Hantavirus Disease and COVID-19

Evaluation of the Hantavirus 5-Point Screen in 139 COVID-19 Patients

Allison K. Joyce, MSc,[1,] Tarrah T. Oliver,[2,*] Aaron D. Kofman, MD,[3] Donna L. Talker,[2] Shahrokh Safaeian,[2] Deniz Peker Barclift, MD,[3] Adam J. Perricone, MD, PhD,[3] Shawn M. D'Andrea, MD,[2] Amy N. Whitesell, MPH,[1] Del Yazzie, MPH,[4] Jeannette Guarner, MD,[3] Mozafar Saleki, MS,[2] Glynnis B. Ingall, MD, PhD,[5] Mary J. Choi, MD,[1] and Ramona Antone-Nez, MPH[4]*

From the [1]National Center for Emerging and Zoonotic Infectious Diseases, CDC, Atlanta, GA, USA; [2]Tséhootsooí Medical Center, Fort Defiance, AZ, USA; [3]Emory University, Atlanta, GA, USA; [4]Navajo Epidemiology Center, Window Rock, AZ, USA; and [5]University of New Mexico Health Sciences Center, Albuquerque, NM, USA.

ABSTRACT

Objectives: Navajo Nation is disproportionately affected by hantavirus cardiopulmonary syndrome (HCPS), a severe respiratory disease that can quickly progress to respiratory failure and cardiogenic shock. The initial signs and symptoms of HCPS are indistinguishable from coronavirus disease 2019 (COVID-19). However, this distinction is critical, as the disease course differs greatly, with most patients with COVID-19 experiencing mild to moderate illness. We set out to determine if the evaluation of peripheral blood smears for five hematopathologic criteria previously identified as hallmarks of hantavirus infection, or "the hantavirus 5-point screen," could distinguish between COVID-19 and HCPS.

Methods: The hantavirus 5-point screen was performed on peripheral blood smears from 139 patients positive for COVID-19 seeking treatment from Tséhootsooí Medical Center and two Emory University hospitals.

Results: Of these 139 individuals, 136 (98%) received a score of 3/5 or below, indicating low suspicion for HCPS. While thrombocytopenia, one of the key signs of HCPS, was seen in the patients with COVID-19, it was generally mild and remained stable on repeat specimens collected 12 to 24 hours later.

Conclusions: Given these findings, the 5-point screen remains a useful rapid screening tool for potential HCPS cases and may be useful to distinguish early HCPS from COVID-19 in HCPS endemic regions.

INTRODUCTION

Hantavirus cardiopulmonary syndrome (HCPS) due to Sin Nombre virus is a severe respiratory disease with average case fatality rates as high as 35%.[1] HCPS was first identified in 1993 in the Four Corners region of the United States—an area largely belonging to Navajo Nation where Utah, Colorado, Arizona, and New Mexico intersect.[2] HCPS is a rare disease, with a 20-year surveillance period reporting 624 cases throughout the United States.[3] However, Navajo Nation continues to be disproportionately affected by HCPS, with Navajos

KEY POINTS

- Hantavirus cardiopulmonary syndrome (HCPS) and coronavirus disease 2019 (COVID-19) can be very difficult for clinicians to distinguish upon initial signs and symptoms.
- Based on peripheral blood smears, patients with COVID-19 do not demonstrate the elevated hemoglobin, left shift, and immunoblasts and plasma cells more than 10% of lymphoid cells signs characteristic of HCPS.
- The low scores that patients with COVID-19 receive on the hantavirus 5-point screen indicate this tool can be used as a rapid screen to differentiate between the two diseases in HCPS endemic regions.

KEY WORDS

Hantavirus; Hantavirus cardiopulmonary syndrome; COVID-19; Rapid screen; Peripheral blood smear; Thrombocytopenia

Am J Clin Pathol XXXX 2021;XX:1–0
HTTPS://DOI.ORG/10.1093/AJCP/AQAB155

Received: April 30, 2021
Accepted: August 16, 2021
Advance publication: October 13, 2021

Corresponding author: Allison K. Joyce, MSc; alliejkim@gmail.com.

*First authors.

making up 1.7% of the US population but accounting for 18% of all HCPS cases.[4]

HCPS begins with a nonspecific febrile prodrome.[5] This initial phase lasts 2 to 6 days and is characterized by fever, malaise, and myalgias.[5,6] Gastrointestinal signs and symptoms have also been reported, including nausea, vomiting, and diarrhea.[5,6] The disease quickly progresses to the cardiopulmonary phase, characterized by the abrupt onset of cough, shortness of breath, and hypoxia.[5-8] These symptoms are caused by the sudden development of severe noncardiogenic pulmonary edema and cardiogenic shock.[5-8] Without immediate medical intervention, most deaths occur within 24 to 48 hours from onset of the cardiopulmonary phase.[5-8] However, early initiation of extracorporeal membrane oxygenation (ECMO) has been shown to improve survival in severe HCPS.[9] Due to the aggressive nature of the disease, early clinical suspicion, timely diagnosis, and proactive clinical management are critical to saving the lives of patients with HCPS.

Current diagnostic options for hantavirus are limited to real-time reverse transcription polymerase chain reaction (rRT-PCR) or serology for immunoglobulin M and immunoglobulin G. However, these tests are not widely available and can take considerable time to return results. To address this problem, the University of New Mexico Health Sciences Center developed a rapid screening tool in 2001 with the aim of quickly classifying patients with suspected hantavirus into low, intermediate, or high risk for HCPS.[10] The screen is based on the five criteria the hematopathologists identified as hallmarks of HCPS: thrombocytopenia, elevated hemoglobin/hematocrit, a left shift on neutrophils, absence of significant toxic granulation of the neutrophils, and immunoblasts and plasma cells more than 10% of lymphoid cells.[10] The "5-point" screen is most accurate when the specimen was collected during the cardiopulmonary phase.[10] In addition, the thrombocytopenia seen in patients with hantavirus tends to be profound, with platelet counts decreasing more than 20×10^3 µL per 12 hours.[10] A decade-long retrospective review confirmed that individuals with hantavirus score high on the 5-point screen, receiving an average score of 4.22 out of 5.[11] The review also found that by using a score cutoff of 4 out of 5, the screen demonstrated a sensitivity of 89% and a specificity of 93% for HCPS, thus validating its use as a rapid screen for HCPS.[11] Therefore, in areas endemic for hantavirus, the 5-point screen is a useful tool to quickly screen for potential HCPS cases where rapid commercial diagnostic tests are not available and would take time to return when critical decisions regarding patient care need to be made.

Navajo Nation has also been heavily affected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a highly transmissible novel zoonotic virus that emerged in 2019 and causes coronavirus disease (COVID-19).[12] In May 2020, Navajo Nation surpassed New York and New Jersey as the highest per-capita coronavirus infection rate in the United States.[13] The signs and symptoms of acute COVID-19 overlap with those of HCPS. As a result, in Navajo Nation and other regions endemic for HCPS, it may be difficult to clinically distinguish early symptoms of COVID-19 and HCPS from each other.[14] However, this distinction is critical, as the expected clinical courses differ greatly. Most healthy adults with COVID-19 experience mild to moderate disease, and severe disease tends to develop over days to weeks.[15] In contrast, the clinical course for those with HCPS is more severe and often develops within hours, with most requiring urgent intensive care treatment and some requiring ECMO. Given the ongoing COVID-19 pandemic, a screening tool that could rapidly differentiate between the two disease entities is critical for preventing excess deaths due to hantavirus disease in hantavirus endemic regions. Therefore, we sought to determine whether the hantavirus 5-point screen could be used to differentiate between HCPS and COVID-19.

MATERIALS AND METHODS

This project was conducted at three sites: Tséhootsooí Medical Center (TMC), Emory University Hospital, and Emory University Hospital Midtown. This activity was reviewed by the Centers for Disease Control and Prevention (CDC) and was conducted consistent with applicable federal law and CDC policy (see, eg, 45 C.F.R. part 46, 21 C.F.R. part 56; 42 U.S.C. §241(d); 5 U.S.C. §552a; 44 U.S.C. §3501 et seq.). It was also reviewed by ethical committees at TMC and Emory and received the determination of nonresearch at TMC and exempt research at Emory. Located in Fort Defiance, Arizona, in Navajo Nation, TMC is a 56-bed Public Law 93-638 self-determined hospital serving Navajo Nation. TMC's 25-bed emergency department has 40,000 visits annually. The closest facility with ECMO capability is the University of New Mexico Hospital in Albuquerque, New Mexico, which is 170 miles away. In May 2016, TMC implemented the hantavirus 5-point screen. To date, 189 screens have been performed and four cases of hantavirus disease have been identified (Tarrah T. Oliver, unpublished data, 2021).

Emory University Hospital and Emory University Hospital Midtown are, respectively, 751- and 529-bed academic teaching hospitals located in Atlanta, Georgia, and make up the two largest hospitals within the Emory Healthcare System of metropolitan Atlanta. Emory University Hospital's 36-bed emergency department has 36,000 visits annually.

From April to May 2020, TMC conducted hantavirus screens on all patients who sought treatment from the hospital with signs and symptoms suggestive of COVID-19. At TMC, the screens were performed and interpreted by medical laboratory technicians and medical technologists. In March and April 2020, the Emory sites retrospectively identified all patients with a positive molecular COVID-19 test. Two pathologists performed and interpreted the hantavirus 5-point screens for these individuals. All screens were evaluated in accordance with the protocol established by TMC (Supplementary Figure S1; all supplemental materials can be found at *American Journal of Clinical Pathology* online).[15] Both institutions use automated instruments to perform CBC counts and WBC differentials with the following workflow: the samples were placed on the Sysmex XN-L instrument, which uses flow cytometry technology. If the sample showed any alteration that is flagged based on set instrument parameters, a smear would be produced and stained automatically using a

stainer (SP-50; Sysmex). Using CellaVison DI60 (Sysmex), the stained smear was scanned, and WBCs were photographed and sorted into the different categories. Medical scientists approved the sorting done by the image analyzer or changed particular cells to a different category if necessary as part of the manual differential. These CBCs and smears were used to determine the presence of the five criteria of the 5-point screen based on the following parameters. Thrombocytopenia was defined as a platelet count less than 150×10^9/L. Significant toxic change in neutrophils was defined as a grade 2+ or more. Immunoblasts and plasma cells were present in a concentration more than 10% of lymphoid cells. Different normal ranges for hemoglobin and hematocrit were used for the two sites, as elevation differs between Fort Defiance, AZ, and Atlanta, GA. Hemoglobin values 18 g/dL or more for men and 16 g/dL or more for women, as well as hematocrit values 52% or more for men and 48% or more for women were considered elevated for TMC. Hemoglobin values 16.1 g/dL or more for men and 14.4 g/dL or more for women, as well as hematocrit values 46.5% or more for men and 41.4% or more for women were considered elevated for Emory. Last, there is no specific range for left shift. If the algorithm within the analyzer detects immature granulocytes over 5%, medical scientists or pathologists will conduct a manual differential and look for immature neutrophilic cells to identify left shift.

COVID-19 molecular testing was performed on all project participants. Participants whose COVID-19 test was negative were excluded from the project. For both TMC and the Emory sites, a repeat platelet count that was obtained within 12 to 24 hours was available for a subset of individuals at provider discretion. COVID-19 serology was not performed.

Project investigators reviewed the medical records for all enrolled participants. For each participant, the following information was collected: demographics, medical history (to include comorbidities known to be associated with thrombocytopenia and/or are associated with an increased risk of severe COVID-19), clinical presentation, and outcome. As the hantavirus 5-point screen is most accurate when the specimen is collected during the cardiopulmonary phase, a composite variable of respiratory symptoms was created to determine the percentage of patients with COVID-19 who had their sample collected while they were experiencing respiratory symptoms.[10] Respiratory symptoms were considered present if any of the following criteria was met: presence of cough and/or shortness of breath and/or an oxygen saturation of less than 93%.

Analysis of the clinical data and the hantavirus screen data was conducted in a combination of Excel 2008 (Microsoft) and SAS 9.4 (SAS Institute). Frequencies were calculated for the categorical variables, and descriptive statistics, including mean, median, range, and interquartile range, were calculated for the continuous variables. The χ^2 tests were done for the categorical variables, except where Fisher exact test was appropriate. For the continuous variables, a two-sample *t* test was done for age, and the Mann-Whitney *U* test was done for duration of hospitalization. Statistical tests were also done comparing the average scores received on the hantavirus screen to a hypothesized value of 4/5, a score that indicates high suspicion for HCPS. A one-sample sign test was done for the skewed TMC population, and a one-sample *t* test was done for the normally distributed Emory population.

RESULTS

A total of 143 participants were enrolled in the project, 72 at TMC and 71 at Emory. Three individuals from TMC were later excluded from the analysis because their COVID-19 molecular tests were negative at the time of their sample collection for the screen. One individual from Emory was excluded from the analysis because their peripheral blood smear was uninterpretable. These exclusions resulted in 139 participants included in the project. At TMC, 69 screens were done on 69 unique individuals. Of these, 18 had an additional platelet count performed on a sample that was collected within 12 to 24 hours of the initial screen. At Emory, 70 screens were done on 70 unique individuals. Of these, 13 had an additional platelet count performed on a sample that was collected within 12 to 24 hours of the initial screen.

The two populations differed across demographics, comorbidities, clinical presentation, and outcome **TABLE 1**. The sex distribution was similar at both sites, with 50% male at TMC and 56% male at Emory. Age and race differed between the two populations. The TMC cohort was 100% American Indian and had a mean age of 53 years. Emory represented a slightly older (mean age, 61 years), largely African American (85%) population. The significant differences in comorbidities between the two groups were as follows: patients seeking treatment at TMC were more likely to be obese (63% vs 44% at Emory) and have preexisting liver disease (15% vs 0% at Emory). The Emory cohort had higher rates of hypertension (61% vs 42% at TMC), lung disease (17% vs 3% at TMC), and kidney disease (21% vs 2% at TMC). With regards to clinical presentation at the time of sample collection, 87% of participants at TMC had respiratory symptoms. In the Emory cohort, 76% of participants had respiratory symptoms at the time of presentation. In the TMC cohort, 46% of individuals had an oxygen saturation less than 90%, compared with 12% at Emory. However, individuals at Emory were more likely to be treated with invasive ventilation (41% vs 20% at TMC), and one individual received ECMO.

The scores received on the hantavirus 5-point screen differed slightly between the two groups **FIGURE 1**. The mean score from 69 individuals from TMC was 1.48 (median, 1.00; range, 1.00-4.00). The mean score from 70 individuals from Emory was 2.00 (median, 2.00; range, 0.00-4.00). None of the 139 individuals in the project positive for COVID-19 received a score of 5 on the hantavirus 5-point screen. One individual at TMC and two individuals at Emory received a score of 4. The individual from TMC had thrombocytopenia, elevated hemoglobin/hematocrit, a left shift on neutrophils, and absence of significant toxic granulation of the neutrophils. The two individuals from Emory had thrombocytopenia, a left shift on neutrophils, absence of significant toxic granulation of the neutrophils, and immunoblasts and plasma cells more than 10% of lymphoid cells. For the individual at

HTTPS://DOI.ORG/10.1093/AJCP/AQAB155

TABLE 1 Characteristics of Patients Positive for COVID-19 in Two Hospitals[a]

Characteristic	TMC (n = 69)	Emory (n = 70)	*P* Value
Demographics			
Age, mean (range), y[b]	53 (21-98)	61 (21-92)	.874
Male	34/68 (50)	39 (56)	.501
Indian/Alaska Native	67/67 (100)	0/68 (0)	<.0001[c]
African American	0/67 (0)	58/68 (85)	<.0001[c]
White	0/67 (0)	9/68 (13)	.003[c]
Asian	0/67 (0)	1/68 (1)	1.000
Medical history			
Obesity	33/52 (63)	31 (44)	.036[c]
Hypertension	28/66 (42)	43 (61)	.027[c]
Diabetes	26/66 (39)	25 (36)	.658
Preexisting thrombocytopenia	9/61 (15)	4 (6)	.141
Preexisting liver disease	10/66 (15)	0 (0)	.001[c]
Coronary artery disease	8/66 (12)	12 (17)	.409
Steroid/immunosuppressants	6/59 (10)	11 (16)	.354
Active or former smoker	4/46 (9)	10 (14)	.561
Preexisting lung disease	2/66 (3)	12 (17)	.009[c]
Chronic kidney disease	1/66 (2)	15 (21)	.001[c]
Active cancer on chemotherapy	0/66 (0)	3 (4)	.245
HIV	0/66 (0)	1 (1)	1.000
Clinical presentation upon sample collection			
Composite respiratory symptoms variable	60 (87)	53 (76)	.813
Cough	51/63 (81)	38 (54)	.001[c]
Shortness of breath	36/63 (57)	37 (53)	.620
Oxygen saturation 90%-93%	17/59 (29)	13/69 (19)	.184
Oxygen saturation <90%	27/59 (46)	8/69 (12)	<.0001[c]
Temperature ≥38°C	12/59 (20)	19/69 (28)	.343
Diarrhea	15/63 (24)	17 (24)	.949
Outcome			
Noninvasive ventilation	40/60 (67)	27 (39)	.001[c]
Invasive ventilation	12/60 (20)	29 (41)	.009[c]
ECMO	0/60 (0)	1 (1)	1.000
Hospitalized	48/64 (75)	70 (100)	<.0001[c]
Duration of hospitalization, median, d[d]	4	10	<.0001[c]
Survived to hospital discharge	62/68 (91)	56 (80)	.062

COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; HIV, human immunodeficiency virus; TMC, Tséhootsooí Medical Center.
[a]Data are presented in a n/N (%) format unless otherwise indicated, where N equals the number of individuals the data were available for.
[c]Indicates a statistically significant result.
[b]Age was available for 68 of the 69 individuals from the TMC cohort and all 70 of the Emory cohort.
[d]Duration of hospitalization was available for 40 of the 69 individuals from the TMC cohort and all 70 of the Emory cohort.

TMC, it was believed their clinical presentation was not consistent with hantavirus, and therefore hantavirus serologies were not sent. Hantavirus serologies were also not sent for the two individuals at Emory, as hantavirus is not endemic to Georgia and the individuals had not recently traveled. Statistical tests were done to compare the average

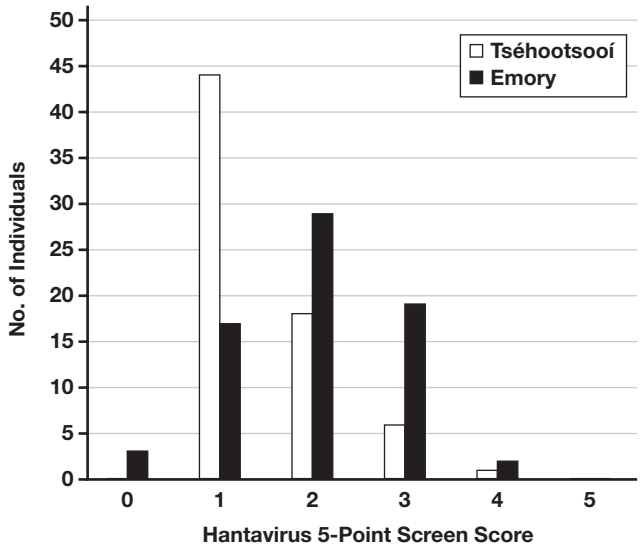

FIGURE 1 Hantavirus 5-point screen score frequencies from two populations of patients with coronavirus disease 2019.

score each cohort of the patients with COVID-19 received on the screen to a hypothesized value of 4, which would indicate high risk for HCPS. A one-sample sign test was done for the skewed TMC population, and a one-sample *t* test was done for the normally distributed Emory population. Both statistical tests returned a *P* value less than .0001, indicating very strong statistical evidence that the score patients with COVID-19 receive on the hantavirus screen is different from the score patients with HCPS receive.

There were several notable differences in the criteria met on the screen between TMC and Emory FIGURE 2. The most common criterion of the screen met at both institutions was absence of significant toxic granulation, seen in 100% of individuals at TMC and 80% at Emory. Thrombocytopenia was seen in 30% of both cohorts. Elevated hemoglobin and hematocrit were rarely seen in either cohort, with 4% at TMC and 0% at Emory. The TMC cohort demonstrated fairly low rates of the remaining two criteria: with 7% of participants having left shift and 3% having immunoblasts and plasma cells more than 10% of lymphoid cells. This was distinctive from the Emory cohort, in which 51% of participants had left shift and 39% with immunoblasts and plasma cells more than 10% of lymphoid cells.

The median platelet count was similar between the TMC (185×10^9/L) and Emory cohorts (183×10^9/L) TABLE 2. Among individuals with thrombocytopenia, the median platelet count was 107×10^9/L at TMC and 123×10^9/L at Emory. In total, 31 participants had a repeat platelet count performed 12 to 24 hours after the hantavirus screen. Of these, the median platelet count was 180×10^9/L and 208×10^9/L at TMC and Emory, respectively. None of the thrombocytopenic individuals in either the TMC or Emory cohort demonstrated a 20% or higher drop in the repeat platelet count performed 12 to 24 hours after the initial screen.

DISCUSSION

Our findings suggest the criteria on the 5-point screen can be used to differentiate between HCPS and COVID-19 in regions endemic for

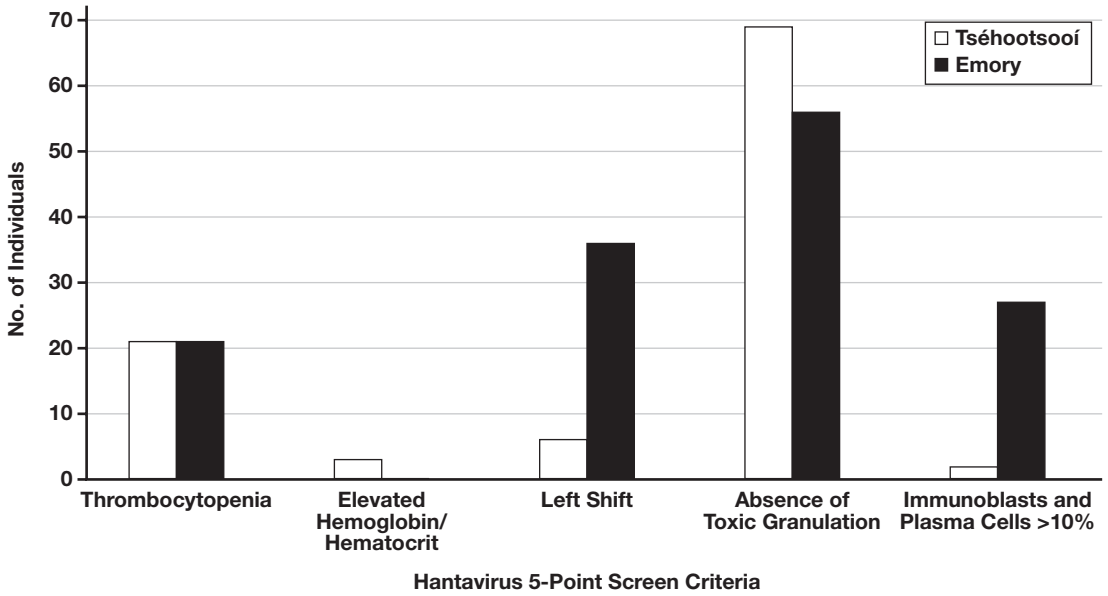

FIGURE 2 Hantavirus 5-point screen criteria frequencies from two populations of patients with coronavirus disease 2019.

TABLE 2 Platelet Count Details From Initial Hantavirus Screen and Repeat Platelet Count Performed Within 12 to 24 Hours for Two Populations of Patients With COVID-19

Initial Platelet Count	TMC (n = 69)	Emory (n = 70)
Platelet count, median (IQR), × 10^9/L	185 (140-234)	183 (138-236)
Individuals with thrombocytopenia, No. (%)	21/69 (30)	21/70 (30)
Thrombocytopenic platelet count, median (IQR), × 10^9/L	107 (95-132)	123 (104-135)
No. of patients with repeat platelet count (12-24 hours)	18	13
Platelet count, median (IQR), × 10^9/L	180 (136-244)	208 (175-224)
Individuals with thrombocytopenia, No. (%)	6/18 (33)	2/13 (15)
Thrombocytopenic platelet count, median (IQR), × 10^9/L	122 (64-131)	110 (102-117)
Individuals with thrombocytopenia on initial and repeat platelet count, No. (%)	2/18 (11)	2/13 (15)
Individuals with thrombocytopenia on initial platelet count and who had ≥20% drop in repeat platelet count, No. (%)	0/2 (0)	0/2 (0)

COVID-19, coronavirus disease 2019; IQR, interquartile range.

HCPS. There were a number of differences in the 5-point screen results for these two cohorts. First, there were differences in the distribution of scores between the two groups, with 64% of individuals at TMC receiving a score of 1, compared with only 24% at Emory. In addition, Emory showed higher frequencies of left shift and immunoblasts and plasma cells more than 10% of lymphoid cells. The reasons for these differences are likely varied and may include the following. First, the participants enrolled at Emory and TMC were very different from one another in terms of demographics, medical history, clinical presentation, and outcome. Notably, at Emory, all patients went on to be admitted to the hospital for their COVID-19 illness, whereas a lesser number (75%) of TMC patients were admitted. Second, there were differences in who performed the 5-point screens. At TMC, the screens were performed by medical technicians and technologists with previous experience implementing the screens. At Emory, the screens were performed by pathologists. Third, although most individuals from both cohorts had respiratory symptoms at the time of sample collection, not all did. Thus, individuals may not have been at the same stage in their disease progression when the sample was collected for the screen. Perhaps different severity of COVID-19 disease affected the peripheral blood findings. Fourth, the medical chart reviews performed at Emory were more complete compared with TMC. The demographic, medical history, clinical presentation, and outcome variables were available for 97% to 100% of the Emory cohort but ranged from 67% to 100% for the TMC cohort. Finally, it is important to acknowledge the hantavirus 5-point screen contains some subjective criteria and is subject to interobserver variability. However, because the purpose of the screen is to distinguish individuals at high risk for HCPS (scores of 4-5) from those at intermediate (3) or low (1-2) risk, we contend these cutoffs allow for a difference in interpretation of the markers that ultimately do not change the results.

We found that irrespective of who performed the 5-point screen, the demographics of the population screened, or when in the COVID-19 disease course the sample was taken, individuals positive for COVID-19 received a low score on the screen. None of the 139 individuals in the project positive for COVID-19 demonstrated all five hallmarks of hantavirus infection, and only 3 (2%) individuals received a score of 4 on the screen. Although there were differences in the frequency of scores 1, 2, and 3 between the TMC and Emory populations FIGURE 1, these scores would all be considered non–high risk for HCPS. Thrombocytopenia was seen in 30% of the project participants but was mild, with thrombocytopenic individuals having a median platelet count of 107 × 10^9/L at TMC and 123 × 10^9/L at Emory. This is consistent with other studies in patients positive for COVID-19.[16-18] In contrast, thrombocytopenia seen in HCPS patients is typically more profound, with some platelet counts dipping to dangerously low levels of less than 30 × 10^9/L.[10] In addition, none

of the individuals with thrombocytopenia who had a repeat platelet count done within 12 to 24 hours demonstrated the 20% or more drop that is characteristic of patients with HCPS. Therefore, while thrombocytopenia was seen in our cohort of 139 patients positive for COVID-19, it is generally milder than what is seen in patients with HCPS.

Given the overlap in signs and symptoms, it is difficult to distinguish early HCPS and COVID-19 disease. In May 2020, a mother and her 11-year-old son died after a brief severe respiratory illness in Arizona.[14] Initial testing of tissue collected from the child's trachea and lung were positive for SARS-CoV-2 by rRT-PCR. Testing of the mother's lung tissue was negative for SARS-CoV-2 by rRT-PCR but demonstrated clinicopathologic features suggestive of HCPS. Subsequent immunohistochemical evaluation of lung tissue from both the mother and the child confirmed hantavirus infection. This case underscores the importance of considering hantavirus disease in the differential diagnosis in patients presenting with respiratory illness who live in hantavirus endemic areas. In addition, clinicians in hantavirus endemic areas should consider performing the hantavirus 5-point screen even in patients positive for COVID-19 to identify potential instances of coinfection.

CONCLUSIONS

In conclusion, we validated the use of the 5-point screen as a screening tool for immediate decision making in remote areas. We found that patients positive for COVID-19 receive low scores on the hantavirus 5-point screen, thus validating its use as a rapid tool to differentiate between these two disease entities in hantavirus endemic areas.

Acknowledgments: This project was supported in part by an appointment to the Research Participation Program at the Centers for Disease Control and Prevention administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the US Department of Energy and the Centers for Disease Control and Prevention.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

REFERENCES

1. MacNeil A, Ksiazek TG, Rollin PE. Hantavirus pulmonary syndrome, United States, 1993-2009. *Emerg Infect Dis*. 2011;17:1195-1201.
2. Nichol ST, Spiropoulou CF, Morzunov S, et al. Genetic identification of a hantavirus associated with an outbreak of acute respiratory illness. *Science*. 1993;262:914-917.
3. Knust B, Rollin PE. Twenty-year summary of surveillance for human hantavirus infections, United States. *Emerg Infect Dis*. 2013;19:1934-1937.
4. Ryan A, Yazzie D, Antone-Nez R. Navajo Nation Hantavirus Surveillance Report 1992-2016. Navajo Epidemiology Center. 2016. https://www.nec.navajo-nsn.gov/. Accessed November 9, 2020.
5. Butler JC, Peters CJ. Hantaviruses and hantavirus pulmonary syndrome. *Clin Infect Dis*. 1994;19:387-395.
6. Duchin JS, Koster FT, Peters CJ, et al. Hantavirus pulmonary syndrome: a clinical description of 17 patients with a newly recognized disease. The Hantavirus Study Group. *N Engl J Med*. 1994;330:949-955.
7. Hallin GW, Simpson SQ, Crowell RE, et al. Cardiopulmonary manifestations of hantavirus pulmonary syndrome. *Crit Care Med*. 1996;24:252-258.
8. Mertz GJ, Hjelle BL, Bryan RT. Hantavirus infection. *Adv Intern Med*. 1997;42:369-421.
9. Wernly JA, Dietl CA, Tabe CE, et al. Extracorporeal membrane oxygenation support improves survival of patients with hantavirus cardiopulmonary syndrome refractory to medical treatment. *Eur J Cardiothorac Surg*. 2011;40:1334-1340.
10. Koster F, Foucar K, Hjelle B, et al. Rapid presumptive diagnosis of hantavirus cardiopulmonary syndrome by peripheral blood smear review. *Am J Clin Pathol*. 2001;116:665-672.
11. Dvorscak L, Czuchlewski DR. Successful triage of suspected hantavirus cardiopulmonary syndrome by peripheral blood smear review: a decade of experience in an endemic region. *Am J Clin Pathol*. 2014;142:196-201.
12. Zhu N, Zhang D, Wang W, et al; China Novel Coronavirus Investigating and Research Team. a novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med*. 2020;382:727-733.
13. Silverman H, Toropin K, Sidner S, et al. Navajo Nation surpasses New York State for the highest COVID-19 infection rate in the US. CNN. 2020. https://www.cnn.com/2020/05/18/us/navajo-nation-infection-rate-trnd/index.html. Accessed December 7, 2020.
14. Wilson TM, Paddock CD, Reagan-Steiner S, et al. Intersecting paths of emerging and reemerging infectious diseases. *Emerg Infect Dis*. 2021;27:1517-1519.
15. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19)—China, 2020. *China CDC Wkly*. 2020;2:113-122.
16. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395:497-506.
17. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. *JAMA*. 2020;323:1061-1069.
18. Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382:1708-1720.