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MAJOR ARTICLE

Incidence and Outcome of Severe and Nonsevere Thrombocytopenia Associated With Zika Virus Infection—Puerto Rico, 2016

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Background. Zika virus (ZIKV) infection has been associated with severe thrombocytopenia. We describe the incidence, clinical manifestations, and outcomes of patients with ZIKV infection and thrombocytopenia.

Methods. We reviewed medical records of patients with ZIKV infection and thrombocytopenia (platelet count <100 $\times 10^9$ cells/L) in Puerto Rico during 2016. Severe thrombocytopenia was defined by platelet count <20 $\times 10^9$/L or a platelet count <50 $\times 10^9$/L and treatment for immune thrombocytopenia (ITP).

Results. Of 37 878 patients with ZIKV infection, 47 (0.1%) had thrombocytopenia in the absence of an alternative etiology (1.4 cases/100 000 population), including 12 with severe thrombocytopenia. Most patients with thrombocytopenia were adult (77%) and male (53%). Platelet nadir occurred a median (range) of 6 (1–16) and 5 (0–34) days after symptom onset for patients with severe and nonsevere thrombocytopenia, respectively. Among patients with severe thrombocytopenia, all had bleeding, 33% were admitted to the intensive care unit, and 8% died; 50% were treated for ITP. Among 5 patients with severe thrombocytopenia who received intravenous immunoglobulin, the median platelet count increase (range) was 112 (65–202) $\times 10^9$/L. In contrast, among 4 patients who received platelet transfusion, the median increase in platelet count (range) was 8.5 (–6 to 52) $\times 10^9$/L.

Conclusions. Patients with severe thrombocytopenia and ZIKV infection experienced prominent acute morbidity. Consistent with recommended management, administration of ITP treatments to such patients may be more efficacious than platelet transfusion in resolving thrombocytopenia. Severe thrombocytopenia should be considered a rare outcome of ZIKV infection.

Keywords. Zika; thrombocytopenia; immune thrombocytopenia; ITP; platelets.

Zika virus (ZIKV), a flavivirus primarily transmitted by *Aedes* species mosquitos, was first identified in 1947 in a nonhuman primate in the Zika Forest in Uganda [1, 2]. Only 13 human cases of ZIKV infection were documented in the following 60 years. After outbreaks in the Pacific in 2007 and 2014, ZIKV emerged in the Americas, where large outbreaks were reported in most countries and territories [2–4]. The first case of ZIKV infection in Puerto Rico was detected in late 2015, and 37 878 laboratory-positive cases had been reported to the Puerto Rico Department of Health (PRDH) by the end of 2016 [5, 6]. Although most ZIKV infections are asymptomatic, those individuals who do become ill experience rash, fever, arthralgia, and/or myalgia [3, 7]. Complications associated with ZIKV infection include congenital Zika syndrome, Guillain-Barré syndrome, and severe thrombocytopenia [8–24].

Thrombocytopenia is often a secondary complication of viral infections, including hepatitis C virus (HCV), HIV, and dengue virus (DENV) [25–27]. Such infections can result in multiple etiologic mechanisms of thrombocytopenia, including impairment of platelet production in the bone marrow, platelet consumption through disseminated intravascular coagulation (DIC), and platelet destruction through immune thrombocytopenia (ITP). ITP is an immune-mediated hematologic condition with a diverse constellation of signs and symptoms, characterized by isolated thrombocytopenia due to immune-mediated platelet destruction, inhibition of platelet release by megakaryocytes, and immune dysfunction [28–30]. Primary ITP occurs in the absence of any obvious cause, whereas secondary ITP occurs in association with other disorders, including viral infections [28–30].

Thrombocytopenia is common among patients infected with DENV and has been proposed to be the result of inhibition of bone marrow progenitor cells, bone marrow hypoplasia, platelet consumption, complement activation, peripheral

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sequestration, and platelet destruction [31, 32]. Destruction may be due to the development of antiplatelet IgM antibodies and autoantibodies against endothelial and blood coagulation pathway cells that cross-react with platelets; increased macrophage phagocytosis may also play a role [31]. Because DENV is a flavivirus closely related to ZIKV, similar mechanisms could contribute to thrombocytopenia in patients with ZIKV infection. In support of an immune-related mechanism of severe thrombocytopenia, multiple reports have documented patients with ZIKV infection and a clinical presentation consistent with ITP [11–14, 33, 34].

In this investigation, we describe the incidence, clinical manifestations, and outcomes of patients with ZIKV infection and severe or nonsevere thrombocytopenia. We identified patients with ZIKV infection and thrombocytopenia in Puerto Rico utilizing accepted case definitions to determine if hematologic characteristics were consistent with ITP or other etiologies of thrombocytopenia [28, 29, 35].

METHODS

The protocol for this investigation was reviewed by human subjects' research advisors at the Centers for Disease Control and Prevention (CDC) and was deemed to be public health practice, not research. As such, institutional review board review was not required.

Patients with suspected ZIKV disease were reported to PRDH [5]. In brief, patients for whom a clinician suspected ZIKV disease had case report forms collecting demographic and clinical information submitted to PRDH, along with a serum specimen for diagnostic testing by real-time reverse transcriptase polymerase chain reaction (rRT-PCR) and/or immunoglobulin M antibody capture enzyme-linked immunosorbent assay (MAC-ELISA) to detect evidence of infection with ZIKV, DENV, and chikungunya virus [36, 37]. Copies of medical records were requested for (1) patients who tested positive for ZIKV infection by rRT-PCR or MAC-ELISA; (2) patients who had a reported date of illness onset between January 1 and December 31, 2016; and (3) patients for whom the variable "thrombocytopenia" (unquantified) on the case report form was reported in the affirmative.

Medical records were reviewed to confirm thrombocytopenia, as evidenced by a platelet count <100 $\times 10^9$/L [28, 29]. Such cases were defined as having confirmed thrombocytopenia. Medical records of cases with confirmed thrombocytopenia were abstracted to collect information on demographics, history of illnesses, clinical interventions, and outcomes. Severe thrombocytopenia was defined by (1) platelet count <20 $\times 10^9$/L or (2) platelet count <50 $\times 10^9$/L, along with a clinical diagnosis of and treatment for ITP (ie, administration of intravenous immunoglobulin [IVIG] or steroids). Cases with confirmed thrombocytopenia that did not meet the case definition of severe thrombocytopenia were defined as having nonsevere thrombocytopenia.

Cases with a platelet count <100 $\times 10^9$/L and an alternative etiology of thrombocytopenia were excluded from further analysis. Patients taking medications that could affect platelet count (eg, aspirin, antiplatelet agents, ranitidine, antidepressants) were only excluded if there was clinical documentation of thrombocytopenia as a result of the medication. Cases without another etiology of thrombocytopenia identified were defined as having ZIKV-associated severe or nonsevere thrombocytopenia.

Anatomical sites and severity of bleeding were abstracted. Bleeding manifestations were graded from 0 to 5 based on severity using the ITP-specific bleeding assessment tool (ITP-BAT) [35]. In summary, grade 2 was clinically significant bleeding requiring at least outpatient care. Grade 3 required hospital admission or surgical intervention in response to bleeding. Grade 4 required red blood cell transfusion or a decrease in hemoglobin of >2 g/dL. Grade 5 was fatal bleeding. A patient with evidence of bleeding (eg, decrease in hemoglobin >2 g/dL) but no objective evidence of bleeding was defined as having an occult hemorrhage. Available information from blood smear reports was reviewed for platelet number and size, fragmented red blood cells including schistocytes and other abnormalities to identify malignancy, DIC, pseudothrombocytopenia, or other etiologies of thrombocytopenia.

Cases were classified as confirmed or possible ITP. Confirmed ITP was defined by a clinical discharge diagnosis or end-of-visit diagnosis of ITP. Possible ITP was defined by (1) the absence of other causes or disorders that may be associated with thrombocytopenia except ZIKV and (2) a clinical course consistent with ITP as determined by a hematologist (E.V.) after medical record review.

Cases of severe thrombocytopenia were evaluated for the primary end points of platelet count 96 hours after administration of IVIG or corticosteroids, platelet count immediately after transfusion, and clinical response. Clinical response was defined as a platelet count ≥30 $\times 10^9$/L and ≥2-fold greater than baseline and the absence of bleeding [29]. Ninety-six-hour platelet count after ITP treatment was selected because peak response to IVIG occurs 2–7 days postadministration, and initial response to corticosteroids occurs 2–14 days after administration [28, 29]. Grade of bleeding manifestations was a secondary outcome [29].

The 2016 US Census population estimate for Puerto Rico (3 411 307 residents) was used to calculate annual incidence [38]. Data were collected and managed using Research Electronic Data Capture (REDCap; Nashville, TN) and analyzed with SAS, version 9.4 (Cary, NC).

RESULTS

Identification of Patients With Thrombocytopenia Associated With ZIKV Infection

Among 37 878 patients with ZIKV infection reported to PRDH during 2016, 436 (1.2%) had reported thrombocytopenia (Figure 1). Among 124 patients for whom medical records were available for review, 56 (45%) had confirmed thrombocytopenia.

Among these cases, alternative etiologies of thrombocytopenia were identified for 9, including 2 cases of myelodysplastic syndrome and 1 case each of bone marrow failure, hepatocellular carcinoma on treatment, leptospirosis [19], May-Hegglin anomaly, immunosuppresants after renal transplant, multiple myeloma, and underlying thrombocytopenia likely due to medication. The remaining 47 (0.1%) patients were defined as having ZIKV-associated thrombocytopenia. Twelve (26%) of these patients had severe thrombocytopenia, and 35 (74%) had nonsevere thrombocytopenia. Therefore, the incidence of ZIKV-associated thrombocytopenia in 2016 was at least 1.4 cases per 100 000 population, including 0.4 and 1.0 cases of severe and nonsevere thrombocytopenia per 100 000, respectively. The month of reported illness onset among patients with ZIKV-associated severe or nonsevere thrombocytopenia was similar to that of all reported cases with ZIKV infection (Figure 2).

ZIKV infection was confirmed by rRT-PCR among 6 of 11 (55%) and 26 of 32 (81%) patients with severe and nonsevere thrombocytopenia, respectively (Supplementary Table 1). No patients had evidence of coinfection with DENV or chikungunya virus by rRT-PCR. Among 14 patients with thrombocytopenia who were only positive by anti-ZIKV IgM ELISA, 3 (21%) had anti-DENV IgM detected, suggestive of cross-reactive flavivirus antibodies. One patient with nonsevere thrombocytopenia had HCV infection, 1 had *Klebsiella pneumonia* isolated from a urine culture, 1 had a sputum culture positive for *Candida albicans*, and 1 had evidence of active infection with Epstein-Barr virus. One patient with severe and 2 patients with non severe thrombocytopenia were also positive for influenza virus infection.

Characteristics of Patients With ZIKV-Associated Thrombocytopenia

The median age of patients with severe and nonsevere thrombocytopenia (range) was 39.5 (2–88) and 49 (1–88) years, respectively, and 7 (58%) and 18 (51%) were male (Table 1). A greater proportion of patients with severe thrombocytopenia were aged 0–9 years (8% vs 3%, respectively) or 30–49 years (42% vs 17%) compared with those with nonsevere thrombocytopenia. Cases of nonsevere thrombocytopenia were more frequent among patients aged 10–29 and >40 years (Supplementary Figure 1).

Two (17%) patients with severe and 3 (9%) patients with nonsevere thrombocytopenia reported a history of ITP. One (8%) patient with severe and 11 (31%) patients with nonsevere thrombocytopenia were taking medications that could have contributed to reduced platelet count. No patients were taking antibiotics before onset of illness, 2 patients with nonsevere thrombocytopenia reported chronic HCV infection, and 1 patient with nonsevere thrombocytopenia reported having a rheumatic autoimmune condition.

Signs and Symptoms Among Patients With ZIKV-Associated Thrombocytopenia

All patients reported symptoms of illness consistent with ZIKV disease within the 34 days before platelet nadir. The most frequently reported signs and symptoms included fever, rash, myalgia, and arthralgia (Table 2). Splenomegaly (n = 3) and lymphadenopathy (n = 2) were identified among patients with

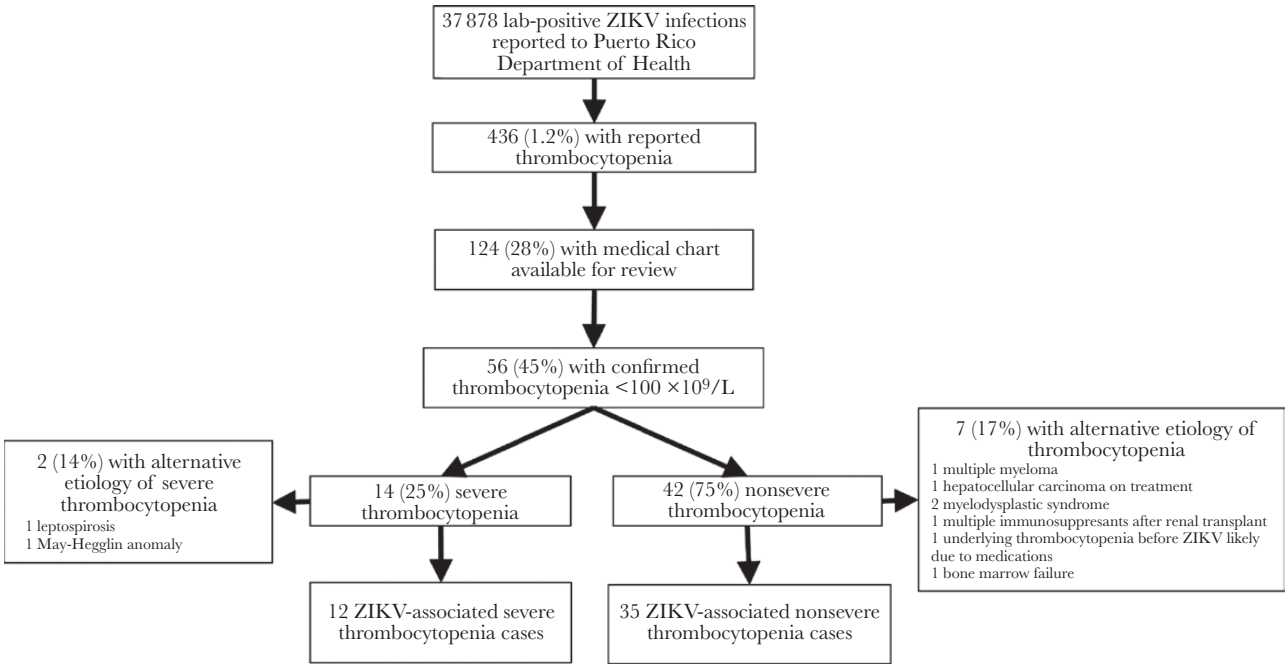

Figure 1. Flow diagram of investigation procedures leading to identification of cases of Zika virus–associated thrombocytopenia—Puerto Rico, 2016. Abbreviation: ZIKV, Zika virus.

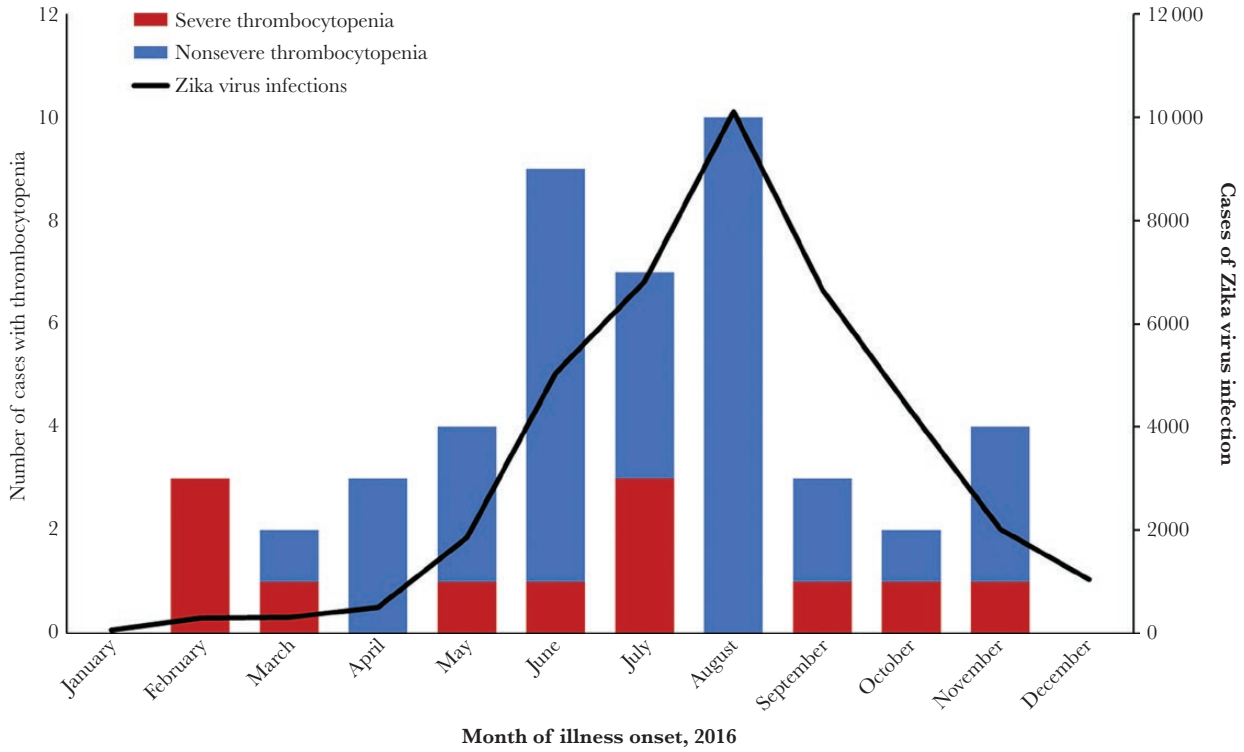

Figure 2. Number of cases of Zika virus–associated severe and nonsevere thrombocytopenia by reported month of illness onset—Puerto Rico, 2016 (n = 47).

nonsevere thrombocytopenia but not among those with severe thrombocytopenia. Altered mental status was documented among 2 patients, 1 with severe and the other with nonsevere thrombocytopenia.

All 12 patients with severe thrombocytopenia had bleeding manifestations, as compared with 11 (31%) patients with nonsevere thrombocytopenia. The median grade of bleeding among patients with bleeding manifestations was higher among patients with severe (median, grade 3) than nonsevere (median, grade 2) thrombocytopenia. Of 12 patients with grade 2 or above, 8 (67%) were patients with severe thrombocytopenia. Among patients with nonsevere thrombocytopenia, the most common bleeding manifestations were petechiae and hematuria. Among patients with severe thrombocytopenia, bleeding manifestations included ecchymoses (50%, n = 6), gastrointestinal bleeding (25%, n = 3), and intracranial hemorrhage (8.3%, n = 1).

Hematologic Characteristics, Medical Interventions, and Illness Outcome Among Patients With ZIKV-Associated Thrombocytopenia

The median (range) nadir platelet count was 12.5 (1.0–30.3) $\times 10^9$/L among patients with severe and 69.0 (24.0–98.0) $\times 10^9$/L among patients with nonsevere thrombocytopenia. Timing of platelet nadir occurred a median (range) of 5 (1–16) days after symptom onset among severe cases and 4 (0–34) days after symptom onset among nonsevere cases (Table 3). None of the patients with severe thrombocytopenia who had blood smears (n = 9) had fragmented red blood cells, whereas 1 of 18 patients with nonsevere thrombocytopenia who had blood smears had fragmented red blood cells. Visualization of platelets was consistent with low platelet counts in all patients with blood smears. Among those with blood smears, 6 of 18 (33%) patients with nonsevere thrombocytopenia had abnormal red blood cells, and 2 (11.1%) patients with nonsevere thrombocytopenia had abnormal white blood cells.

Corticosteroids were administered to two-thirds of patients with severe thrombocytopenia and one-quarter of patients with nonsevere thrombocytopenia; however, only those with severe thrombocytopenia received platelet transfusions (n = 4, 33%) or IVIG (n = 5, 42%) (Table 4). Outcomes among patients with severe or nonsevere thrombocytopenia included hospitalization (100% vs 51%, respectively), admission to the intensive care unit (33% vs 0%), and death (8% vs 0%). Three (25%) patients with severe thrombocytopenia received a clinical diagnosis of viral syndrome, as compared with 22 (63%) patients with nonsevere thrombocytopenia. Two (17%) and 10 (29%) patients with severe or nonsevere thrombocytopenia, respectively, were clinically diagnosed with dengue, dengue-like illness, dengue hemorrhagic fever, or severe dengue. Six (50%) patients with severe thrombocytopenia had confirmed ITP as compared with none with nonsevere thrombocytopenia. All 12 patients with severe thrombocytopenia had possible ITP, as compared with 31 (89%) with nonsevere thrombocytopenia. Among patients with severe thrombocytopenia, patients had normal coagulation testing and no features of DIC.

Table 1. Demographic Characteristics and Medical History Among Patients With Zika Virus–Associated Thrombocytopenia—Puerto Rico, 2016 (n = 47)

	Severe Thrombocytopenia (n = 12)	Nonsevere Thrombocytopenia (n = 35)
Demographic characteristics		
Age, median (range), y	39.5 (2–88)	49 (1–88)
Male sex, No. (%)	7 (58)	18 (51)
Medical history related to thrombocytopenia or platelet function, No. (%)		
Previously diagnosed with ITP	2 (17)	3 (9)
Previously diagnosed with chronic ITP	0	2 (6)
Previously received any blood product transfusion	3 (25)	2 (6)
Comorbid medical conditions, No. (%)		
History of malignancy	0	2 (6)
Obesity	3 (25)	7 (20)
Hypertension	4 (33)	14 (40)
Diabetes	2 (17)	10 (29)
Asthma	1 (8)	6 (17)
Other[a]	1 (8)	4 (11)
Medications, No. (%)		
Medication that could cause thrombocytopenia[b]	1 (8)	11 (31)
Aspirin	0	2 (6)

Abbreviation: ITP, immune thrombocytopenia.

[a]One severe case with lung disease; 2 nonsevere cases with hepatitis C, 1 with renal disease, 8 with cardiovascular disease, 1 with a chronic immunologic/rheumatologic condition, and 1 with lung disease.

[b]Aspirin, antiplatelet agents, ranitidine, antidepressants.

Among patients with severe thrombocytopenia, 2 (17%) received platelets, IVIG, and corticosteroids; 2 (17%) received platelets and corticosteroids; 3 (25%) received IVIG alone; 4 (33%) received corticosteroids alone; and 1 (8%) received none of the 3 treatments (Table 5). All patients with severe thrombocytopenia who received IVIG (n = 5) had an increasing platelet count within 96 hours of IVIG administration (median platelet count [range], 112 [65–202] $\times 10^9$L). In contrast, among those who received platelet transfusion (n = 4), the median platelet count after the initial transfusion (range) was 8.5 (6–52) $\times 10^9$/L, and the change in platelet count immediately after transfusion compared with immediately before transfusion (range) was 6 (−5 to 43) $\times 10^9$/L. Successful clinical response to treatment, as defined by a platelet count ≥30 $\times 10^9$/L and a >2-fold increase in platelet count in the absence of bleeding, was observed in 5 of 6 (83%) patients diagnosed with ITP and 9 of 11 (82%) patients with severe thrombocytopenia who received ITP treatment.

DISCUSSION

As of February 1, 2018, 13 cases of severe thrombocytopenia (platelet count <20 $\times 10^9$/L without other underlying etiology) or ITP associated with ZIKV infection had been reported

Table 2. Signs and Symptoms During Acute Illness of Patients With Zika Virus–Associated Thrombocytopenia—Puerto Rico, 2016 (n = 47)

	Severe Thrombocytopenia (n = 12)	Nonsevere Thrombocytopenia (n = 35)
Signs and symptoms, No. (%)		
Fever	11 (92)	25 (71)
Rash	11 (92)	23 (66)
Myalgia	8 (67)	21 (60)
Arthralgia	8 (67)	14 (40)
Cough	6 (50)	7 (20)
Abdominal pain	5 (42)	7 (20)
Dehydration	5 (42)	9 (26)
Conjunctivitis	4 (33)	5 (14)
Sore throat	3 (25)	6 (17)
Hepatomegaly	1 (8)	2 (6)
Weight loss	1 (8)	0
Altered mental status	1 (8)	1 (3)
Splenomegaly documented by imaging	0	3 (9)
Lymphadenopathy	0	2 (6)
Bleeding manifestations during acute illness		
Any bleeding	12 (100)	11 (31)
Clinically significant hemorrhage (grade 2 and above)[a]	8 (67)	4 (11)
Severe hemorrhage (grade 3 and above)[b]	5 (42)	4 (11)
Petechiae	8 (67)	7 (20)
Ecchymoses	6 (50)	0
Hematuria	4 (33)	4 (11)
Oral or gingival bleeding	3 (25)	1 (3)
Subcutaneous hematoma	3 (25)	0
Hematochezia	2 (17)	0
Occult bleed	2 (17)	2 (6)
Epistaxis	1 (8)	0
Intracranial hemorrhage	1 (8)	0
Hematemesis	1 (8)	0
Pulmonary hemorrhage	1 (8)	0
Clinically significant[a] bleeding manifestations during acute illness		
Acute drop in hemoglobin >2 g/dL (within 7 d)	5 (42)	3 (9)
Petechiae	2 (17)	1 (3)
Hematuria	2 (17)	1 (3)
Gingival bleeding	1 (8)	0
Hematochezia	2 (17)	0
Occult	2 (17)	2 (6)
Skin bleeding caused by minor skin wounds/cuts or venipuncture	1 (8)	0
Central nervous system/neurologic (intracranial bleed)	1 (8)	0
Hematemesis	1 (8)	0
Pulmonary (tracheobronchial bleeding)	1 (8)	0

[a]Clinically significant ≥grade 2. Grade 2 bleeding was defined as clinically significant bleeding requiring at least an outpatient level of care (eg, macroscopic hematuria, bleeding lasting >5 minutes or interfering with daily activities).

[b]Grade 3 bleeding was defined by required hospital admission or surgical intervention in response to bleeding.

Table 3. Hematologic Findings in Patients with Zika Virus–Associated Thrombocytopenia—Puerto Rico, 2016 (n = 47)

	Severe Thrombocytopenia (n = 12)	Nonsevere Thrombocytopenia (n = 35)
Nadir platelet count, median (range), $\times 10^9$/L	12.5 (1.0–30.3)	69.0 (24.0–98.0)
Days from ZIKV symptoms to platelet nadir, median (range)	5 (1–16)	4 (0–34)
Maximum MPV, median (range), fL	12.4 (8.2–15.9)	10.5 (5.8–15.1)
Minimum hemoglobin, median (range), g/dL	12.6 (9.2–12.5)	12.8 (8.3–17.20)
Maximum WBC count per participant, median (range), $\times 10^9$/L	10.2 (4.2–19.8)	4.8 (2.8–14.8)
Minimum WBC count per participant, median (range), $\times 10^9$/L	5.8 (1.5–17.8)	3.7 (1.5–10.5)
Blood smear performed, No. (%)	9 (75)	18 (51)
Normal or large platelets[a]	7 (100)	10 (100)
Fragmented RBCs[b]	0	1 (6)
Abnormal RBC morphology	0	6 (33)
Abnormal WBC morphology	0	2 (11)
Reduced No. of platelets without fragmented RBCs	9 (100)	17 (94)

Abbreviations: MPV, mean platelet volume; RBC, red blood cell; WBC, white blood cell; ZIKV, Zika virus.

[a]Not all blood smears had platelet information recorded; percentage is based on those with platelet size information recorded.

[b]Fragmented RBCs include schistocytes or alternate shape consistent with hemolysis.

Table 4. Medical Interventions, Outcome, and Clinical Diagnoses Among Patients With Zika Virus–Associated Thrombocytopenia—Puerto Rico, 2016 (n = 47)

	Severe Thrombocytopenia (n = 12)	Nonsevere Thrombocytopenia (n = 35)
Interventions, No. (%)		
Steroids administered	8 (67)	9 (26)
Platelet transfusion[a]	4 (33)	0
IVIG administered	5 (42)	0
Intubated	1 (8)	0
Outcome, No. (%)		
Admitted to inpatient ward	12 (100)	18 (51)
Admitted to intensive care unit	4 (33)	0
Intubated	1 (8)	0
Died	1 (8)	0
Diagnoses, No. (%)		
ZIKV infection documented by clinician[b]	0	1 (8)
ZIKV infection by case definition[c]	12 (100)	35 (100)
Viral syndrome documented by clinician[d]	3 (25)	22 (63)
Confirmed ITP[e]	6 (50)	0
Possible ITP[f]	12 (100)	31 (89)

Abbreviations: ITP, immune thrombocytopenia; IVIG, intravenous immunoglobulin; ZIKV, Zika virus.

[a]No other blood products were transfused.

[b]ZIKV infection documented in clinical discharge diagnosis or end-of-visit diagnosis by clinician providing direct patient care.

[c]Positive diagnostic test results for ZIKV infection by either real-time reverse transcription polymerase chain reaction or immunoglobulin M antibody capture enzyme-linked immunosorbent assay and reported date of illness onset between January 1 and December 31, 2016.

[d]Dengue-like illness, vector-borne viral infection, viral infection, or viral syndrome documented in clinical discharge diagnosis or end-of-visit diagnosis by clinician providing direct patient care.

[e]Confirmed ITP: clinical discharge diagnosis or end-of-visit diagnosis of ITP by clinician providing direct patient care.

[f]Possible ITP: platelet count <100 $\times 10^9$/L, the absence of other causes or disorders that may be associated with thrombocytopenia except ZIKV, and clinically consistent with ITP as determined by clinician on review of medical documentation available.

[10–15, 17]. This report nearly doubles the number of documented cases of severe ZIKV-associated thrombocytopenia that could be due to ITP. Moreover, this was the first investigation to determine the population-based incidence of ZIKV-associated thrombocytopenia. With 1.4 cases per 100 000 population and among 0.1% of patients reported with ZIKV disease, thrombocytopenia appears to be a rare but potentially severe manifestation associated with ZIKV infection. This analysis provided strong evidence that at least 33 patients with ZIKV-associated thrombocytopenia were possible cases of ITP and 6 were confirmed cases of ITP. Among the 12 patients with severe thrombocytopenia identified, 11 received treatment with IVIG or corticosteroids, and 9 responded to clinical treatment.

Similar to the patients identified in this investigation, case series from other countries reported patients with ZIKV infection and thrombocytopenia having acute phase bleeding manifestations, including gum bleeding, skin hematomas, oral mucosal bleeding, and hematuria [10–12, 14, 23, 33]. Blood abnormalities related to ZIKV infection are only sporadically reported but include thrombocytopenia, mild leucopenia, and the presence of activated lymphocytes [4]. In past case series of thrombocytopenia associated with ZIKV infection, bone marrow biopsies were consistent with ITP and Evan's syndrome (hypercellularity and without dysplasia) [10, 12]. Findings from blood smears showed macroplatelets and marked reductions in platelets. One blood smear in a patient with nonsevere thrombocytopenia was consistent with hemolytic anemia.

Previous estimates indicate that up to 1.4% of adults and 0.4% of children with ITP experience intracranial hemorrhage, whereas 15% of patients with ITP experience other forms of severe bleeding [29, 39]. Predictors of severe bleeding include platelet count <20 $\times 10^9$/L, newly diagnosed ITP, and previous episodes of bleeding [39]. Among the 12 patients with severe thrombocytopenia reported here, death occurred in 1 patient. This patient was elderly, had intracranial hemorrhage, and detection of thrombocytopenia and treatment occurred late in the clinical course. In elderly patients with ITP, although platelet counts are similar to those of younger age groups, prognosis can be poor [40]. Therefore, due to the risk of fatal outcome among elderly patients with ZIKV-associated thrombocytopenia, heightened vigilance and rapid treatment are warranted to prevent severe bleeding and minimize mortality.

Table 5. Characteristics of Patients with Zika Virus–associated Severe Thrombocytopenia—Puerto Rico, 2016 (n = 12)

Case	Age, y	Sex	Underlying Medical Conditions	Location/Type of Bleeding	Lowest Platelet Count, $\times 10^9$/L	Schistocytes or Abnormal RBCs on Blood Smear	No. of Platelet Transfusions	First Platelet Count After Initial Transfusion, $\times 10^9$/L	IVIG?	Highest Platelet Count ≤96 Hours After IVIG, $\times 10^9$/L	Cortico-Steroids?	Highest Platelet Count ≤96 Hours After Corticosteroids, $\times 10^9$/L	Response to Treatment?[a]	Confirmed ITP[b]	Possible ITP[c]	Outcome
1	72	M	Hypertension, high triglycerides and cholesterol	Petechiae, bullae, intracranial, tracheal, hematuria, gum bleeding	1	N/A	0	N/A	No	N/A	Yes	N/A	No	No	Yes	Death
2	38	M	Obesity	Petechiae, ecchymoses, gum bleeding	2	No	2	6	Yes	202	Yes	83	Yes	Yes	Yes	Admitted to ICU, recovered
3	41	F	None	Hematuria, occult bleed	18	N/A	0	N/A	No	N/A	Yes	101	Yes	No	Yes	Recovered
4	48	F	Diabetes, hypertension	Petechiae, ecchymoses, subcutaneous hematoma, hematuria, occult bleed	2	No	2	10	No	N/A	Yes	168	Yes	No	Yes	Recovered
5	88	M	Hypertension, diabetes, diverticulosis, alcohol use disorder	Petechiae, ecchymoses, subcutaneous hematoma, gum bleeding, skin bleeding, hematemesis	6	No	4	7	Yes	65	Yes	105	Yes	Yes	Yes	Admitted to ICU, recovered
6	30	M	None	Petechiae	9	No	1	52	No	N/A	Yes	96	Yes	No	Yes	Recovered
7	45	M	None	Ecchymoses	3	No	0	N/A	No	N/A	Yes	5	Yes	No	Yes	Recovered
8	22	F	History of ITP, hypothyroidism	Lower gastrointestinal bleed, ecchymoses	18	No	0	N/A	No	N/A	No	N/A	N/A	No	Yes	Recovered
9	2	F	None	Petechiae, subcutaneous hematoma, rectal bleed	30	No	0	N/A	Yes	112	No	N/A	Yes	Yes	Yes	Admitted to ICU, recovered
10	56	F	Deep vein thrombosis, hypothyroidism, history of ITP	Hematuria, epistaxis, petechiae	29	N/A	0	N/A	No	N/A	Yes	50	No	Yes	Yes	Recovered
11	13	M	Asthma, history of pyloromyotomy	Ecchymoses	16	No	0	N/A	Yes	110	No	N/A	Yes	Yes	Yes	Recovered
12	15	M	Viral illness in last 28 d, biliary atresia, asthma	Petechiae, epistaxis	29	No	0	N/A	Yes	149	No	N/A	Yes	Yes	Yes	Admitted to ICU, recovered

Abbreviations: F, female; ICU, intensive care unit; ITP, immune thrombocytopenia; IVIG, intravenous immunoglobulin; M, male; N/A, not applicable or data not available.

[a]Clinical response: platelet count ≥30 $\times 10^9$/L, a >2-fold increase in platelet count from baseline, and the absence of bleeding.

[b]Confirmed ITP: clinical discharge diagnosis or end-of-visit diagnosis of ITP by clinician providing direct patient care.

[c]Possible ITP: platelet count <100 $\times 10^9$/L, the absence of other causes or disorders that may be associated with thrombocytopenia except ZIKV, and clinically consistent with ITP as determined by clinician on review of medical documentation available.

Among the 12 patients with severe thrombocytopenia, response to platelet transfusion seemed minimal. According to the evidence-based practice guidelines, in newly diagnosed pediatric patients with ITP, initial management recommendations for patients with no or mild bleeding should include observation alone regardless of the platelet count [28]. Initial pharmacologic treatment recommendations when indicated in pediatric patients include IVIG or a short course of corticosteroids [28]. In adults, treatment is recommended for patients with a newly diagnosed platelet count $<30 \times 10^9$/L, and longer-course corticosteroids are the preferred firstline treatment with IVIG used in conjunction when a more rapid platelet increase is required [28]. IVIG and Rho(D) immune globulin (anti-D) is the firstline treatment when corticosteroids are contraindicated [28]. Five out of 6 (83%) patients diagnosed with ITP who received IVIG and/or corticosteroids responded to treatment. Moreover, these responses were consistent with initial and peak responses to IVIG of 1–3 and 2–7 days, respectively, dexamethasone of 2–14 and 4–28 days, and prednisone of 4–14 and 7–28 days [28, 29]. Platelet transfusions may be indicated in severe and life-threatening bleeding when a rapid rise in platelet count is needed to achieve adequate hemostasis.

This investigation was subject to limitations. First, because not all medical records were available for review and not all patients with ZIKV-associated severe thrombocytopenia were likely reported, the identified incidence of thrombocytopenia is likely an underestimate of the true incidence. Second, because diagnostic testing for patients with thrombocytopenia is not standardized across hospitals in Puerto Rico, etiologies of thrombocytopenia other than ZIKV may have been responsible for thrombocytopenia in some patients. Similarly, half of the cases with thrombocytopenia only had serologic evidence of ZIKV infection. Because the duration of anti-ZIKV IgM antibody has not been defined but is likely to be at least several months, some individuals with residual IgM antibody may have been misclassified; however, 90% of patients had signs and symptoms consistent with ZIKV infection within 1 week of thrombocytopenia. Last, although anti-ZIKV IgM antibody may cross-react with DENV antigen and vice versa [36], DENV transmission was at a historic low in Puerto Rico in 2016 [6]. Hence, all patients in this report for which anti-ZIKV IgM antibody was detected were likely to have been the result of infection with ZIKV and not DENV.

Though rare, ZIKV-associated severe thrombocytopenia can be fatal. Treatment of ZIKV-associated thrombocytopenia might be indicated in some cases based on clinical expertise and recommendations. As demonstrated here, platelet transfusion alone does not appear to be sufficient to elicit an appropriate clinical response, whereas administration of corticosteroids, IVIG, or other ITP treatment could benefit some patients. Further investigation is needed to identify the mechanism of pathogenesis in patients with ZIKV-associated severe thrombocytopenia. This aspect is also relevant in the design of a vaccine to prevent ZIKV infection, as individual viral epitopes may be responsible for antibodies that cross-react with platelets and lead to severe thrombocytopenia [41]. Regardless of the mechanism, the findings from this investigation demonstrate that timely diagnosis of ITP among patients with ZIKV-associated severe thrombocytopenia is crucial to initiating life-saving interventions.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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