET does not collect information regarding clinical signs and symptoms or specific laboratory findings (e.g., cerebrospinal fluid findings), misclassification of the various syndromes caused by WNV (i.e., encephalitis, meningitis, acute flaccid paralysis, and uncomplicated fever) cannot be detected. There were small numbers of case-patients with some underlying conditions (e.g., solid organ transplant), limiting power to detect associations. Case-patients who were hospitalized may have had a more complete medical history than those case-patients not hospitalized; this bias would likely have resulted in artificially inflated risk estimates. However, the proportion of case-patients missing risk factor data did not differ by disease severity. It is also possible that patients with severe neuroinvasive disease may not have been able to provide accurate medical histories, because such patients often present with altered mental status. This lack of accuracy could have led to an underreporting of underlying conditions, which would have biased risk estimates to the null. Finally, we had no information on severity of the underlying medical conditions (e.g., uncontrolled versus controlled diabetes and hypertension or specific type and dose of immunosuppressive medications), which could be important in determining if and to what degree these conditions increase the risk of severe disease.

In summary, hypertension, diabetes, history of alcohol abuse, history of cancer, and chronic renal disease seem to be significant medical risk factors for severe illness after WNV infection. As many as one of four cases of severe WNV illness may be attributable to hypertension or diabetes. The role of other low-prevalence medical conditions is less clear and not easily assessed through a population-based method. Because no specific treatment for WNV disease exists and no human vaccine is available, healthcare providers should encourage use of personal protection during the WNV transmission season, particularly among the high-risk groups for severe disease identified in this study. Prevention messages should be particularly targeted to persons with medical conditions identified in this analysis as well as older people.

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