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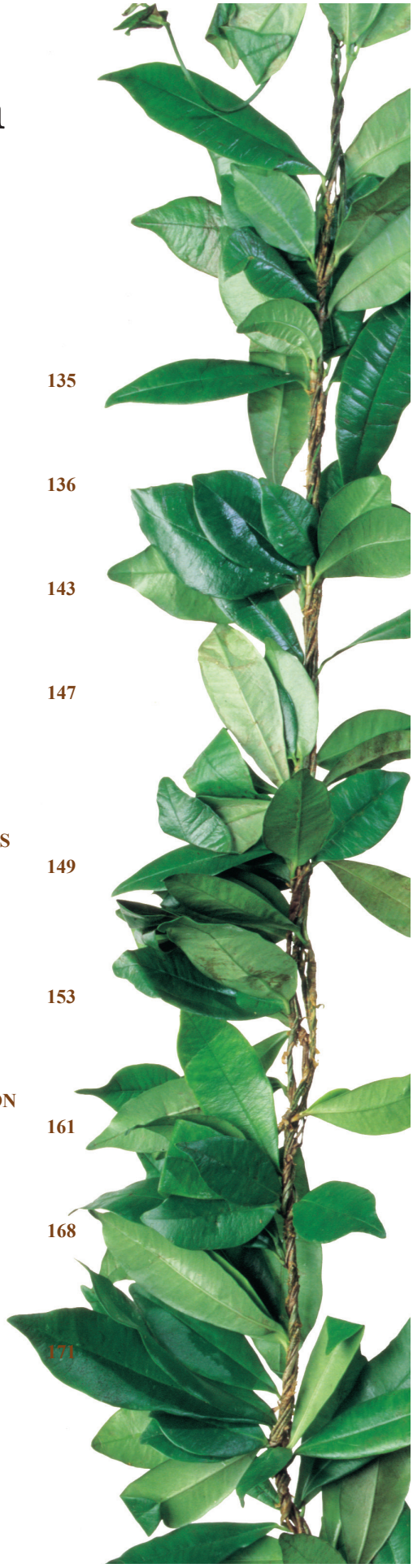

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Aim:
The aim of the Hawai‘i Journal of Health & Social Welfare is to advance knowledge about health and social welfare, with a focus on the diverse peoples and unique environments of Hawai‘i and the Pacific region.

History:
In 1941, a journal then called The Hawai‘i Medical Journal was founded by the Hawai‘i Medical Association (HMA). The HMA had been incorporated in 1856 under the Hawaiian monarchy. In 2008, a separate journal called the Hawai‘i Journal of Public Health was established by a collaborative effort between the Hawai‘i State Department of Health and the University of Hawai‘i at Mānoa Office of Public Health Studies. In 2012, these two journals merged to form the Hawai‘i Journal of Medicine & Public Health, and this journal continued to be supported by the Hawai‘i State Department of Health and the John A. Burns School of Medicine.

In 2018, the number of partners providing financial backing for the journal expanded, and to reflect this expansion the name of the journal was changed in 2019 to the Hawai‘i Journal of Health & Social Welfare. The lead academic partners are now the six units of the UH College of Health Sciences and Social Welfare, including the John A. Burns School of Medicine, UH Public Health, the Myron B. Thompson School of Social Work, the School of Nursing and Dental Hygiene, the UH Cancer Center, and the Daniel K. Inouye College of Pharmacy. Other partners are the Hawai‘i State Department of Health and the UH Office of the Vice Chancellor for Research. The journal is fiscally managed by University Health Partners of Hawai‘i.

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HAWAIʻI JOURNAL WATCH

KAREN ROWAN MS

Highlights of recent research from the University of Hawaiʻi and the Hawaiʻi State Department of Health

A Multidisciplinary Approach Helps Surgeons to Repair Complex Hernias

In patients with complex ventral hernias, the abdominal contents protrude through the abdominal fascia, the connective tissue that encloses the internal organs. In a new paper, researchers including Dean Mikami MD, of the John A. Burns School of Medicine, note that a better understanding of how surgical mesh achieves its effect in hernia repair is needed. The authors report on performing repairs in 56 patients at Macquarie University Hospital in Australia. The authors used measurements from CT scans to calculate the size of the mesh needed to repair the fascia. The mesh was cut by hand with extra fabric along the edges to reduce complications. Seventeen patients developed complications, but all lived, and only one developed a hernia recurrence. The researchers concluded that a variety of techniques can be used in complex ventral hernia repair.

- Rodriguez-Acevedo O, Elstner K, Jacombs A, et al. The Macquarie system for comprehensive management of complex ventral hernia. *Hernia.* 2019. https://doi.org/10.1007/s10029-019-02092-7

Why Hawaiʻi's Choose Healthy Now Program Was Successful

The Choose Healthy Now (CHN) program, which aimed to increase awareness of healthier food and beverage options at Hawaiʻi convenience stores though in-store signage and product placement, was successful in part because of leadership buy-in. Toby Beckelman MS, MPH, of the Hawaiʻi State Department of Health, is the lead author of an article describing program details for health departments and others to model. Results of 139 store exit surveys showed 25.2% of customers purchased at least 1 item that met CHN nutrition guidelines such as bottled water or bananas. Data from Hawaiʻi Behavioral Risk Factor Surveillance System showed 34.8% of respondents recalled seeing or hearing a CHN advertisement. Campaign materials that were co-branded with store logos and having the First Lady of Hawaiʻi as a spokesperson helped the campaign. However, the price of CHN items remains a challenge for many in purchasing.

- Beckelman T, Sinclair-White BM, McGurk MD, et al. Encouraging adults to choose healthy now: A Hawaiʻi convenience store intervention. *J Nutr Educ Behav*. 2020;52:330−334. doi:10.1016/j.jneb.2019.11.016.

Disaster Nursing Competencies Established Globally

During disasters or emergency events, nurses will be called to contribute to response efforts. In a new publication, nurse leaders from around the globe, including Kristine Qureshi, PhD, RN, of the School of Nursing and Dental Hygiene, detail the competencies nurses will need to be ready for such efforts. For example, nurses must be competent in adapting infection-control practices to the available resources, able to perform rapid physical and mental health assessments based on triage principles, understand the utilitarian principles that guide ethical practice during disaster responses, possess basic crisis communication skills, and contribute their observations and experiences to post-event evaluations. These competencies establish a common approach to preparedness, and can be used by schools to frame educational programs or by individual nurses to self-assess their education priorities.

- Al-Maaitah R, Conlon L, Hutton A, et al. Core competencies in disaster nursing. Geneva: International Council of Nurses. https://www.icn.ch/sites/default/files/inline-files/ICN_Disaster-Comp-Report_WEB.pdf.

Native Hawaiian Interdisciplinary Health Program Is Decolonizing the Academic Space

The Native Hawaiian Interdisciplinary Health program (NHIH) was created in 2012 to support Native Hawaiians interested in entering professions such as social work and medicine. In a recent paper, Michael C. DeMattos MSW, with the Myron B. Thompson School of Social Work, writes that the NHIH was designed to include Indigenous teaching methods in pre-professional curricula. The planners focused on culturally-resonant programming and validating the Indigenous worldview. The NHIH gives *haumāna* (students) an overview of Native Hawaiian values, provides lessons in cultural historical trauma, and holds sessions in the community rather than only on campus. Participating in the program may encourage non-Indigenous instructors to recognize their position in the colonial system. DeMattos concludes that the NHIH program is helping to reposition traditional Native Hawaiian values at the center of today's educational spaces.

- DeMattos MC. Native Hawaiian Interdisciplinary Health Program: Decolonizing academic space, curriculum, and instruction. *Intersectionalities: A Global Journal of 2019 Social Work Analysis, Research, Polity, and Practice*. 2019;7(1):51-67.

Diet Quality Linked to Nonalcoholic Fatty Liver Disease in the Multiethnic Cohort Study

Nonalcoholic fatty liver disease (NAFLD) is likely caused by a combination of factors, including genetic and environmental factors. To investigate the role of diet quality in NAFLD, researchers led by Song-Yi Park PhD, of the UH Cancer Center, conducted a nested case-control analysis of data from the Multiethnic Cohort study, which includes African-American, Japanese-American, Latino, Native Hawaiian, and white participants. The analysis included 2959 people with NAFLD and 29,292 matched controls; the researchers used 4 diet quality indexes to examine the association. Results showed inverse associations between diet quality and NAFLD risk for 2 of the indexes, which was stronger for NAFLD with cirrhosis than for NAFLD without cirrhosis. The findings suggest having better diet quality may reduce NAFLD risk in this ethnically diverse population.

- Park SY, Noureddin M, Boushey C, Wilkens LR, Setiawan VW. Diet quality association with nonalcoholic fatty liver disease by cirrhosis status: The Multiethnic Cohort. *Current Developments in Nutrition*. 2020;4(3):nzaa024. doi:10.1093/cdn/nzaa024

Editors' Note:

The co-editors of the Hawai'i Journal of Health & Social Welfare extend our warmest wishes to our readers during the COVID-19 pandemic. Our health care brethren around the world and here in Hawai'i are bringing their collective expertise to help quell the pandemic and minimize the loss of human life. In this issue, we are pleased to offer three non-peer reviewed guest columns to help our readers understand some of the key issues of COVID-19. Stay safe and be well. — ***S. Kalani Brady and Tonya Lowery St. John***

COVID-19 Special Column: Principles Behind the Technology for Detecting SARS-CoV-2, the Cause of COVID-19

Lauren Ching BS; Sandra P. Chang PhD; and Vivek R. Nerurkar PhD

Abstract

Nationwide shortages of tests that detect severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and diagnose coronavirus disease 2019 (COVID-19) have led the US Food and Drug Administration (FDA) to significantly relax regulations regarding COVID-19 diagnostic testing. To date the FDA has given emergency use authorization (EUA) to 48 COVID-19 in vitro diagnostic tests and 21 high complexity molecular-based laboratory developed tests, as well as implemented policies that give broad authority to clinical laboratories and commercial manufacturers in the development, distribution, and use of COVID-19 diagnostic tests. Currently, there are 2 types of diagnostic tests available for the detection of SARS-CoV-2: (1) molecular and (2) serological tests. Molecular detection of nucleic acid (RNA or DNA) sequences relating to the suspected pathogen is indicative of an active infection with the suspected pathogen. Serological tests detect antibodies against the suspected pathogen, which are produced by an individual's immune system. A positive serological test result indicates recent exposure to the suspected pathogen but cannot be used to determine if the individual is actively infected with the pathogen or immune to reinfection. In this article, the SARS-CoV-2 diagnostic tests currently approved by the FDA under EUA are reviewed, and other diagnostic tests that researchers are developing to detect SARS-CoV-2 infection are discussed.

Keywords

COVID-19, SARS-CoV-2, RT-PCR, molecular diagnostic testing, serological diagnostic testing

Abbreviations

ACE2 = angiotensin-converting enzyme 2
cDNA = complementary DNA
CDC = Centers for Disease Control and Prevention
CLIA = clinical laboratory improvement amendments
COVID-19 = coronavirus disease 2019
DNA = deoxyribonucleic acid
E = envelope protein
ELISA = enzyme-linked immunosorbent assay
EUA = emergency use authorization
FDA = Food and Drug Administration
IgA = immunoglobulin A
IgG = immunoglobulin G
IgM = immunoglobulin M
LFIA = lateral flow immunoassay
M = membrane protein
MERS-CoV = Middle East respiratory syndrome coronavirus
MIA = microsphere immunoassay
N = nucleocapsid protein
NAT = nucleic acid test
NAAT = nucleic acid amplification test
nsp = non-structural protein
ORF = open reading frame
POC = point-of-care
qRT-PCR = real-time reverse transcription-polymerase chain reaction
RNA = ribonucleic acid
RP = human RNase P protein
S = spike protein
SARS-CoV = severe acute respiratory syndrome coronavirus
SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2
WHO = World Health Organization

Introduction

In late 2019 an outbreak of pneumonia of unknown etiology emerged in Wuhan City, Hubei Province, China, and quickly spread throughout the world.[1] On March 11, 2020, the WHO declared the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causative agent of coronavirus disease 2019 (COVID-19), a global pandemic, as the numbers of cases outside of China began to eclipse those found within the country.[2] Since then, cases of COVID-19 have been reported in more than 200 countries, areas or territories worldwide.[3] Recent reports of the outbreak in China, have demonstrated the important role of mild to asymptomatic SARS-CoV-2 infections in viral transmission, estimating that as many as 86% of infections were undocumented with mild, limited, or no symptoms.[4] Therefore, access to accurate and timely testing and detection of the virus is essential to limiting the spread of SARS-CoV-2.

The Centers for Disease Control and Prevention (CDC) developed the first diagnostic test approved for clinical detection of SARS-CoV-2 and diagnosis of COVID-19 in the United States (US). The CDC COVID-19 diagnostic panel is a real-time

reverse transcription-polymerase chain reaction (qRT-PCR) test. In qRT-PCR, oligonucleotide primers are used to amplify pieces of nucleic acid (ie, RNA or DNA), which can be detected by a fluorescently labeled probe. In the CDC diagnostic test, 2 regions of the SARS-CoV-2 nucleocapsid (N) gene, as well as an internal control, the human RNase P gene (RP), are amplified. Detection of all 3 genes is considered presumptive positive for SARS-CoV-2, in conjunction with a patient's clinical signs/symptoms and/or epidemiological criteria for COVID-19 infection (ie, travel history, close contact with a confirmed COVID-19 case).[5]

Early technical issues with this CDC-developed COVID-19 diagnostic panel, coupled with logistical and technical difficulties in large-scale manufacturing of diagnostic tests for a rapidly emerging COVID-19 disease, has led to widespread shortages of diagnostic tests throughout the US. To address these shortages, the Food and Drug Administration (FDA) has given emergency use authorization (EUA) for 41 molecular diagnostic tests (Table 1 [http://hawaiijournalhealth.org/past_issues/COVID-19_Diagnostics_Table1.xlsx]), 21 high complexity molecular-based laboratory developed tests (Table 2 [http://hawaiijournalhealth.org/past_issues/COVID-19_Diagnostics_Table2.xlsx]), and 7 serological diagnostic tests (Table 3 [http://hawaiijournalhealth.org/past_issues/COVID-19_Diagnostics_Table3.xlsx]) to date.[6] EUA is a mechanism by which the FDA fast tracks diagnostic and therapeutic medical devices to diagnose and respond to public health emergencies such as COVID-19. EUA devices are not FDA licensed, however, an EUA application has been reviewed and approved by the FDA for these devices. These EUA in vitro diagnostic tests include molecular diagnostics (that detect viral RNA sequences) and serological tests (that detect antibodies [ie, IgA, IgG, IgM] directed towards viral antigens). Furthermore, on March 16, 2020, the FDA released a COVID-19 diagnostic guidance document that enacted several unprecedented policy changes for diagnostic procedures during a public health emergency.[7] Briefly, the FDA enacted 4 new policies regarding COVID-19 diagnosis that: (A) Allow clinical laboratory improvement amendments (CLIA) certified laboratories capable of high-complexity testing to use internally validated tests prior to EUA submission; (B) expand state authority over requirements for high-complexity testing; (C) allow commercial manufacturers to develop and distribute tests prior to EUA submission; and (D) allow commercial manufacturers to develop and distribute serology tests without an EUA. These policies gave sweeping authority to CLIA-certified laboratories and commercial manufacturers to use COVID-19 diagnostic tests in a clinical setting without FDA review.

Basic Virology of SARS-CoV-2

SARS-CoV-2 belongs to the *Coronaviridae*, a family of large, enveloped, positive-sense, single-stranded RNA viruses known to infect a wide variety of animals. Prior to 2003, these viruses were thought to cause only mild, common cold-like disease in humans. SARS-CoV-2 is the seventh coronavirus known to infect humans, including the 4 common cold coronaviruses (229E, OC43, NL63, and HKU1) and 2 other strains, known to cause severe pneumonia associated respiratory disease that can become fatal: severe acute respiratory syndrome coronavirus (SARS-CoV), which emerged in 2003, and Middle East respiratory syndrome coronavirus (MERS-CoV), which emerged in 2012.[8] SARS-CoV-2 is also known to cause a severe pneumonia associated respiratory disease, which can become fatal in humans. SARS-CoV, MERS-CoV, and SARS-CoV-2 all have zoonotic origins, emerging in human populations from spillover events, which occur when a pathogen-carrying animal reservoir comes into contact with a novel host population, in this case humans. Genomic sequencing has demonstrated that SARS-CoV-2 is closely related to 2 bat-derived SARS-like *Betacoronaviruses*.[9]

SARS-CoV-2 Genome

The genome of SARS-CoV-2 is approximately 30-kb in length and consists of 6 open reading frames (ORFs), which includes ORF1a/b, spanning 16 non-structural proteins (nsp) relating to the replication-transcription complex, 4 structural proteins, spike (S), envelope (E), membrane (M), and nucleocapsid (N), along with several other non-structural, special structural, and/or accessory ORFs (ORF3a/b, 6, 7a, 7b, 8, and 10).[9-11] Genome sequencing alignment among different coronaviruses reveals more conservation among the non-structural proteins (58% identity) as compared to structural proteins (48% identity).[12] The diversity in structural proteins has allowed coronaviruses to adapt to new hosts. Therefore, sensitive and specific diagnostic techniques should target both structural and non-structural proteins. Multiple sequence alignment and phylogenetic analysis of SARS-CoV-2 among 95 strains of the virus isolated from COVID-19 patients around the world have revealed high sequence homology at both the nucleotide level (99.99%; range 99.91-100%) and the amino acid level (99.99%; range 99.99-100%).[10, 13] This indicates a low mutation rate for SARS-CoV-2.

SARS-CoV-2 Diagnostic Targets

Most diagnostic tests target a combination of structural (S, N, and/ or E) and non-structural (ORF1ab region) SARS-CoV-2 genes, along with positive and negative controls. This testing strategy ensures that the diagnostic targets include a non-structural protein, highly conserved across coronaviruses, as well as structural protein(s), highly specific for SARS-CoV-2.

S protein. Much of the literature has focused on understanding the mechanisms by which the clubbed-shaped SARS-CoV-2 S protein allows the virus to enter host cells. The S protein of SARS-CoV-2 binds to the host cells and enters the cell using the angiotensin-converting enzyme 2 (ACE2) cell receptor.[9, 14] SARS-CoV S protein also utilizes the ACE2 cell receptor to enter host cells; however, genetic analysis has demonstrated

that the 2 viruses bind to the receptor at different amino acid residues. Further, SARS-CoV-2 binding is stronger than that of SARS-CoV, suggesting that this new virus is more successful at viral entry, providing a mechanism to explain the explosive spread of SARS-CoV-2 as compared to SARS-CoV.[15] Wrapp and colleagues reported that the SARS-CoV-2 spike protein's binding affinity to ACE2 is 10-20 times higher than that of the SARS-CoV spike protein, suggesting efficient person-to-person transmission.[16] Among the structural proteins, the highest sequence diversity between SARS-CoV and SARS-CoV-2 occurs in the S protein (24%).[10,13] Therefore, use of the spike protein as part of SARS-CoV-2 diagnostic testing will provide high specificity.

N protein. The N gene encodes a ribonucleoprotein that contains the viral genome.[8] There is little sequence diversity in the N gene between SARS-CoV and SARS-CoV-2 (9.6%).[13] Further, the mechanism by which coronaviruses replicate and transcribe their genomes results in a set of nested RNAs.[11,17] As the N gene sits at the end of the coronavirus genome, this nested strategy makes the N gene the most abundant nucleotide sequence during virus replication, and therefore an excellent diagnostic target.[18] Furthermore, because SARS-CoV is currently rare in human populations, this conserved region remains a useful target for SARS-CoV-2 detection.

E protein. The E gene encodes a small polyprotein found in low amounts in all coronavirus envelopes.[8] There is little sequence diversity in the E gene between SARS-CoV and SARS-CoV-2 (5.3%).[13] A recent report by Corman and colleagues has demonstrated high specificity for the E gene in COVID-19 diagnostic testing.[19] During viral replication the E gene is present in such low abundance that replication of these sequences has high positive predictive value for infection with SARS-CoV-2.

ORF1ab segment. ORF1ab comprises two-thirds of the SARS-CoV-2 genome, encoding 16 nsp relating to the replication-transcription complex responsible for all the machinery associated with viral replication, such as the RNA-dependent RNA polymerase (nsp12; RdRp), and a 3'-5' exoribonuclease (nsp14; ExoN).[8] ExoN is a unique feature of the replication-transcription complex of all coronaviruses, conferring a unique proofreading mechanism across the virus family and resulting in a low mutation rate among coronaviruses. The essential role of the replication-transcription complex, in particular RdRp, in viral replication, makes targeting regions of ORF1ab desirable for diagnostic tests.[11]

Strategy for Testing SARS-CoV-2 Infection

Symptomatic Infection

The primary symptoms of COVID-19 include fever, cough, and shortness of breath.[20,21] There is growing evidence of gastrointestinal symptoms (ie, abdominal pain, diarrhea, nausea, vomiting), as well as altered sense of smell and taste from US and international case reports.[22] With severe diagnostic testing shortages, the CDC has developed guidance for clinicians on testing people suspected to have COVID-19. This guidance ranks different groups in decreasing level of testing priority: (1) hospitalized patients and healthcare facility workers with symptoms; (2) high risk individuals (ie, individuals in long-term care facilities, >65 years, with underlying conditions) and first responders with symptoms; (3) critical infrastructure workers and any other individuals with symptoms, healthcare facility workers and first responders without symptoms, and individuals with mild symptoms in communities experiencing high numbers of COVID-19 hospitalizations.[23]

Asymptomatic Infection

Person-to-person spread via respiratory droplets is thought to be the primary route of transmission for SARS-CoV-2. Direct transmission via fomites, the fecal-oral route, and aerosol particles have been speculated as other important routes of transmission.[24] The role of asymptomatic and even pre-symptomatic individuals has slowly emerged as important sources of transmission in the ongoing pandemic.[4] Asymptomatic refers to individuals who become infected and shed infectious particles without developing symptoms, while pre-symptomatic refers to the shedding of infectious particles prior to symptom onset. Virus transmission by these populations can be very successful, as these individuals do not know that they are carrying the virus, and consequently may not be taking any of the recommended precautions (social distancing, hand-washing, etc.). Due to diagnostic shortages, the CDC considers potentially exposed individuals with no symptoms of COVID-19 to be a low priority for testing.

COVID-19 Situation in Hawai'i

The first confirmed case of COVID-19 in the US was reported on January 20, 2020 in a 35-year old male in Snohomish County, Washington, who had history of travel to Wuhan, China.[21] The first confirmed case of COVID-19 in a resident of Hawai'i was reported on March 6, 2020, in a person who had returned home from a cruise.[25] As of April 25, 2020, there have been 604 confirmed cases of COVID-19 in the state of Hawai'i, of which 11% (n=68) have required hospitalization. Fourteen people have died of the infection (2.3% case fatality rate [CFR]). Confirmed COVID-19 cases have been reported in all 4 Hawai'i counties, however Honolulu County accounts for 65% (n=395) of the state's cases.[26] More than 80% of the cases have been associated with travel or travel-associated contact.[26] Similar to the nationwide response, the state of Hawai'i has been under a stay-at-home, work-at-home order since March 25, 2020, with exemptions for essential workers.[27] Further, 14-day self-quarantine for all visitors and residents returning to Hawai'i was implemented on March 26, 2020,[28] and was extended to include interisland travelers on April 1, 2020.[29] All

these restrictions are been accompanied with fines and possible imprisonment for individuals who do not follow these quarantine requirements and/or social distancing measures.

Diagnostic testing for COVID-19 is being conducted by the Hawai'i State Laboratories Division, commercial laboratories (ie, Clinical Labs of Hawaii, Diagnostic Laboratory Services), as well as hospital laboratories (ie, Kaiser Permanente). The majority of the tests are sent to commercial laboratories on the US mainland, resulting in extended delays for individuals waiting for the results of their COVID-19 testing.[30] As of April 25, 2020, there have been 27,572 tests performed by commercial clinical and state laboratories for the state of Hawai'i, with a 2.2% rate of COVID-19 positivity.[31] The state has adopted CDC's COVID-19 testing guidance to determine testing priorities, expanding these priorities to include asymptomatic close-contacts of confirmed COVID-19 cases.

Molecular Diagnostic Tests

Sample Collection and Preparation for Molecular Testing of COVID-19 and RNA Extraction

Typically, specimens for detecting SARS-CoV-2 are collected from upper or lower respiratory tracts of individuals with clinical signs/symptoms and/or who fulfill the epidemiological criteria for COVID-19. Upper respiratory tract specimens include nasopharyngeal, oropharyngeal swabs, and nasal wash/aspirates. Collection of such specimens is quick and easy, without requirement of specialized skills and/or equipment. Lower respiratory tract specimens include sputum, tracheal aspirates, and bronchoalveolar lavage fluid. These specimens require much more invasive techniques and are typically collected from hospitalized patients. In patients with active SARS-CoV-2 infections, these specimens contain cells with SARS-CoV-2 viral RNA. Samples can be stored at 2-8ºC for 72 hours, or -70ºC or below if delays in testing are anticipated. Following specimen collection, the cells are lysed and total RNA is isolated from the cells. Total RNA can be isolated through a variety of techniques, such as using a spin column or magnetic beads. The procedures include RNA binding steps and sample washing to remove all other cellular products (ie, DNA, proteins, organelles).[23]

Tests and Their Principles Employed for Detection of COVID-19

A nucleic acid test (NAT) is used in infectious disease diagnostic testing to directly detect nucleic acid (RNA or DNA) sequences of the suspected pathogen. From patient specimens, total nucleic acid is extracted, including nucleic acid from the host; therefore, the amount of genetic material of the suspected pathogen in the sample can be very low, making direct detection of the pathogen's nucleic acids difficult. As a result, the genetic material of interest must be amplified by creating millions of copies of sequences specific to the pathogen of interest, for easier detection. This is why this is called a nucleic acid amplification test (NAAT). For most current diagnostic tests available for COVID-19, amplification of RNA specific for the SARS-CoV-2 virus is accomplished using qRT-PCR.

Real-time reverse transcription polymerase chain reaction (qRT-PCR). Most of the COVID-19 diagnostics with FDA EUA use the technique of qRT-PCR, in which a specific sequence(s) of the SARS-CoV-2 genome is amplified and detected with fluorescently labeled probe(s), quantifying patient's viral copy number in real-time. Detection by qRT-PCR is the most sensitive and specific diagnostic tool currently available.

By this technique, following RNA isolation from the specimen, the unstable single-stranded RNA must be stabilized into double stranded molecules by adding complementary DNA (cDNA) by reverse transcription. The isolated RNA with cDNA can then be amplified using oligonucleotide primers and fluorescently labeled probe(s) specific to region(s) of the SARS-CoV-2 genome by PCR. At this time, 39 qRT-PCR diagnostic assays have been given FDA EUA, of which 6 are only approved for use in specific commercial CLIA laboratories (Wadsworth Center, New York State Department of Health (New York, NY); Laboratory Corporation of America (Burlington, NC); Quest Diagnostics Infectious Disease, Inc. (San Juan Capistrano, CA); Avellino Lab USA, Inc. (Menlo Park, CA); Ipsum Diagnostics, LLC (Atlanta, GA); and KorvaLabs, Inc. (Menlo Park, CA)) (Table 1). Further, the FDA has given EUA to an additional 18 high complexity molecular-based laboratory developed tests that are approved for use only in the clinical laboratory for which the tests were developed (Table 2).

These diagnostic tests are either (1) manual, which can take a trained laboratory technician several hours from sample processing to results; (2) partially automated, which utilizes specialized equipment to reduce hands-on time; or (3) fully automated, walk-away techniques, which require only minutes of hands on-time for sample loading, single-use cartridges for each patient specimen to be tested, and expensive, highly specialized equipment to perform all of the assays. Further, depending on the technology employed, these assays have estimated testing times from 50 minutes to 4 hours for the semi-automated to fully automated/walk-away assays, and 6-14 hours for the manually performed assays.

Point-of-Care (POC) PCR-based Lateral Flow assay and Isothermal NAAT. Currently there are 2 true POC molecular diagnostic tests available (Table 1). These tests can produce results in minutes, and therefore, can be done during a typical office visit for patients who have clinical symptoms and epidemiological risk factors for COVID-19. First, the Mesa Biotech Inc., Accula™ SARS-CoV-2 test (Mesa BioTech, Inc.; San Diego, CA) uses PCR to amplify a portion of the N gene, and

lateral flow along a test strip for detection of this amplicon. These reactions occur entirely within the Accula™ Dock or Silaris™ Dock and the estimated testing time, from sample collection to results, is 30 minutes. The test cassette contains a sample pad, where patient sample is added and PCR occurs, a conjugate pad with nucleic acids labeled with a chromatographic probe, which sits on a nitrocellulose membrane with lines coated with capture sequences that are complementary to the viral target and control sequences, followed by an absorbent pad. Lateral flow assays work by capillary action across the nitrocellulose membrane. Second, the Abbott Diagnostics Scarborough, Inc. ID NOW COVID-19 (Abbott Diagnostics Scarborough, Inc.; Scarborough, ME) assay is an isothermal NAAT to amplify a portion of the RdRp gene and uses fluorescently-labeled molecular beacons to identify these RNA targets. All reactions occur within the Abbott ID NOW™ instrument and the estimated testing time is 5-13 minutes.

These POC molecular diagnostic tests are very easy to perform, require little specialized training for the clinician, and produce rapid results to guide clinician care. However, these tests can only be performed on specific instruments and amplify a single genomic target of SARS-CoV-2, reducing their sensitivity and specificity as compared to traditional qRT-PCR based molecular diagnostics. Therefore, under conventional circumstances, the results of these POC must be validated using molecular diagnostic testing. However, in light of the severe shortages of tests for SARS-CoV-2, these POC molecular diagnostics are typically not validated by qRT-PCR testing.

Serological Tests

Sample Preparation for COVID-19 Serological Testing

The typical specimens used for serological testing of COVID-19 include serum, plasma, or whole blood. Serum and plasma are both the liquid, cell-free portions of whole blood. Serum is collected following coagulation of whole blood and does not contain clotting factors. Plasma is collected by centrifugation from whole blood that has been treated with anticoagulants and contains all the clotting factors of the blood, which is thought to make it less stable for long-term storage. Antibodies are proteins that can be found in all 3 specimens.

IgM, IgG, IgA in SARS-CoV-2

Antibody responses arise about a week following infection, with the multimeric IgM, as the first antibody arising, often concurrent with active infections. IgM, therefore, is often used as an indicator of newly acquired infection. IgM antibody responses are typically short lived, and wane as the infection is no longer active. IgG antibodies appear towards the end of the active infection and can persist for months to years following infection. IgA is associated with mucosal immunity and considered to be an important player in respiratory infections.

Scientists are still learning about the natural history of COVID-19; however, preliminary serological reports suggest that the SARS-CoV-2 antibody response follows this typical pattern, with a majority of patients seroconverting within 2-week following symptom onset and all patients seroconverting by one month after symptom onset.[32-34] In these reports, IgM and IgA are the first antibody isotypes detected 1-week following symptom onset, followed by IgG, which typically arise 2-weeks following symptom onset, as the patient's symptoms resolve.[32,34] Further, To and colleagues report a strong correlation ($R^2 > 0.9$) between anti-SARS-CoV-2-NP and anti-SARS-CoV-2-RBD IgG and neutralizing antibody titers, which are indicative of an individual's immunity to SARS-CoV-2.[33]

Tests and Their Principles Employed for Serological Detection of SARS-CoV-2

Serological testing involves detection of antibodies, typically IgM and IgG, against specific proteins of the pathogen, called antigens. In an individual suspected for COVID-19, the presence of antibodies for SARS-CoV-2 indicates history of exposure to the virus and does not indicate or rule out active infection or predict immunity to reinfection. Serological testing for detection of SARS-CoV-2 is appealing to clinicians because results can be obtained quickly and the presence of SARS-CoV-2 antibodies in convalescing patients indicates that the individual was able to mount an immune response to the virus, suggestive of some level of immunity against the virus. Therefore, seropositivity in an individual who has recovered from COVID-19, may make that individual a potential donor of convalescent serum/plasma for the treatment of other patients with active COVID-19 infections.[35] Seven clinical trials have been initiated or are being planned to evaluate the efficacy of passive immunoglobulin therapy for severe COVID-19 (NCT04261426 [China];[36] NCT04264858 [China];[37] NCT04332380 [Colombia];[38] NCT04332835 [Colombia];[39] NCT04323800 [US, Johns Hopkins];[40] NCT04325672 [US, Mayo Clinic];[41] NCT04333251 [US, Baylor]).[42] These studies will also provide insight into the use of serology to assess immunity to SARS-CoV-2 infection.

Currently, testing for active SARS-CoV-2 infection is the priority for diagnostic testing to identify and isolate patients, both at a national and local level. However, public health officials and researchers alike plan to conduct future seroprevalence studies, to determine the true prevalence of SARS-CoV-2 infection in populations.

Lateral Flow Immunoassay (LFIA). A simple POC serological diagnostic assay with results in minutes is the LFIA. Similar to the PCR lateral flow assay described above, a LFIA comprises of a test strip containing a sample pad, a conjugate pad containing viral antigen conjugated to a chromatographic tag (ie, colloidal gold, latex, fluorophore), which sits on nitrocellulose membrane with lines coated with capture antibodies against human antibody isotypes (ie, IgG, IgM, IgA), a control line, and

an absorbent pad. If a patient has had a past viral infection, their antibodies will bind to tagged viral antigen, and these antibody-tagged antigen complexes will bind to immobilized capture antibodies, which can be visualized as a line by the conjugated chromatographic tag. There are 3 LFIA with FDA EUA that can identify an individual seropositive for SARS-CoV-2 IgG and IgM antibodies in 15-20 minutes; the qSARS-CoV-2 IgG/IgM Rapid Test (Cellex, Inc.; Research Triangle Park, NC); the DPP COVID-19 IgM/IgG System (Chembio Diagnostic System, Inc.; Medford, NY); and the Anti-SARS-CoV-2 Rapid Test (Autobio Diagnostics Co. Ltd.; Santa Maria, CA) (Table 3).

Enzyme-Linked Immunosorbent Assay (ELISA). ELISA is the most common serological test used to detect the presence of antibodies specific to an antigen of interest in a patient serum. In an ELISA, viral antigens are immobilized on a surface, and then a patient's blood or serum is added, allowing for any antibodies specific for the viral antigens to bind, while all other antibodies are washed away. Then an enzyme-conjugated secondary antibody, specific for the antibody isotype being targeted (ie, IgM, IgG, or IgA) is added, followed by the enzyme substrate, resulting in production of a colored product when viral antigen-antibody complex is detected. There are 4 ELISA with FDA EUA; the VITROS Immunodiagnostic Products Anti-SARS-CoV-2 Total and IgG Reagent Packs (Ortho Clinical Diagnostics, Inc.; Rochester, NY); the COVID-19 ELISA IgG Antibody Test (Mount Sinai Laboratory (MSL); New York, NY), only approved for use at the MSL; and the LIAISON SARS CoV-2 S1/S2 IgG (DiaSorin, Inc.; Stillwater MN).

Microsphere Immunoassay (MIA). The MIA is a variant of an ELISA which couples viral antigens to magnetic carboxylated microspheres and fluorescently labeled secondary antibodies to detect serum antibodies in antigen-antibody complexes. The microspheres are impregnated with dye that makes each microsphere a spectrally-distinct set or region, making this a unique technology that allows for multiplexing of several antigens, each coupled to spectrally distinct microspheres, within a single reaction. The different antigens may correspond to different proteins of the same virus or of different pathogens, allowing for differential diagnosis among a panel of pathogens that may present with similar clinical symptoms and/or co-circulate in the same geographic region.

Serological analysis by ELISA and MIA are much more sensitive and specific diagnostic tools as compared to lateral flow chromatographic immunoassays, however, the testing time required is at least 5 hours for ELISA, and 3-8 hours for MIA. The MIA is a newer technology that requires more costly reagents and highly expensive equipment to perform as compared to an ELISA.

In addition to these 7 serological tests which have received FDA EUA, there are numerous commercial manufacturers and high complexity CLIA laboratories that are working on or have developed their own LFIA, ELISA, and MIA based serological tests for the detection of SARS-CoV-2 antibodies.[43] While none have received FDA EUA, internally validated tests may be used for clinical diagnostics under Section D of the FDA's March 16, 2020 expanded COVID-19 diagnostic guidelines.[7] Many of these tests are likely to receive FDA EUA in the next weeks to months as transmission in the US subsides and the need emerges for public health programs and researchers to conduct community-wide serological screening studies of SARS-CoV-2 asymptomatic and symptomatic infection.

Conclusion

As of April 25, 2020, the FDA has granted EUA for 48 COVID-19 in vitro diagnostic tests and 21 high complexity molecular based laboratory developed tests.[6] Most of these tests work on the principle of identifying specific regions of the SARS-CoV-2 genome, primarily the ORF1ab, RdRp, S, E, and N genes. Clinical understanding of SARS-CoV-2 and COVID-19 is evolving day-by-day; however, from what is known now, it is important to include gene targets highly conserved across all coronaviruses, such as non-structural proteins, as well as gene targets with some diversity between the different coronaviruses, such as the structural proteins, to ensure high levels of sensitivity and specificity. Patients with positive results from these tests, along with clinical signs/symptoms and/or epidemiological factors consistent with COVID-19 can be considered as presumptive positive cases of active SARS-CoV-2 infection. Four serological tests, identifying SARS-CoV-2 specific IgG/IgM antibodies have been granted FDA EUA. Positive results of these serological tests indicate recent infection with SARS-CoV-2, and these results, along with ongoing research into the natural history of COVID-19, could be useful in determining the susceptibility of an individual to future SARS-CoV-2 infection.

Aside from these diagnostic tests with FDA EUA, in order to address national diagnostic shortages, the FDA enacted a new policy on March 16, 2020 regarding guidance for COVID-19 diagnosis during the public health emergency.[7] This policy has allowed high complexity CLIA laboratories and commercial manufacturers to use diagnostic kits developed internally with proper validations in place for clinical testing prior to FDA review of EUA applications. Patients must be informed that although these diagnostic tests have been internally validated, independent review by the FDA is pending. Further, this new policy has also allowed for expanded use of SARS-CoV-2 serological testing without EUA. Here also, patients must be informed that the FDA has not reviewed the test.

Conflicts of Interest

The authors report no conflicts of interest.

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COVID-19 Special Column: COVID-19 Hits Native Hawaiian and Pacific Islander Communities the Hardest

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The United Nations warned that the coronavirus disease 2019 (COVID-19) pandemic would disproportionately impact Indigenous peoples across the world because of underlying health inequities and social determinants of health (eg, crowded living conditions and poor access to healthcare) that place them at a greater risk for infection and severe symptoms if infected.[1] In the United States (US), public health officials also expected this novel virus to infect Indigenous communities, such as American Indians and Alaska Natives, at a higher rate.[2] The rates of COVID-19 positive cases among members of the Navajo Nation, the largest American Indian tribe in the US, are among the highest of any group with 1716 cases in their population of about 300 000.[3] This raises the question, what about Native Hawaiians and Pacific Islanders (NHPI)?

It is important to know that NHPI hold on to bitter memories of how infectious diseases decimated our thriving populations throughout our history. The Native Hawaiian population declined from roughly 700 000 in 1778 to barely 40 000 by 1900 due to infectious diseases such as smallpox, whooping cough, dysentery, tuberculosis, influenza, and measles.[4,5] The recent measles outbreak in Sāmoa and elsewhere in the Pacific is a harsh reminder to NHPI communities of our vulnerability to infectious diseases as close-knit island communities.[6] This vulnerability has taken hold of the NHPI diaspora with the arrival of COVID-19.

The COVID-19 Cases and Data Concerns for NHPI Communities

Several US states with large numbers of NHPI residents report higher rates of COVID-19 positive cases among the Indigenous peoples of the Pacific than in other racial and ethnic groups.

Table 1. Confirmed COVID-19 Cases Per 100 000 by Race/Ethnicity in 5 Western States

Race/Ethnicity	Native Hawaiian/ Pacific Islander	Statewide
California	217.7	62.43
Hawai'i	44	40
Oregon	154	55
Utah	197.6	142.2
King Country, Washington	189.5	182.1

Note. Because Hawai'i only reported percentages of total COVID-19 cases by ethnicity, Hawai'i data was recalculated here using the 2010 census data as the denominator.

Table 1 shows the number of COVID-cases per 100 000 for NHPI compared to statewide rates within five states. California data show NHPI have the highest rate of all racial and ethnic groups, with 217.7 cases per 100000 NHPI, while the statewide overall rate is 62.43 per 100 000.[7] Data from King County, Washington also indicate NHPI as having the highest rate, at 189.5 cases per 100 000, and Asians as having the lowest rate, at 68.8 cases per 100 000.[8] Oregon too shows that COVID-19 cases are higher among NHPI, at 154 cases per 100 000 while the statewide rate is 55 cases per 100 000 residents. In Utah, the COVID-19 positive cases among NHPI are 197.6 per 100 000, compared to 142.2 cases per 100 000 for the entire state. In Salt Lake County, Utah, the rate for NHPI is 287.8 per 100 000.[9] The rates of COVID-19 positive cases among NHPI within these states are greater than those reported for African Americans and American Indians, two racial/ethnic groups receiving much national attention regarding COVID-19 risk.[10,11]

In Hawai'i, non-Hispanic whites and NHPI have higher rates than other racial and ethnic groups.[12] The rate of cases among NHPI is 44 per 100 000 in Hawai'i as of this writing, but this is likely a gross underestimate because of the state's narrow definition of NHPI.[12] In the state's calculations, NHPI who reported more than one race or ethnicity, such as NH and Japanese, were not included in the NHPI count. The United States Office of Management and Budget (OMB) classifies NHPI as "a person having origins in any of the original peoples of Hawai'i, Guam, Samoa, or other Pacific Islands,"[15] which would include NHPI who also have multiple racial/ethnic ancestries. There are also missing racial/ethnic data from 60 people who tested positive for COVID-19.

In a public health crisis like this, reliable and timely data are vital to protecting the health of our citizens. The public health data reviewed above highlight the need for timely, accurate, and meaningful data collection, analysis, and dissemination, which have been longstanding issues for NHPI communities.[13,14] NHPI communities have been calling for better data collection methods and analytical practices (eg, the disaggregation of data from NHPI and Asian populations) to ensure they are counted, and counted fairly and accurately in these public health reports and data surveillance systems. These issues predate the COVID-19 crisis.[15] This is an important topic because these data are used to allocate and prioritize the distribution of resources in times of emergency and to inform public health policies aimed at reducing health inequities.

The Health Inequities Underlying the COVID-19 Inequities

As defined by the World Health Organization (WHO), health inequities are differences in health status or the distribution of health determinants between population groups, and they are avoidable and unjust.[16] The higher risk of infection among NHPI is linked to preexisting and underlying inequities in the social determinants of health across racial and ethnic groups that are ubiquitous in the US.[17] The risk for severe symptoms and death due to COVID-19, if contracted, is strongly linked to preexisting and underlying inequities in chronic medical conditions, such as diabetes, asthma, and cardiovascular disease (CVD).

According to the Centers for Disease Control and Prevention (CDC), people with underlying chronic medical conditions, such as obesity, diabetes, asthma, kidney disease, cancer, and CVD, are highly vulnerable to severe symptoms and death due to COVID-19 if they become infected.[18] NHPI have among the highest rates of these chronic medical conditions, and associated mortality rates in Hawai‘i as well as the US,[19-21] and the rates of these conditions in the Pacific nations and territories are among the highest in the world.[22-24] NHPI acquire many of these chronic diseases at younger ages than other ethnic groups,[25] and many NHPI elders live with multiple chronic diseases.[19,26] People with respiratory conditions such as asthma, which is found at a high rate among NHPI, are most susceptible to COVID-19 because it is a respiratory illness.[27] Chronic medical conditions have long been linked to inequities in social determinants of health.[28] The shelter in place order, although necessary to stop the spread of COVID-19, may present a challenge to people managing their chronic medical conditions by increasing sedentary behavior and reliance on calorie-dense processed foods with low nutritional value. With COVID-19 already burdening the health care systems, the need to continue to monitor existing chronic conditions and maintain positive health initiatives is critical.

People who use tobacco and e-cigarette products are also highly vulnerable to experiencing severe symptoms and death due to COVID-19.[29] Smoking and vaping thicken the air sacs and cause inflammation of the lungs, which make a person highly susceptible to severe symptoms should they contract COVID-19. NHPI, especially adolescents and young adults, have the highest rates of smoking and vaping compared to other racial and ethnic groups.[30,31] The psychological stress caused by the shelter in place and social distancing orders are likely to increase the frequency and intensity of these behaviors among those who smoke and vape.

Access to quality health care services is also a concern for NHPI who often have poor or no medical insurance coverage. About 20% of NHPI are uninsured compared to 11.4% of non-Hispanic whites.[32] Even more are on public health insurance programs (ie, Medicaid and Medicare). These types of medical benefits can affect access to and the timeliness of receiving health care services as well as the quality and range of those services.[33] In addition, NHPI often face discrimination in clinical settings and already have a mistrust or hesitancy in seeking health care services.[34] These are all factors that could delay diagnosis and treatment and thereby increase the risk of spreading COVID-19 to others and having severe symptoms should it be contracted. Data from Utah show NHPI and American Indians/Alaska Natives as having the most hospitalizations due to COVID-19 of all ethnic groups, with rates of 141 and 210.5 per 1000 cases, respectively, compared to 83.3 hospitalizations per 1000 cases statewide.

The Economic Conditions of NHPI and COVID-19 Risk

Aside from the health care issues, other inequities in the social determinants of health are affecting the COVID-19 disparities. For example, 24% of the Native Hawaiian population is comprised of essential workers, with heavy representation in the military, security, service, and healthcare industry, and these individuals are at increased risk of contracting COVID-19 due to greater face-to-face interactions with patrons and co-workers. NHPI essential workers are being asked to put their health and the health of their families at risk in order to serve the larger community. Many of these jobs, especially the service-related ones, often do not provide a livable wage. NHPI are more likely than many other ethnic groups to have fewer financial resources and live in larger multi-generational households and densely populated neighborhoods.[35-37] Living in denser households and neighborhoods increases the risk of exposure to more individuals possibly carrying the COVID-19 virus. Coupled with the higher likelihood of working in essential businesses, this further increases the risk of exposure for many NHPI.

NHPI are disproportionately represented in the incarcerated and homeless populations who are very vulnerable to contracting COVID-19. Native Hawaiians alone comprise 43% of the prison population Hawai‘i and, 39% of the homeless population on O‘ahu.[38] It is difficult to practice social distancing in prison or while living on the streets, and the conditions in these environments are unsanitary. In Hawai‘i and across the US, some prisoners have already been released as part of COVID-19 induced interventions to reduce prison overcrowding. At the time of publication, 716 inmates have been released from prisons in Hawai‘i.[39]

The Emerging Behavioral Health Impact of COVID-19

Although an issue not directly linked to the medical side of the COVID-19 crisis, the shelter at home and social distancing measures are placing a heavy emotional toll on NHPI communities. In particular are the psychosocial and financial stressors caused by the COVID-19 crisis leading to elevated levels of interpersonal violence and substance abuse in our NHPI com-

munities – behavioral problems that are often interrelated.[40] Before COVID-19, the prevalence of interpersonal violence and substance abuse were already high in many NHPI communities[41] so any increases will surely have detrimental and long-term repercussions, making recovery efforts more challenging.

The Resilience and Cultural Assets of NHPI Communities

Despite the higher COVID-19 risk among NHPI, it is important to remember and recognize the resiliency and fortitude of NHPI communities and their cultural assets that can be leveraged to reduce the adverse impact of COVID-19. Despite 2 centuries of colonization, occupation, and exploitation by Western powers,[42,43] NHPI communities continue to flourish while maintaining their unique cultural values, perspectives, practices, and aspirations. The values and practices of *aloha* (compassion), *mālama* (caring), and *lōkahi* (unity), although said differently across the different NHPI languages, provide the guiding principles to overcome any challenge.

NHPI hold Indigenous wisdom and perspectives to overcome adversity and thrive. In Hawai‘i, many individuals from the NHPI community have hosted virtual concerts and jam sessions to help people through the stressors caused by the shelter in place order. Others have started webinar series, such as the *Lei ʻĀnuenue* and *He Huewai Ola* series, to connect and support people and communities. NHPI communities were among the first to start programs to ensure the elderly in our communities were fed and looked after. In the Western region of the continental US, the Pacific Islander community has banned together to form a National Pacific Islander COVID-19 Response Team – something that has yet to happen for Hawai‘i and the larger Pacific.

Initial Recommendations and Thoughts for the COVID-19 Response and Recovery Efforts

To lessen the impact of the COVID-19 crisis on NHPI communities, immediate and longer-term plans for response and recovery efforts should be aimed at and informed by NHPI communities. The longer-term recovery plans must include public policy changes to earnestly and effectively address racial and ethnic inequities in the social determinants of health and in the US healthcare system to eliminate the structural racism pervasive in our society. These are preexisting and longstanding weaknesses in our society exacerbated and exposed by the COVID-19 crisis. This longer-term recovery plan will need to address employment, education, the racial wealth gap, food insecurity, housing, healthcare, criminal justice, and legal issues, and be in effect not just during states of emergency.

The immediate concern is the need for an emergency response plan to reduce the risk among NHPI communities across Hawai‘i and the continental US. This plan needs to be informed by and developed through engagement with NHPI stakeholders, and should include strategies to address NHPI needs and vulnerabilities during this COVID-19 crisis and any subsequent resurgence. There needs to be reliable and meaningful data collection and analyses and quick dissemination of data to inform decision-making and response efforts as well as to monitor the morbidity and mortality rates. The plan needs to be sensitive to the diversity and unique needs of specific NHPI communities at the county, state, and federal levels, and all levels of government will need to work synergistically. Although aggregated by the federal government as a single racial and ethnic group,[15] NHPI are culturally, linguistically, socioeconomically, and geographically diverse, and this will need to be taken into account. The emergency response plan needs to ensure that essential workers are protected (eg, provided with personal protective equipment), given free SARS-CoV-2 testing, and paid sick leave. Hazard pay or increased wages for essential workers should be considered. Other facets of this plan should deal with the need for quarantine facilities for people who cannot self-quarantine at home because of crowded households, and identify resources in the community should healthcare facilities exceed their capacity to protect NHPI. Of course, many of the aforementioned planning activities are taking place, but they do not currently account for the disparities in risk across subpopulations, except for the homeless and incarcerated.[44]

Also important at this time is the ability of NHPI communities' to engage in their cultural practices while abiding by shelter in place and social distancing orders. Some hula schools and other cultural-based programs, such as those promoted by Kanaeokana (a network of Hawaiian language, culture, and ʻāina-based organizations), have used social media and other online platforms to engage their members and communities during this crisis. Despite this flexibility in the modes of cultural practices, NHPI are culturally impacted by this crisis because of their strong connection to *ʻāina* (land) and the natural elements.

On county, state, regional, and national levels, government and public health officials trusted with the welfare of citizens need to ensure that there are response and recovery plans for NHPI who are disproportionately burdened by COVID-19. Many ethical and social justice issues are being brought to the forefront because of this crisis. A huge ethical issue all hospitals are dealing with is who should have access to medical resources and lifesaving measures if their capacity is pushed beyond its limit (eg, no ventilators for patients over the age of 80).[45] This has resulted in shock from many in the community, upset that their parent or grandparent may not have equal access to medical resources based on age and nothing else. These ethical questions reach across racial and ethnic groups and socioeconomic status and should elevate the discussion of inequities due to structural racism and implicit biases. The COVID-19 crisis has brought these issues to the surface, and stakeholders need to engage in these critical conversations now.

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COVID-19 Special Column: The Crisis of Non-Communicable Diseases in the Pacific and the Coronavirus Disease 2019 Pandemic

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Abstract

Globally, coronavirus disease 2019 (COVID-19) is threatening human health and changing the way people live. With the increasing evidence showing comorbidities of COVID-19 and non-communicable diseases (NCDs), the Pacific region, where approximately 75% of deaths are due to NCDs, is significantly vulnerable during this crisis unless urgent action is taken. Whilst enforcing the critical mitigation measures of the COVID-19 pandemic in the Pacific, it is also paramount to incorporate and strengthen NCD prevention and control measures to safeguard people with NCDs and the general population; keep people healthy and minimise the impact of COVID-19. To sustain wellbeing of health, social relationships, and the economy in the Pacific, it is a critical time for all governments, development partners and civil societies to show regional solidarity in the fight against emerging COVID-19 health crisis and existing Pacific NCDs crisis through a whole of government and whole of society approach.

Keywords

coronavirus disease 2019, non-communicable diseases, health crisis, Pacific

Introduction

Emerging diseases such as coronavirus disease 2019 (COVID-19) are threatening human health and global stability, forcing countries to make difficult decisions, and changing the way people live, work, and interact. Given the evolving situation of COVID-19, new information and recommendations to prevent and control the transmission of COVID-19 have been constantly issued by various scientific institutions. Amid the developing evidence, it is becoming increasingly clear that older adults, and people with pre-existing non-communicable diseases (NCDs) such as diabetes, heart diseases, hypertension, chronic lungs diseases and cancers, are more susceptible to becoming severely ill or dying from the virus.[1,2] COVID-19 does not discriminate and is affecting both rich and poor, with vulnerable groups likely to suffer the most. Of particular concern are the people in the small Pacific island nations where NCDs have already posed heavy burden to all, and a challenge to achieving the United Nations Sustainable Development Goals.[3]

Existing Pacific NCDs Crisis and Emerging COVID-19 Pandemic

The Pacific region has been called the NCDs capital of the world, given that NCDs are the leading cause of death in the region, accounting for approximately 75% of mortalities.[4] Pacific Island countries and territories (PICTs) are among the top 10 countries with the highest rates of diabetes in the world. Approximately one third of the adult population aged 20-79 years in the Federated States of Micronesia, Marshall Islands, Tokelau, and Kiribati have diabetes.[5] The prevalence of NCD risk factors such as smoking, alcohol abuse, unhealthy diet and physical inactivity are also high. For example, approximately half of the adult population smoke daily in American Samoa, Federated States of Micronesia, Kiribati, Tokelau, and Nauru.[6] These high prevalence of NCDs and associated risk factors have resulted in disability, premature deaths, and loss of productivity, and are creating a "health, social, and economic crisis" across the Pacific.[7]

With the increasing evidence showing comorbidities of COVID-19 and NCDs, the Pacific represents a region that is significantly vulnerable to this health crisis. The most prevalence comorbidities were hypertension and diabetes, followed by cardiovascular diseases and respiratory system diseases.[8] A recent study of patients in China showed that smokers comprised more than 25% of the COVID-19 patients who were admitted to intensive care unit, needed mechanical ventilation, or died.[9] These NCD comorbidities may intensify COVID-19 crisis and will significantly impact health, economic, and social development across the Pacific unless urgent action is taken.

Addressing COVID-19 and NCDs Concurrently

To prepare for and response to the COVID-19 outbreak, several recommended population-based measures have been undertaken to minimize the spread in most PICTs. Examples of these mea-

sures include quarantine or isolation, contact tracing, closure of non-essential businesses, locking down affected areas or cities, promoting hand washing and respiratory hygiene, and social or physical distancing.

Some measures taken to fight COVID-19 are likely to increase the risk of NCDs[10] in the long term. For example, trade and movement restrictions within and between countries has reduced availability and accessibility to healthier foods, and increased reliance on unhealthy processed foods. In addition, there is potential for individuals becoming less physically active as a result of curfews and restricted movement; abuse of tobacco and alcohol while being isolated at home; and increase in domestic violence compounded by further isolation due to quarantine, social disengagement and unemployment. All these impact individuals' mental well-being and overall risks of NCDs.

Hence, while enforcing these urgent critical mitigation measures during the COVID-19 pandemic, it is important to incorporate or strengthen NCD prevention and control measures to safeguard people with NCDs. This will help to keep them healthy and minimise the impact of COVID-19.[11,12] These include, but are not limited to, measures that promote access to and consumption of a well-balanced diet and nutritious healthy foods including fruits and vegetables where possible; discourage use or consumption of unhealthy products such as tobacco, alcohol and betel nuts; facilitate access to essential health care services for people with NCDs; promote physical activity and mental wellness to help alleviate the psychological impact of the pandemic; and enhance information sharing and awareness to practice preventive measures for this fast-moving global health emergencies of COVID-19 and NCDs.

With mounting evidence that NCDs increase the risk of dying from the COVID-19 and other viral infections such as seasonal influenza,[13] it is of the utmost importance for the Pacific to intensify a multi-sectoral response to NCDs to minimize the impact of COVID-19 and to prepare for similar potential emerging health crisis or re-emerging diseases in the future. This is a crucial time to strengthen national action on Pacific leaders' commitment for the implementation of the Pacific NCD Roadmap recommendations[1] that are in line with NCDs best-buy interventions[2] and addressing the NCD-related policy and legislation gaps identified in the Pacific Monitoring Alliance for NCD Action (MANA) Dashboard report.[3] These regional recommendations include strengthening fiscal policies to discourage use of unhealthy products such as tobacco, alcohol and sugar-sweetened beverages and promote healthier food options; polices and legislation that address NCD risk factors such as tobacco, alcohol, unhealthy foods and drinks, and physical inactivity; and programs that promote primary and secondary prevention of NCDs. Addressing NCDs and COVID-19 concurrently will help shape, improve, and sustain physical, mental and social wellbeing in long term and contribute to achieving healthy island vision.[4]

Conclusion

Health has been increasingly regarded as a fundamental human right and the backbone of sustainable societies and economies. To sustain wellbeing of health, social relationships, and the economy in the Pacific, it is a critical time for all governments, development partners, and civil societies across the Pacific to show regional solidarity in the fight against the emerging COVID-19 pandemic, remerging diseases such as measles, and existing Pacific crises such as NCDs and climate change in a whole of government and whole of society approach.

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Incidence of Acute Post-Streptococcal Glomerulonephritis in Hawai‘i and Factors Affecting Length of Hospitalization

Blair Limm-Chan MD; James Musgrave MD; Rhiana Lau MD; Hyeong Jun Ahn PhD; Lynn Nguyen BS; and David Kurahara MD

Abstract

Acute post-streptococcal glomerulonephritis (APSGN) is a disorder of inflammation in the glomeruli and vasculature of the kidneys that is caused by immune-complex formation after Streptococcus pyogenes infection. Most patients with APSGN present with macroscopic hematuria, edema, and hypertension, however presentation can vary from no symptoms to severe proteinuria, or even acute renal failure. This study sought to estimate the incidence of APSGN among children in Hawai‘i, to identify populations at increased risk for APSGN, and to recognize risk factors correlated with the length of hospitalization by subtype of APSGN (eg, pyoderma-associated, pharyngitis-associated). This retrospective review of 106 patients found that the incidence of APSGN in Hawai‘i is greater than 4 per 100,000 children, which is significantly higher than the incidence of APSGN in high-income countries at 0.3 per 100,000 children. This increased incidence may be due to Hawai‘i’s unique racial group composition and therefore the unique immunologic response of the children of Hawai‘i (particularly Pacific Islanders, who represent 62% of patients with APSGN in this study, but only represent 10% of Hawai‘i’s general population). In addition, there may be increased prevalence of nephritogenic strains of Streptococcus pyogenes in Hawai‘i. The length of hospitalization was significantly increased in children with elevated serum creatinine levels (P <.0001) and lower bicarbonate levels (P =.0003).

Keywords

Acute post-streptococcal glomerulonephritis, Length of hospitalization, Pediatric, Streptococcus, Pacific Islander

Introduction

Acute post-streptococcal glomerulonephritis (APSGN) is a disorder of inflammation in the glomeruli and vasculature of the kidneys, caused by immune-complex formation secondary to *Streptococcus pyogenes* infection.[1] The clinical presentation can vary from no symptoms to acute renal failure; however, most patients present with edema, hypertension, and macroscopic hematuria.[1,2] While APSGN is considered rare in high-income nations (incidence is estimated to be about 0.3 new cases per 100,000 individuals per year),[1] the incidence in low-income countries is estimated to be much higher (between 9.5 and 28.5 new cases per 100,000 individuals per year).[3,4]

By investigating all cases of APSGN in pediatric patients at one local health care facility, we studied children hospitalized with APSGN in Hawai‘i, particularly the incidence, demographic information, and clinical characteristics. Most children with APSGN are hospitalized for severe hypertension or acute renal failure, but there may be other factors (ie, age, sex, level of fluid overload, laboratory results) that affect the length of hospitalization in these patients. To our knowledge, the length of hospitalization in children with APSGN and the risk factors that may prolong hospitalizations have never been investigated in Hawai‘i or elsewhere. A better understanding of these factors could help to predict the severity of APSGN in children.

Methods

This study included all young people hospitalized at Kapi‘olani Medical Center for Women and Children, the only pediatric hospital in Hawai‘i, between January 2008 and December 2014 with the diagnosis of APSGN. We included all patients aged 21 and younger who were hospitalized for APSGN. APSGN was defined by the following criteria: acute onset of glomerulonephritis with hematuria and/or proteinuria, depression of serum C3 levels, and evidence of streptococcal infection.

Medical records of all patients were reviewed by author B.L. Descriptive characteristics (ie, age, sex, race), clinical features (ie, history of streptococcal infection, blood pressure at hospital admission, blood urea nitrogen, creatinine, streptococcal titers), as well as length of hospitalization were obtained for all patients. Estimated glomerular filtration rates were calculated using the Schwartz formula,[5] which includes the patient’s height and serum creatinine level in the calculation.

Demographic and clinical information were summarized using means and standard deviations (SD) for continuous variables and frequencies and percentages for categorical variables. Due to skewed distributions of length of hospitalization ranging from days to weeks, Wilcoxon rank-sum tests were used to evaluate whether significant differences existed between 2 or more groups. Pearson correlation tests were also used to evaluate the association between length of hospitalization and continuous variables. Two-sided $P \leq .05$ were considered statistically significant. Data analysis was conducted using SAS statistical software version 9.3 (SAS Institute Inc.:Cary, NC).

The Hawai‘i Pacific Health Research Institute provided Institutional Review Board (IRB) exemption for this study. This study conforms to the provisions of the Declaration of Helsinki, as revised in 2013.

Results

There were 106 patients aged 21 and younger hospitalized with APSGN at Kapiʻolani Medical Center for Women and Children between 2008 and 2014. Therefore the calculated incidence of APSGN in Hawai'i is 4 new cases per 100,000 people aged 21 and younger per year. This calculated incidence is obtained by using 106 as the numerator, and 372,955 as the denominator (the estimated population of people 21 years and younger in Hawai'i each year during the time period 2008-2014),[6] and then further divided by the duration of 7 years.

In this cohort, the mean age was 8.3 ± 3.8 years (range 2-21 years) and there were more males (64%) than females (Table 1). The majority of patients identified themselves as Pacific Islanders (62%), while 22% identified as Asian, 4% as white, 1% as African American, and 11% as Other. This racial breakdown differs from the general population of Hawai'i because Pacific Islanders comprise only 10% of the general population.[6]

Table 1. Demographic and Clinical Characteristics of the 106 Participants at Time of Admission

Characteristic	Value
Age, mean ± SD	8.3 ± 3.8 years
Sex, n (%)	
Male	68 (64%)
Female	38 (36%)
Race, n (%)	
Pacific Islander	66 (62%)
Asian	23 (22%)
White	4 (4%)
African American	1 (1%)
Hispanic	0 (0%)
Other	12 (11%)
Clinical Manifestations, n (%)	
Adenitis	35 (33%)
Edema	67 (63%)
Hypertension	79 (75%)
Pyoderma	43 (41%)
Pharyngitis	50 (47%)
Laboratory Data, mean ± SD	
Blood Urea Nitrogen, serum (normal range 7-17 mg/dL)	30 ± 23 mg/dL
Creatinine, serum (normal range 0.3-1.1 mg/dL)	1.1 ± 0.8 mg/dL
Potassium, serum (normal range 3.6-5.3 mmol/L)	4.3 ± 0.5 mmol/L
Bicarbonate, serum (normal range 20-30 mmol/L)	21 ± 2.9 mmol/L
C3 level (normal range 87-158 mg/dL)	27 ± 25 mg/dL
C4 level (normal range 12-36 mg/dL)	18.5 ± 6.8 mg/dL
ASO titer (normal range 87-158 IU/mL)	791 ± 805 IU/mL

SD, standard deviation; ASO, antistreptolysin O (antibodies against streptolysin O, a substance produced by *Streptococcus pyogenes*)

Urine microscopy was performed for all 106 patients, and all patients presented with microscopic hematuria and proteinuria. Hypertension was exhibited in 74% of patients, while 63% had edema, and 33% had adenitis. From history, examination, or diagnostic tests, clinicians identified a likely source of infection in 93 patients (88%). Streptococcal pharyngitis was the likely source in 47% of patients, while streptococcal pyoderma (a skin infection) was the likely source of infection in 41% of patients. There was no source identified in the remaining 13 patients. At hospital admission, serum creatinine was elevated in 67% of patients, estimated glomerular filtration rate was elevated in 50% of patients, serum blood urea nitrogen (BUN) was elevated in 58% of patients, serum bicarbonate was depressed in 31%, and serum antistreptolysin O (ASO) titer was elevated in 83% of patients. ASO titers measure antibodies against streptolysin O, a hemolytic toxic substance produced by *Streptococcus pyogenes*.[3,7]

The length of hospitalization ranged from 2 to 21 days, with a mean of 4.7 days (Figure 1). Using correlation analysis, increased length of hospitalization was associated with higher admission serum creatinine ($P < .0001$) (Table 2). Length of hospitalization was inversely associated with admission serum bicarbonate ($P = .0003$). Other factors such as systolic blood pressure, diastolic blood pressure, admission serum BUN, serum potassium, and ASO titers were not associated with the length of hospitalization.

Wilcoxon rank-sum tests were used to determine whether length of hospitalization differed between patients who had pyodema and/or pharyngitis upon admission compared to those who did not have these conditions. No statistically significant difference was found among the groups.

Table 2. Pearson Correlation Coefficients of Characteristics and Length of Hospitalization

Variable	Pearson Correlation Coefficient	*P*-Value
Length of hospitalization (LOH)	1	—
Blood urea nitrogen, serum	0.186	.057
Creatinine, serum	0.382	< .0001
Potassium, serum	0.100	.308
Bicarbonate, serum	-0.349	.0003
ASO titer	0.053	.604
Systolic blood pressure	-0.123	.211
Diastolic blood pressure	-0.090	.361
Percent weight change	0.139	.154

ASO, antistreptolysin O (antibodies against streptolysin O, a substance produced by *Streptococcus pyogenes*)

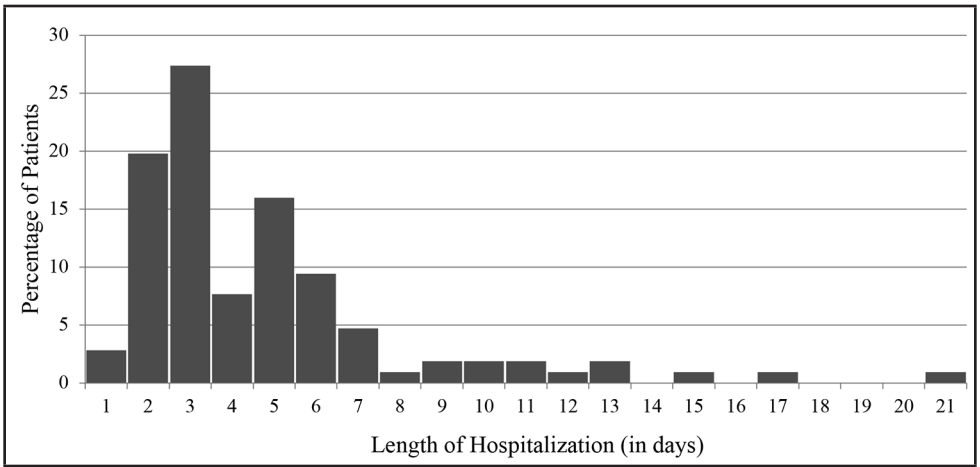

Figure 1. Length of Hospitalization Among APSGN Patients

Discussion

Hawai‘i’s incidence of ASPGN is 4.0 per 100,000 children per year, which is much higher than the reported incidence of 0.3 per 100,000 children per year in high-income countries.[1] Instead, Hawai‘i’s incidence of APSGN approaches the incidence of low-income countries (incidence of 9.5 to 28.5 per 100,000 children).[3,4] Furthermore, our calculated incidence is likely an underestimate of the true incidence because our study did not capture outpatient data (it is possible that some children with APSGN do not require hospitalization) and because our study only captured hospitalizations in 1 hospital in Hawai‘i. The reason for Hawai‘i’s high incidence of APSGN is unclear; it may be due to the unique genetic composition of the residents of this state (in part due to the high influx of people immigrating from low-income countries), as well as the particular strains of *Streptococcus pyogenes* in this environment.

Although Pacific Islanders (including Native Hawaiians, Polynesians, and Micronesians) comprise only 10% of Hawai‘i’s population,[6] Pacific Islanders represent 62% of patients with APSGN in this study. This over-representation of indigenous populations among APSGN cases in Hawai‘i is similarly seen in Australia, where Aboriginal Australians disproportionally represent the patients who develop APSGN. Some of the largest studies conducted on APSGN have been conducted in Australia and have found increased rates in Aboriginal populations compared to non-Aboriginal populations. Blyth, et al, found that Aboriginal Australians represent 30% of patients with APSGN, yet only comprise 2.4% of Australia’s population.[8] Meanwhile, Marshall et al found the rate ratio of cases in Aboriginal Australians to non-Aboriginal Australians was elevated at 53.6 (95% CI =32.6-94.8).[4] This over-representation of APSGN in Pacific Islanders in Hawai‘i and Aboriginal Australians in Australia may suggest that there are immunologic differences between racial groups that may increase the susceptibility of APSGN in these racial groups.

In addition to host factors, the particular strains of *Streptococcus pyogenes* in Hawai‘i may also be contributing to the higher incidence of ASPGN. There are hundreds of strains of *Streptococcus pyogenes*, each with a different cell wall-associated M protein, which is encoded by the *emm* gene.[7] The M protein is an antigenic epitope and virulence factor, and therefore forms the basis for serotyping of *Streptococcus pyogenes*.[7,9] Reports of serotyping in Hawai‘i found that 54% of *Streptococcus pyogenes* serotypes identified in Hawai‘i were not commonly identified elsewhere.[10] The most common *Streptococcus pyogenes emm* serotypes in Hawai‘i were 1, 2, 4, 12, 22, 28, 49, 58, 65, 74, 77, 81, 85, 92, 101.[10] Of these *emm* serotypes, serotypes 1, 2, 4, 12 and 49 are known to be nephritogenic strains of *Streptococcus pyogenes*.[9]

Our study found that length of hospitalization is increased in patients with higher admission serum creatinine levels (Pearson correlation factor: 0.382, $P < .0001$). Length of hospitalization is also increased in patients with lower admission bicarbonate levels (Pearson correlation factor: -0.349, $P = .0003$). Higher creatinine and lower bicarbonate levels indicate a higher severity of kidney injury and disease, which may require longer hospitalization. Patient discharge is often delayed while waiting for improvement of creatinine or signs of acute renal failure. Although a lower bicarbonate level could suggest renal tubular acidosis, the injury of APSGN involves immune complex deposition in the glomeruli; injury of the tubules has not been described.[1] In addition, renal tubular acidosis often results in sodium wasting however the patients in this study had preserved serum sodium levels.

Severity of hypertension and fluid overload (as calculated by percent weight change throughout hospitalization) were not significantly associated with the length of hospitalization. Although APSGN patients are often hospitalized specifically for hypertension and fluid overload, these manifestations can be addressed with intravenous diuretics and antihypertensives. These medications act quickly and rarely delay discharge.

Our study is the first to estimate the incidence of APSGN in Hawai‘i. To our knowledge, no study has looked at risk factors prolonging the length of ASPGN hospitalizations. Although our study provides novel information, our results should be interpreted in the context of some limitations. First, our study has a relatively small sample of patients. Second, our study has a retrospective and uncontrolled study design. Third, we calculated the annual incidence of APSGN for the entire state of Hawai‘i (rather than the island of O‘ahu) despite collecting cases from only 1 O‘ahu hospital. We did this because we found that a significant portion of the 106 patients with ASPGN came from neighboring islands based on their residential zip codes (11 from Hawai‘i, 7 from Maui, 6 from Kaua‘i, and 2 from Moloka‘i).

Conclusion

The incidence of APSGN in Hawai‘i is higher than the typical rates seen in high-income countries, which may be due to the population's unique racial composition, the differences of immunologic response between different racial groups (particularly the Pacific Islanders), or possibly increased nephritogenic strains of *Streptococcus pyogenes* in Hawai‘i. Hospitalizations were longer in patients with higher admission creatinine levels and lower bicarbonate levels. Further studies should be conducted to determine the reasons for the increased incidence in Hawai‘i and the differences between pyoderma-associated and pharyngitis-associated APSGN.

Conflict of Interest

None of the authors identify a conflict of interest.

Disclosure

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Prevalence and Risk Factors for Self-Reported Postpartum Depression Symptoms (SRPDS) in Hawai'i, 2012-2015

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Abstract

Postpartum depression (PPD) affects an estimated 10% to 20% of women in the United States, but little is known about the risk factors for PPD in Hawai'i. This study sought to identify PPD risk factors and examine whether disparities exist in Hawai'i. Aggregated 2012-2015 Hawai'i Pregnancy Risk Assessment Monitoring System (PRAMS) data from 5572 women with a recent live birth were analyzed. Two questions on the PRAMS survey about mood and interest in activities were used to create a brief measure of Self-Reported Postpartum Depression Symptoms (SRPDS). Multivariate generalized logit analysis was conducted to identify risk factors associated with SRPDS or possible SRPDS, adjusting for maternal race and age, intimate partner violence (IPV), prenatal anxiety, prenatal depression, illicit drug use before pregnancy, and stressful life events (SLEs). About 10.0% of women surveyed had SRPDS and 27.7% had possible SRPDS. SRPDS was more common among Native Hawaiians (adjusted odds ratios=1.77; 95% confidence interval: 1.17-2.70), Filipinos (2.16; 1.33-3.50), Japanese (2.88; 1.67-4.98), and other Pacific Islanders (OPI; 3.22; 1.78-5.82), when compared to white. Women aged 20-29 years (0.39; 0.24-0.65) and 30-52 years (0.41; 0.24-0.69) were less likely to have SRPDS than those 19 years and younger. SRPDS was highest among women who experienced IPV (2.65; 1.37-5.13), prenatal anxiety (2.10; 1.28-3.42), prenatal depression (2.78; 1.47-5.25), or used illicit drugs before pregnancy (1.97; 1.21-3.20). There was an upward trend in SRPDS based on the number of SLEs. Possible SRPDS had similar but smaller effects, suggesting the importance of clinical screening and appropriate follow-up for these high-risk groups.

Keywords

Postpartum depression, risk factors, prenatal depression, stressful life events

Abbreviations

AOR = Adjusted odds ratios
CI = Confidence Interval
IPV = Intimate Partner Violence
OPI= Other Pacific Islanders
PPD = Postpartum Depression
PRAMS = Pregnancy Risk Assessment Monitoring System
SLE = Stressful Life Event
SRPDS = Self-Reported Postpartum Depression Symptoms

Introduction

According to the Centers for Disease Control and Prevention (CDC), about 1 in 9 women experiences postpartum depression (PPD), which is one of the most common mental health disorders that occurs after childbirth, with symptoms including sadness, loss of interest, feelings of hopelessness, and worthlessness.[1] A study of 27 states in the United States (US) found that in 2012, prevalence for PPD symptoms ranged from 8.0% to 20.1%, with an overall rate of 11.5%.[2] Although the Diagnostic and Statistical Manual of Mental Disorder (DSM-5) defined PPD as a major depressive episode "with peripartum onset" during pregnancy or within 4 weeks of delivery,[3] significant heterogeneity exists in the onset and severity of symptoms.[4,5] Data showed that women with prenatal depression experienced more severe PPD symptoms, compared with those with later onset of symptoms after giving birth.[5] PPD limits the ability of the woman to care for her new infant resulting in increased use of health care services and more hospitalizations, and has detrimental effects on the newborn and the mother's life.[6-8] In severe cases, women with PPD may harm themselves.[9] PPD is diagnosed by mental health professionals through interviews, depression screening tools, and lab tests to rule out other problems that might cause the symptoms.[10] Distinguishing between PPD and natural consequences of childbirth (eg, changes in weight, sleep, and energy), or a major depressive episode occurring at any other time in a woman's life might be challenging to clinical diagnosis.[11,12] PPD might persist for many months beyond the perinatal period, and women who suffer from it might experience relapses in subsequent pregnancies even after successful treatment.[13]

Past researchers have identified risk factors associated with PPD including prenatal depression, prenatal anxiety, stressful life events (SLEs), low self-esteem, socioeconomic status, and history of abuse.[8,14-18] For example, a meta-analysis conducted by Robertson et al. (2004) of over 22 000 participants from studies between 1990 and 2002 revealed that depression and anxiety during pregnancy, SLEs, low social support, and history of depression were strongly associated with PPD.[16]

In addition to these risk factors, recent researchers have examined the associations between PPD and selected sociodemographic characteristics including race, age, education, and household income.[2,8,19-21] For example, Ko, et al, (2017) analyzed 2012 data from the 27-state Pregnancy Risk Assessment Monitoring System (PRAMS) and reported that the overall prevalence of PPD symptoms was higher among American Indian/Alaska Native and Asian/Pacific Islanders, those who had experienced 3 or more prenatal stressful life events, or women who gave birth to low birthweight infants.[2] Segre, et al, (2007) reported significant associations of financial poverty, occupation, and age with PPD.[22] Others researchers showed an increased risk

for PPD among certain racial groups such as black[20,23] and Hispanic women[20] compared with white women, after adjusting for the covariates in their studies. These results revealed that PPD symptoms appeared to be highly associated with certain race or other sociodemographic groups.

Hawai'i consists of diverse populations of Native Hawaiian, Asian, and other Pacific Islander (OPI) that are not commonly reported in the scientific literature. According to 2015 American Community Survey, there were approximately 1.4 million persons living in Hawai'i with 37.1% classified as Asian, 26.0% as white, 9.4% as Native Hawaiian and OPI, and 24.5% as 2 or more races.[24] Using 2004-2007 Hawai'i PRAMS data, Hayes, et al, (2010) reported that Asian and OPI women with a recent live birth were significantly more likely to experience PPD symptoms than their white counterparts,[21] suggesting PPD occurred more frequently in some racial groups than others in Hawai'i. However, to date, few studies have examined risk factors for PPD in Hawai'i. The present study aims to determine the risk factors for PPD symptoms in Hawai'i using the PRAMS data from 2012-2015, and to examine the associations between PPD symptoms with racial groups and other selected demographic characteristics.

Methods

Aggregate data from the 2012-2015 Hawai'i PRAMS were used for this study. Developed in 1987, PRAMS is a national surveillance project conducted by the CDC in collaboration with state and metropolitan health departments. The Hawai'i State Department of Health has conducted PRAMS data collection since 2000. PRAMS provides an ongoing state-specific, population-based surveillance system for selected maternal behaviors before, during, and the first few months after pregnancy, with aims to identify high-risk women and infants for adverse health outcomes and monitor progress towards improving maternal and infant health.[25] Based on birth certificate data, participants are selected among women with a recent live birth (within the last 2 months), and are mailed a self-administered questionnaire focusing on maternal and infant health behaviors and experiences around the time of pregnancy.[25] Non-respondents are further contacted with subsequent questionnaire mailings and telephone interviews up to 6 months postpartum. In this study, a total of 8741 women were contacted, with an overall response rate of 63.7%, resulting in a total of 5572 respondents.

Self-reported postpartum depression symptoms (SRPDS) were measured in PRAMS using 2 questions on a 5-point Likert scale: (1) "Since your new baby was born, how often have you felt down, depressed, or hopeless?"; and (2) "Since your new baby was born, how often have you had little interest or little pleasure in doing things?" Respondents could choose from 5-response option categories: (1) "always", (2) "often", (3) "sometimes", (4) "rarely", and (5) "never". Similar to the classification reported in Hayes, et al, (2010),[21] respondents were classified as having SRPDS if they answered "always" or "often" to either question. They were defined as having possible SRPDS if they answered "sometimes" to either question and did not choose "always" or "often" for either question. Those who answered "rarely" or "never" but did not choose the other response categories were classified as not having SRPDS. Those who answered only one question (0.3%) were also included in the analyses. Forty respondents (0.7%) who did not answer both questions were classified as missing and were excluded from the analyses, resulting in 5532 participants. These 2 questions were developed and slightly modified based on the 2 screening questions from Patient Health Questionnaire-2 (PHQ-2), a screening instrument with high sensitivity in identifying adults in the general population with high and intermediate risk for depression.[26-28] The modification of the questions was assessed, reviewed, and piloted by the CDC before use by PRAMS.

For our analysis, the 22 single-coded maternal racial groups were recategorized by the Office of Health Status Monitoring in the Hawai'i State Department of Health,[29] into 6 racial groups for larger samples in order to get reliable estimates: white, Native Hawaiian, Filipino, Japanese, OPI, and others/unknown. Mothers who were coded as Native Hawaiian and part-Hawaiian were included in the Native Hawaiian group. Those who were coded as Caucasian or Portuguese were included in the white group. Portuguese was also included in the white group based on the work by Sorensen, et al, (2003) and on previous Hawaii PRAMS analyses.[21,29] Guamanian, other Pacific Islanders, and Samoan were classified as OPI. For this analysis, Chinese, Korean, Vietnamese, other Asians, Asian Indian, American Indian, Hispanic (ie, Puerto Rican, Cuban, and Mexican), those who were not grouped into the above groups, and the "unknown" (0.57%) were included in the others/unknown group.

PRAMS included a question with 14 maternal SLEs within the 12 months before the birth of the child such as losing a job, illness of a family member, financial difficulties, separation or divorce, homelessness, or moving to a new address. The total of the 14 events were obtained and was categorized as 0, 1-2, 3-5, and ≥ 6, which aligned with standard PRAMS categorization. The other covariates (ie, unintended pregnancy, intimate partner violence [IPV], prenatal depression, and prenatal anxiety) for this analysis were recategorized and described as below. Women were classified as having an unintended pregnancy if they chose the option category "I wanted to be pregnant later" or "I didn't want to be pregnant then or at any time in the future." Conversely, women were classified as having an intended pregnancy if they reported "wanting to be pregnant then or sooner", and those who answered "I wasn't sure what I wanted" were classified as "Not Sure" (19.5%). Women who experienced IPV were defined as those who answered "yes" to physical abuse during pregnancy or 12 months before pregnancy by husband or partner. Illicit drug use before pregnancy was defined as those who answered "yes" to the use of marijuana, amphetamines, cocaine, tranquilizers or hallucinogens, or sniff-

ing products such as gasoline, glue, hairspray, or other aerosols at least 1 time in the month before pregnancy. Respondents were classified as having prenatal depression if the women answered "yes" to being told by a doctor, nurse, or health care provider that they had depression before pregnancy, and as having prenatal anxiety if they self-reported as having anxiety 3 months before pregnancy.

Prevalence estimates of selected sociodemographic data and other characteristics by SRPDS categories were obtained. Multivariate generalized logit modeling was used to obtain crude and adjusted odds ratios for SRPDS and possible SRPDS, with those without SRPDS as the reference group for both outcomes. The model controlled for maternal race and age, pregnancy intendedness, IPV before or during pregnancy, illicit drug use before pregnancy, prenatal depression, prenatal anxiety, and SLE before pregnancy. The final model included a total of 4735 participants, after listwise deletion of missing values in the independent and outcome variables. All analyses were conducted using SAS 9.4 (SAS Institute, Inc.: Cary, NC) with $P < .05$ considered statistically significant.

Results

Table 1 reports that the 2 largest racial groups represented in the 2012-2015 Hawai'i PRAMS data were white (24.1%) and Native Hawaiian (27.5%). Two of the major Asian subgroups, Filipino (17.0%) and Japanese (9.2%), together made up about a quarter of live births in the state. Approximately 48.7% of women were 20-29 years, 46.5% were 30-52 years, and 4.8% were under 20 years.

SRPDS

Results showed that 10.0% of women with a recent live birth in Hawai'i had SRPDS (Table 2). The prevalence of SRPDS was significantly higher among Native Hawaiian and OPI women compared to whites, who had the lowest estimate (Table 2). Estimates of SRPDS were highest among women under 20 years, those "not sure" on pregnancy intendedness, those who experienced IPV, used illicit drugs before pregnancy, had prenatal anxiety, had prenatal depression, or those who experienced ≥6 SLEs before pregnancy (Table 2).

Many of these differences were demonstrated in the final adjusted model (Table 3). Women who are Native Hawaiian (adjusted odds ratios [AOR] = 1.77; 95% CI: 1.17-2.70), Filipino (AOR = 2.16; 95% CI: 1.33-3.50), Japanese (AOR = 2.88; 95% CI: 1.67-4.98), and OPI (AOR = 3.22; 95% CI:1.78-5.82) had a higher likelihood of SRPDS than white women (Figure 1). Women aged 20-29 years (AOR = 0.39; 95% CI: 0.24-0.65) and 30-52 years (AOR = 0.41; 95% CI: 0.24-0.69) were less likely to have SRPDS than those under 20 years. Women who experienced IPV (AOR = 2.65; 95% CI: 1.37-5.13) or used illicit drugs before pregnancy (AOR = 1.97; 95% CI: 1.21-3.20) had higher odds of SRPDS than those who did not (Table 3). SRPDS was most common among women who had prenatal anxiety (AOR = 2.10; 95% CI: 1.28-3.42) or prenatal depression (AOR = 2.78; 95% CI: 1.47-5.25). There was an upward trend in SRPDS among women who experienced 1-2 SLEs (AOR = 2.27; 95% CI: 1.58-3.27, 3-5 SLEs (AOR = 3.50; 95% CI: 2.36-5.20), ≥6 SLEs (AOR = 5.84; 95% CI: 2.89-11.80) compared to those with no SLE (Figure 1). There were no significant differences in the likelihood of SRPDS for pregnancy intendedness.

Possible SRPDS

Approximately 27.7% of women with a recent live birth in Hawai'i had possible SRPDS (Table 2).

Compared to whites, the prevalence of possible SRPDS was significantly higher among Filipino, OPI women, and those in the other/unknown race category. Estimates of possible SRPDS were highest among women under 20 years, had an unintended pregnancy, those who experienced IPV, used illicit drugs before pregnancy, had prenatal anxiety, had prenatal depression, and those who experienced ≥6 SLEs (Table 2).

In the final adjusted model (Table 3), Native Hawaiian (AOR = 1.33; 95% CI: 1.03-1.72), Filipino (AOR = 2.13; 95% CI: 1.58-2.87) or OPI women (AOR = 2.02; 95% CI: 1.37-3.00) were more likely to have possible SRPDS compared with white women (Figure 2). Those with an unintended pregnancy (AOR = 1.72; 95% CI: 1.39-2.12) or those who were not sure what they wanted (AOR = 1.31; 95% CI: 1.02-1.67) were more likely to have possible SRPDS than women who intended to be pregnant (Table 3). After adjustment, possible SRPDS was most likely among women who had prenatal anxiety (AOR = 1.60; 95% CI: 1.07-2.40), prenatal depression (AOR = 2.26; 95% CI: 1.32-3.87) as well as those who experienced 1-2 SLEs (AOR = 1.69; 95% CI: 1.36-2.10), 3-5 SLEs (AOR = 2.03; 95% CI: 1.57-2.64), or ≥ 6 SLEs (AOR = 3.35; 95% CI : 2.11-5.33; Table 3, Figure 2).

Table 1. Selected Sociodemographic Characteristics of Pregnancy Risk Assessment and Monitoring System (PRAMS) Study Sample, Hawai'i, 2012 to 2015 (N=5572)

	Frequency	Weighted Percentage	95% CI[a]
Maternal Race			
White	1303	24.1	22.6-25.6
Native Hawaiian	1693	27.5	26.0-29.0
Filipino	1025	17.0	15.7-18.3
Japanese	466	9.2	8.1-10.2
Other Pacific Islander[b]	337	6.9	6.0-7.8
Other/Unknown[c]	748	15.3	14.0-16.6
Maternal Age (years)			
Under 20	277	4.8	4.0-5.5
20-29	2625	48.7	47.0-50.5
30-52	2670	46.5	44.7-48.3
Pregnancy Intendedness			
Intended Pregnancy	2766	52.2	50.4-54.0
Unintended Pregnancy	1523	28.7	27.1-30.3
Not Sure	1040	19.1	17.7-20.5
Missing	243		
Intimate Partner Violence			
No	5295	96.8	96.2-97.4
Yes	175	3.2	2.6-3.8
Missing	102		
Illicit Drug Use			
No	4831	93.8	93.0-94.6
Yes	395	6.2	5.4-7.0
Missing	346		
Prenatal Anxiety			
No	4996	93.4	92.5-94.3
Yes	384	6.6	5.7-7.5
Missing	192		
Prenatal Depression			
No	5125	95.8	95.0-96.5
Yes	238	4.2	3.5-5.0
Missing	209		
Stressful Life Events			
0	1799	33.9	32.2-35.6
1-2	2194	41.4	39.7-43.2
3-5	1187	20.4	19.0-21.8
≥ 6	232	4.3	3.5-5.0
Missing	160		

Note: Individual subgroup column totals may not sum to overall total due to missing/unknown data and row percentages may not sum to 100% due to rounding.
[a] CI = confidence interval.
[b] Other Pacific Islander includes Samoan, Guamanian, other Pacific Islander.
[c] Other/Unknown group includes Chinese, Korean, Vietnamese, other Asians, Asian Indian, Puerto Rican, Cuban, Mexican, American Indian, all others, and unknown.

Table 2. Sociodemographic Characteristics of Respondents by Self-Reported Postpartum Depression Symptoms (SRPDS), Pregnancy Risk Assessment and Monitoring System (PRAMS), Hawai'i, 2012-2015

	SRPDS Prevalence (95% CI[a])	Possible SRPDS Prevalence (95% CI)	None Prevalence (95% CI)
Overall	10.0 (8.9-11.0)	27.7 (26.2-29.3)	62.3 (60.6-64.0)
Maternal Race			
White	6.7 (4.9-8.5)	22.9 (19.8-25.9)	70.5 (67.2-73.8)
Native Hawaiian	11.5 (9.5-13.5)	27.9 (25.0-30.7)	60.6 (57.5-63.7)
Filipino	9.3 (7.0-11.5)	35.0 (30.9-39.0)	55.8 (51.5-60.0)
Japanese	11.1 (7.4-14.9)	22.1 (17.1-27.2)	66.7 (61.1-72.4)
Other Pacific Islander[b]	15.1 (9.9-20.3)	33.5 (27.0-40.1)	51.4 (44.4-58.3)
Other/Unknown[c]	10.1 (7.3-13.0)	27.8 (57.5-66.6)	62.1 (57.5-66.6)
Maternal Age (years)			
Under 20	19.4 (13.3-25.5)	34.5 (27.0-42.0)	46.1 (38.4-53.7)
20-29	10.2 (8.7-11.6)	27.2 (24.9-29.4)	62.7 (60.2-65.1)
30-52	8.8 (7.3-10.2)	27.6 (25.3-29.9)	63.6 (61.1-66.1)
Pregnancy Intendedness			
Intended Pregnancy	8.5 (7.1-9.8)	22.8 (20.8-24.9)	68.7 (66.4-71.0)
Unintended Pregnancy	11.1 (9.0-13.1)	34.6 (31.4-37.8)	54.3 (51.0-57.7)
Not Sure	12.5 (9.8-15.3)	30.0 (26.3-33.7)	57.5 (53.4-61.5)
Intimate Partner Violence			
No	9.3 (8.2-10.3)	27.4 (25.8-29.0)	63.3 (61.6-65.1)
Yes	31.1 (21.9-40.4)	36.2 (26.8-45.7)	32.7 (23.4-41.9)
Illicit Drug Use			
No	8.9 (7.8-9.9)	26.8 (25.1-28.4)	64.4 (62.6-66.2)
Yes	20.2 (14.5-25.8)	35.9 (29.4-42.4)	43.9 (37.4-50.5)
Prenatal Anxiety			
No	9.4 (8.3-10.4)	26.7 (25.1-28.3)	63.9 (62.1-65.7)
Yes	19.8 (14.5-25.1)	40.0 (33.3-46.6)	40.3 (33.5-47.0)
Prenatal Depression			
No	9.5 (8.5-10.6)	26.9 (25.3-28.5)	63.6 (61.8-65.4)
Yes	22.2 (15.4-29.0)	42.7 (34.3-51.1)	35.1 (26.8-43.4)
Stressful Life Events			
0	5.5 (4.2-6.9)	22.1 (19.5-24.7)	72.3 (69.6-75.1)
1-2	9.6 (8.0-11.3)	28.5 (26.0-31.0)	61.9 (59.2-64.6)
3-5	15.2 (12.4-17.9)	31.9 (28.3-35.4)	53.0 (49.1-56.8)
≥ 6	23.3 (15.8-30.8)	45.5 (36.8-54.1)	31.2 (23.3-39.2)

[a] CI = confidence interval.
[b] Other Pacific Islander includes Samoan, Guamanian, other Pacific Islander.
[c] Other/Unknown group includes Chinese, Korean, Vietnamese, other Asians, Asian Indian, Puerto Rican, Cuban, Mexican, American Indian, all others, and unknown.

Table 3. Generalized Logit Model: Crude and Adjusted Odds Ratios (OR) for Self-Reported Postpartum Depression Symptoms (SRPDS) by Selected Sociodemographic Characteristics, Pregnancy Risk Assessment and Monitoring System (PRAMS), Hawai'i, 2012-2015

	SRPDS		Possible SRPDS	
	Crude OR[a] (95% CI[b])	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR[e] (95% CI)
Maternal Race				
White	Referent	Referent	Referent	Referent
Native Hawaiian	2.00 (1.40-2.86)	1.77 (1.17-2.70)	1.42 (1.13-1.78)	1.33 (1.03-1.72)
Filipino	1.76 (1.17-2.63)	2.16 (1.33-3.50)	1.93 (1.50-2.49)	2.13 (1.58-2.87)
Japanese	1.77 (1.09-2.86)	2.88 (1.67-4.98)	1.02 (0.72-1.44)	1.23 (0.83-1.82)
Other Pacific Islander[c]	3.10 (1.85-5.20)	3.22 (1.78-5.82)	2.01 (1.42-2.87)	2.02 (1.37-3.00)
Other/Unknown[d]	1.73 (1.12-2.67)	2.15 (1.32-3.50)	1.38 (1.05-1.82)	1.51 (1.11-2.05)
Maternal Age (years)				
Under 20	Referent	Referent	Referent	Referent
20-29	0.36 (0.23-0.56)	0.39 (0.24-0.65)	0.59 (0.41-0.85)	0.67 (0.44-1.01)
30-52	0.34 (0.21-0.57)	0.41 (0.24-0.69)	0.53 (0.35-0.78)	0.83 (0.55-1.27)
Pregnancy Intendedness				
Intended Pregnancy	Referent	Referent	Referent	Referent
Unintended Pregnancy	1.66 (1.25-2.19)	1.22 (0.88-1.70)	1.92 (1.59-2.32)	1.72 (1.39-2.12)
Not Sure	1.77 (1.29-2.43)	1.21 (0.84-1.75)	1.57 (1.27-1.95)	1.31 (1.02-1.67)
Intimate Partner Violence				
No	Referent	Referent	Referent	Referent
Yes	6.52 (3.89-10.91)	2.65 (1.37-5.13)	2.56 (1.58-4.14)	1.57 (0.91-2.69)
Illicit Drug Use				
No	Referent	Referent	Referent	Referent
Yes	3.34 (2.25-4.95)	1.97 (1.21-3.20)	1.97 (1.44-2.68)	1.44 (1.00-2.08)
Prenatal Anxiety				
No	Referent	Referent	Referent	Referent
Yes	3.36 (2.27-4.97)	2.10 (1.28-3.42)	2.38 (1.73-3.27)	1.60 (1.07-2.40)
Prenatal Depression				
No	Referent	Referent	Referent	Referent
Yes	4.22 (2.63-6.77)	2.78 (1.47-5.25)	2.88 (1.92-4.32)	2.26 (1.32-3.87)
Stressful Life Events				
0	Referent	Referent	Referent	Referent
1-2	2.03 (1.47-2.80)	2.27 (1.58-3.27)	1.51 (1.24-1.83)	1.69 (1.36-2.10)
3-5	3.73 (2.66-5.24)	3.50 (2.36-5.20)	1.97 (1.57-2.48)	2.03 (1.57-2.64)
≥ 6	9.73 (5.64-16.79)	5.84 (2.89-11.80)	4.77 (3.11-7.31)	3.35 (2.11-5.33)

[a] CI = confidence interval.

[b] Other Pacific Islander includes Samoan, Guamanian, other Pacific Islander.

[c] Other/Unknown group includes Chinese, Korean, Vietnamese, other Asians, Asian Indian, Puerto Rican, Cuban, Mexican, American Indian, all others, and unknown.

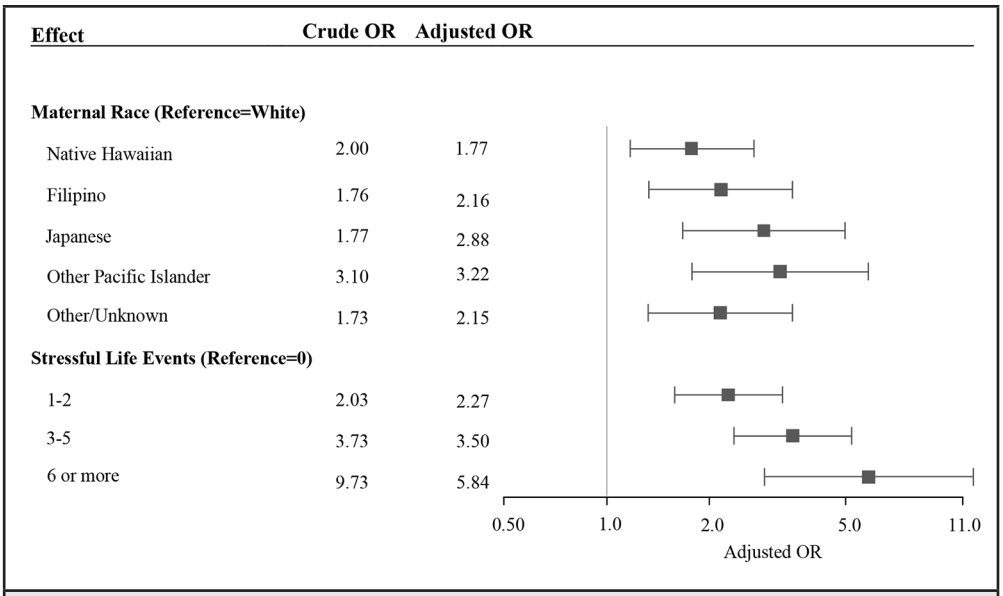

Figure 1. Forest Plot of Adjusted Odds Ratios (OR) for Self-Reported Postpartum Depression Symptoms (SRPDS) by Maternal Race and Stressful Life Events. The Plot Displays the Adjusted Odds Ratio with 95% Confidence Intervals. The Vertical Line Represents an Odds Ratio of 1.0, Where There is No Effect. Note that Other Pacific Islander includes Samoan, Guamanian, Other Pacific Islander; Other/Unknown Group Includes Chinese, Korean, Vietnamese, Other Asians, Asian Indian, Puerto Rican, Cuban, Mexican, American Indian, All Others, and Unknown.

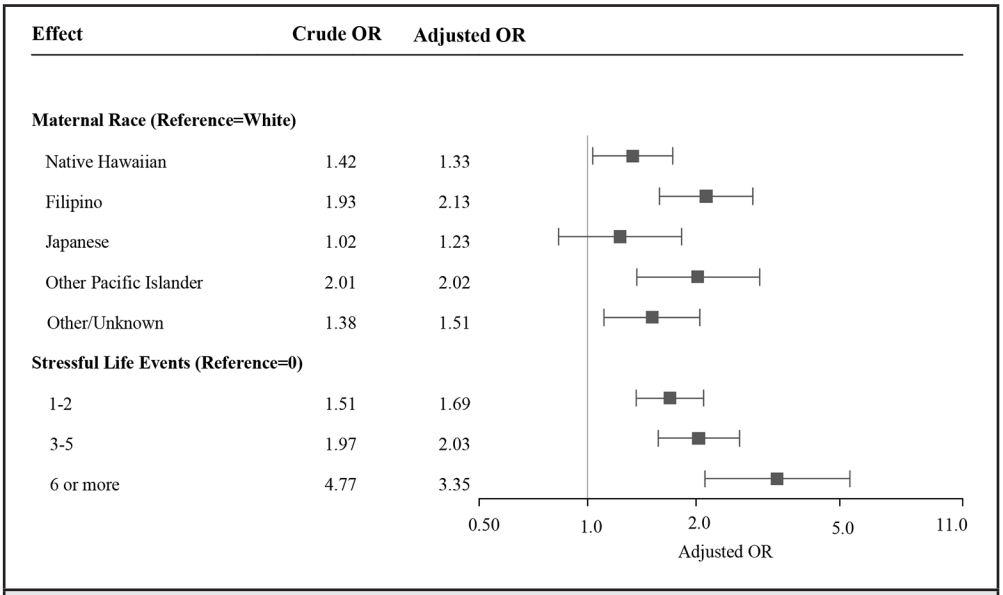

Figure 2. Forest Plot of Adjusted Odds Ratios (OR) for Possible Self-Reported Postpartum Depression Symptoms (SRPDS) by Maternal Race and Stressful Life Events. The Plot Displays the Adjusted Odds Ratio with 95% Confidence Intervals. The Vertical Line Represents an Odds Ratio of 1.0, Where There is No Effect. Note that Other Pacific Islander Includes Samoan, Guamanian, Other Pacific Islander; Other/Unknown Group Includes Chinese, Korean, Vietnamese, Other Asians, Asian Indian, Puerto Rican, Cuban, Mexican, American Indian, All Others, and Unknown.

Discussion

This study examined the risk factors for postpartum depression symptoms in Hawai‘i and revealed that 37.7% of women with a recent live birth reported symptoms of postpartum depression. About 10.0% of women were at high risk, and 27.7% of women were at intermediate risk of postpartum depression. Our study revealed that women who are Native Hawaiian, Filipino, Japanese, and OPI were significantly more likely to have SRPDS than white women. Most of these racial groups also had a higher likelihood of having possible SRPDS. Other significant risk factors for SRPDS included being under 20 years of age, experiencing IPV, illicit drug use before pregnancy, prenatal anxiety, prenatal depression, or experiencing SLEs.

Hawai‘i consists of diverse populations of Native Hawaiian, Asian, and OPI. This study revealed Japanese and OPI women were about 3 times as likely, and Filipino women were about twice as likely, to report SRPDS as white women. Past studies also revealed higher estimates of postpartum depression for Asian and OPI women.[21,30,31] However, other studies of postpartum depression for different ethnic groups showed varying results,[14,32,33] which might be due to contrasting cultural factors, type of data collection instruments, and methodologies used in assessing the prevalence of postpartum depression.

The strongest predictor for SRPDS and possible SRPDS was the experience of SLEs, where relocation, relationship, and financial stress were the most commonly reported stressors for women in Hawai‘i. An incremental, upward trend was found for SLEs, with women who experienced 6 or more stressors to be almost 6 times as likely to have SRPDS compared to those without any stressors. Experiencing multiple stressors might alter the individuals' appraisal of the stressors and perception of their capacity to cope, increase their feelings of lack of control,[34] and increase the likelihood of depressive symptoms.[35] This study provides valuable information of the impact of SLEs on postpartum depression and highlights the need of screening women for prenatal stressors.

In this study, similar effects were found for possible SRPDS, but of a smaller magnitude. Several different effects were found between SRPDS and possible SRPDS. For example, IPV was a significant risk factor for SRPDS but not for possible SRPDS, suggesting that women experiencing IPV were more likely to be in highest risk category for postpartum depression. Unintended pregnancy had significant effects for possible SRPDS but not for SRPDS, indicating women with unintended pregnancy were more likely to be in the intermediate risk category for postpartum depression. These findings demonstrated in this study revealed the importance of identifying women with intermediate risk, in addition to high-risk individuals, for further diagnostic evaluation.

To improve the health of mothers in Hawai‘i, it will be important to develop culturally appropriate programs that will increase awareness of postpartum depression. For example, the Healthy Mothers Healthy Babies Coalition of Hawaii (HMHB) provides resources and referral for maternal mental health counselling for postpartum depression.[36] There are depression treatment centers in Hawai‘i that provide screening and treatment programs for postpartum depression. The Hawai‘i Screening, Brief Intervention, and Referral to Treatment (SBIRT) Program is implemented across the state health system to include screening to identify risk for alcohol and substance abuse, and other behavioral health issues.[37] It aims to implement early screening and provide appropriate referral for early intervention. In addition, the Perinatal Support Services Program within the Maternal and Child Health Branch in the Hawai‘i State Department of Health requires screening for their clients for depression during pregnancy and referrals to appropriate services when needed.

There are limitations of this study and caution is necessary for the interpretation and application of the results. First, the data are from the PRAMS survey, where the source of information is all based on self-report. Response bias, ranging from simply misunderstanding the question to social desirability bias, often exist in self-report data.[38] Moreover, the data in this study was based on the years 2012-2015, where 2016 data was not available yet at the time and there was no data collection between 2017-2018 in Hawai‘i. Also, PRAMS survey measures for PPD symptoms are based on 2 screening questions, which cannot be used for diagnosis purposes. In addition, pregnancy intention might change over the 9-month period from conception through postpartum, which makes results related to unintended pregnancy difficult to interpret. Finally, race categorization from the Hawai‘i birth certificate data is limited to the single race category. A study showed that 33.4% of mothers in Hawai‘i reported more than one of the 5 federally-designated racial groups.[39] As multiracial category for a large proportion of mothers was not accounted for due to the single-race coding, the ability to generalize the results is limited.

Pregnancy and childbirth can be a very rewarding and exciting time, but it can also be a period of severe emotional stress. Educating prenatal care providers to evaluate for signs and symptoms of depression as well as other risk factors and improving knowledge of appropriate referral services is needed to help reduce the impact of postpartum depression symptoms in women. Increasing awareness of disparities in postpartum depression among the Asian and OPI populations and providing additional care, especially for those who experienced prenatal depression and SLEs, would be crucial to help reduce occurrence of postpartum depression symptoms.

Conflict of Interest

The authors declare that they have no conflict of interest.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Hawai‘i State Department of Health.

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A Pilot Study of Racial Differences in the Current Definition of Sarcopenia among Liver Transplant Candidates

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Abstract

Sarcopenia has been shown to have prognostic value in patients awaiting liver transplant. However, the presence of sarcopenia as a prognostic factor among patients awaiting liver transplantation might vary by race. This study aims to assess racial differences of sarcopenia in liver transplant candidates. This retrospective study assessed 102 patients on a liver transplantation list from 2012 to 2016 and used demographic and clinical variables to predict sarcopenia as measured by skeletal muscle index (SMI) and death or removal from the transplant list. Three racial groups were compared in the study: whites (n=34), Asians (n=50), and Native Hawaiians and Other Pacific Islanders (NHOPIs; n=18). NHOPI were more likely to have a body mass index (BMI) ≥ 30 and hepatitis B, and less likely to have alcoholic cirrhosis and sarcopenia than whites. Asians were more likely to have hepatitis B and less likely to have alcoholic cirrhosis and encephalopathy than other races. Using logistic regression, a BMI ≥ 30, multiple waiting list events, alcoholic cirrhosis, and sarcopenia were predictive of death or removal from the list. Although NHOPI had a higher BMI, they had less sarcopenia and similar frequency of ascites, encephalopathy, multiple waiting list events, and death or removal from the list compared to other races. Racial variations in muscle mass might have resulted in fewer NHOPI having sarcopenia as defined by the US criteria. Larger studies of patients with varying ethnicity are needed to develop a universally applicable definition of sarcopenia before we use this for liver transplant listing or allocation.

Keywords

Sarcopenia, Liver transplantation, Racial difference, Pacific Islanders, Chronic liver disease

Abbreviations

BMI = Body mass index
CT = Computed tomography
HCC = Hepatocellular carcinoma
HE = Hepatic encephalopathy
MELD = Model for End-Stage Liver Disease
MRI = Magnetic resonance imaging
NHOPIs = Native Hawaiians and Other Pacific Islanders
PMI = Psoas muscle index
SBP = Spontaneous bacterial peritonitis
SMI = Skeletal muscle index
UNOS = United Network for Organ Sharing

Introduction

Sarcopenia is a state of low muscle mass and has been increasingly been reported to have prognostic value in oncology treatments, aging, malnutrition, and many surgical procedures, especially liver transplantation.[1-5] Initially, sarcopenia was reported descriptively, but more recently, attempts have been made to quantify sarcopenia in order to monitor patient improvement or deterioration, and to standardize reporting between treatment centers and in medical literature. Two commonly-used sarcopenia metrics, skeletal muscle index (SMI) and psoas muscle index (PMI), are cross-sectional imaging measurements from computed tomography (CT) or magnetic resonance imaging (MRI). The indexes represent imaging measurements that have been normalized to patient height as baseline muscle mass differs by height.[6-11]

The use of sarcopenia metrics in liver transplant initially started with evaluation of patients with cirrhosis. Psoas muscle area and thickness were evaluated as predictors of mortality in cirrhosis in several studies.[12,13] Early reports suggested that the presence of sarcopenia had prognostic value for patients while on the liver transplant waiting list and on negative outcomes such as post-transplant complications and mortality, but specific measurements and cutoff values were not determined.[9,14] Two studies suggested that PMI was predictive of outcome after living donor liver transplantation,[8,15] and psoas muscle transversal diameter has been shown to be a predictor of mortality while on the waiting list.[16] A Model for End-Stage Liver Disease (MELD) score is calculated based on laboratory values (bilirubin, prothrombin time and creatinine) to predict 3-month mortality in patients with end-stage liver disease. Currently, the MELD-based score is used to allocate allograft for liver transplantations. The aforementioned studies prompted the addition of sarcopenia to the traditional MELD score creating a MELD-Sarcopenia score which has been shown to be a better predictor of mortality than MELD score alone as sarcopenia status is a non-laboratory assessment of patients' clinical status.[10]

Despite accumulating evidence supporting the importance of sarcopenia in liver transplant candidates, the majority of studies have been conducted with predominantly white populations. Studies that have quantified sarcopenia with cutoff values have only included a small proportion of Asian and Pacific Islander patients.[17] While studies have reported sarcopenia and mortality in Japanese patients, these were done in the setting of living donor liver transplant where lengthy times on a transplant waiting list were not a factor.[18] Consequently, data on deceased-donor liver transplantation in Asians and Native Hawaiians and Other Pacific Islanders (NHOPIs) are limited. As sarcopenia becomes increasingly important as a prognostic factor and allocation tool in liver transplantation, appropriate definition of sarcopenia in different races is crucial. Our hypothesis is that definition of sarcopenia among patients awaiting liver transplantation may

differ by race. This study aims to address potential differences in accepted sarcopenia metrics in liver transplant candidates from a racially-diverse population.

Methods

Study Design

This is a retrospective cohort study conducted at The Queen's Medical Center (QMC) in Honolulu, Hawai'i. QMC is the only transplant and dedicated liver center in the state of Hawai'i, and is the tertiary referral center for liver disease for US territories in the Pacific Rim including American Samoa, Guam, and Micronesia, and for foreign nationals from Asia seeking medical care in the US. This study was approved by the QMC's Research and Institutional Review Committee (RA-2019-029) and was conducted according to the international standards of Good Clinical Practice, applicable government regulations, and institutional research policies and procedures.

Patients

The study identified all patients who successfully completed a liver transplant evaluation and were placed on the United Network of Organ Sharing (UNOS) for liver transplantation during the time period between January 2012 and December 2016. This study included both patients with chronic liver disease and those with fulminant liver failure who required urgent transplant listing. This study collected data on demographics (age and sex), self-reported race (white, Asian, NHOPI, and other), anthropometrics (height, weight, and body mass index [BMI]), etiology of liver disease (hepatitis B, hepatitis C, alcoholic cirrhosis, and nonalcoholic steatohepatitis [NASH]), presence of hepatocellular carcinoma (HCC), MELD score, and dialysis status. Patients who reported being mixed race and had $\geq$50% Asian heritage were classified as Asian. NHOPIs who reported being mixed race, but had $<$50% of another race or ethnicity, were classified as NHOPIs. Whites did not include mixed race. A "significant waiting list event" was defined as having a variceal bleeding episode, ascites, spontaneous bacterial peritonitis (SBP), or hepatic encephalopathy. "Multiple waiting list events" were defined as having 5 or more hospital admission or emergency department visits for liver-related problems. Ascites included documented ascites on medical record, and those patients who required diuretic or paracenteses for management. Hepatic encephalopathy included only those patients receiving treatment for overt encephalopathy as no specific testing was done to identify minimal hepatic encephalopathy.

The team then selected those patients that had cross-sectional images either by CT or MRI done at our institution. Patients who had imaging only done at centers outside our institution were excluded from the analysis. A single investigator analyzed cross-sectional images after receiving training from a radiologist at QMC. Psoas muscle area at the umbilicus and total skeletal muscle area at L3 including paraspinal, psoas, rectus abdominis, transverse abdominis, and external and internal oblique muscles were manually measured by using Vitrea® Enterprise Suite (Vital, a Canon Group Company, Minnetonka, Minnesota).[8,17]

Definition of Sarcopenia

For this study, SMI (cm^2/m^2) was defined by area of total abdominal skeletal muscle (cm^2) divided by patients' height (m^2),[9-11,17,19] and PMI (cm^2/m^2) was defined by area of total psoas muscle (cm^2) divided by patients' height (m^2).[8] Cutoff values for sarcopenia were based upon previously reported studies. A multicenter study done by Carey, et al, (2017) defined sarcopenia by the SMI at L3 with cutoffs of 50 cm^2/m^2 for men and 39 cm^2/m^2 for women while on waiting list for liver transplantation.[17] This study utilized PMI at umbilicus with cutoffs of 6.87 cm^2/m^2 for men and 4.12 cm^2/m^2 for women.[8] The team then divided the cohort into 3 groups by race. This study included only whites, Asians, and NHOPIs as there were too few Hispanics and blacks for adequate comparison. Demographic information, etiology of disease, wait list events, and sarcopenia were compared by race. The primary outcome measures were liver transplant and death or removal from the waiting list; these outcomes were also compared by race. This study included only those patients who were removed from the list for a medical reason. Those patients who were removed because of non-compliance (eg, return to alcohol, drug use) were excluded from the study.

Statistical Analysis

The team performed statistical analysis with R version 3.4.1 (The R Foundation for Statistical Computing, Vienna, Austria) as well as EZR version 1.36 (Division of Hematology, Saitama Medical Center, Jichi Medical University, Japan).[20] Pearson's Chi-squared test was utilized to compare categorical variables among whites, Asians, and NHOPIs. Comparison for age and MELD score at the time of listing for waiting list were made using Kruskal-Wallis test. Odds ratios (OR) with 95% confidence interval (95% CI) for binary variables were obtained using Fisher's Exact Test for Count Data, using whites as the reference group.

Logistic regression was performed to identify the following predictors: (1) sarcopenia by SMI at L3, and (2) death or removal from the waiting list. To predict sarcopenia, we examined baseline characteristics (age, sex, and race), etiologies of chronic liver disease, waiting list complications, and presence of HCC. To predict death or removal from waiting list, we excluded patients who were removed for nonmedical reasons (eg, return to alcohol or other substance abuse, inadequate caregiver support or other evidence of noncompliance) as these did not necessarily represent a deterioration in their medical condition that would warrant removal from the list. Baseline characteristics, etiologies for chronic liver disease, waiting list complications, and sarcopenia defined by SMI at L3 were included as variables in the model. $P < .05$ was considered as statistically significant for both analyses.

Results

During the period between January 2012 to December 2016, 137 patients underwent formal liver transplant evaluation in anticipation of being placed on the transplant waiting list. Many more patients with end-stage liver disease were seen by the hepatologists and surgeons, but were determined to be unsuitable for formal evaluation for various reasons including active substance abuse, extensive hepatocellular cancer or severe cardiovascular disease. Among these 137 patients, 35 (26%) of patients were excluded from analysis for following reasons: 30 (21.9%) of patients did not have cross-sectional images at our medical center, and 5 (4%) had a race other than Asian, white, or NHOPI. In this cohort of 102 patients, the mean age was 55.9 years (standard deviation: 8.83). Fifty-six percent of patients were men, and the race distribution was whites (n=34, 33%), Asians (n=50, 49%), and NHOPIs (n=18, 18%). Etiology of disease was distributed as follows: 16 (16%) of patients had hepatitis B, 36 (36%) had hepatitis C, 28 (28%) had alcoholic cirrhosis, and 15 (15%) had NASH. Other etiologies included autoimmune hepatitis, Budd-Chiari syndrome, polycystic liver disease, primary biliary cholangitis, drug-induced liver injury, and cryptogenic cirrhosis. It is important to note that some patients had more than one etiology of chronic liver disease. HCC was present in 35 (34%) of patients. In terms of outcome, 19 (19%) of patients had multiple waiting list events, 35 (34%) died or were removed from the transplant waiting list, and 57 (56%) underwent liver transplantation. Sarcopenia was identified in 56 (55%) of patients when measured by SMI at L3, and in 10 (13%) of patients when measured by PMI at the umbilicus.

Characteristics by race are summarized in the Tables 1 and 2. We did not observe differences among the 3 races in terms of sex, age, and mean listing MELD score. NHOPIs were much more likely to be obese (78%) compared to whites (27%) and Asians (28%). Asians and NHOPIs (22%, respectively) were more likely to have hepatitis B than whites (3%). Whites were more likely to have alcoholic liver disease (47%) than Asians (18%) and NHOPIs (17%).

A lower proportion of Asians had hepatic encephalopathy compared to whites (OR: 0.31, 95% CI: 0.10-0.88). However, there was no difference between NHOPIs and whites (OR: 0.49, 95% CI: 0.12-2.02).

With respect to sarcopenia, PMI at umbilicus in 76 patients showed no significant difference by race. In analysis of 101 patients for whom for sarcopenia by SMI at L3 was available, NHOPIs (17%) were less likely to have sarcopenia than both whites (70%) and Asians (60%; $P < .001$); however, there was no difference between whites and Asians ($P = .49$). Table 3 summarizes the detailed results of logistic regression regarding predictors of sarcopenia analysis by SMI at L3. Importantly, HCC was a statistically significant positive predictor of sarcopenia, and BMI ≥30, hepatitis C, NASH, and NHOPI were negative predictors. However, age ≥60, sex, ascites, variceal bleeding, significant waiting list events, hepatic encephalopathy, SBP, hemodialysis status, alcoholic liver disease, hepatitis B, and being Asian did not show significant differences compared to whites.

Among the 92 patients in the predictors of death or removal from waiting list analysis, BMI ≥30 (OR: 27.9, 95% CI: 1.05-739) and sarcopenia by SMI at L3 (OR: 84.6, 95% CI: 2.12-3380) were positively associated with death or removal from the waiting list (Table 4). Multiple waiting list events (OR: 0.139, 95% CI: 0.02-0.93) and alcoholic liver disease (OR: 0.05, 95% CI: 0.005-0.48) were negatively associated with death or removal from the waiting list. There was no difference for death or removal from the waiting list among 3 races by Chi-square test (whites: 33%, Asians: 28%, NHOPIs: 13%, $P = .36$, *data not shown*). Age, sex, MELD score at listing, ascites, variceal bleeding, hepatic encephalopathy, SBP, fulminant liver failure, hemodialysis status, HCC, hepatitis B and C, and NASH were not associated with death or removal from the waiting list.

Table 1. Patient Characteristics, Chronic Liver Disease Etiologies, Waiting List Complications, Death or Removal from Waiting List, Transplant Status, and Sarcopenia Status by Race

	White n=34 n (%)[a]	Asian n=50 n (%)	NHOPI n=18 n (%)	*P*-value
Female	14 (41)	23 (46)	8 (44)	.91
Mean Age (SD)[a]	56.1 (8)	56.8 (9)	53.2 (11)	.50
Obesity, BMI≥30	9 (27)	14 (28)	14 (78)	<.001
Ascites	26 (77)	34 (68)	13 (72)	.70
Hepatic encephalopathy	26 (77)	25 (50)	11 (61)	.051
Variceal bleeding	11 (32)	13 (26)	3 (17)	.47
Mean MELD (SD)[a]	18.9 (8)	17.5 (8)	16.9 (8)	.70
Hepatitis B	1 (3)	11 (22)	4 (22)	.044
Hepatitis C	15 (44)	15 (30)	6 (33)	.41
Alcoholic liver disease	16 (47)	9 (18)	3 (17)	.007
NASH	2 (6)	10 (20)	3 (17)	.188
Liver cancer	9 (27)	18 (36)	8 (44)	.40
Significant waiting list event	9 (27)	6 (12)	4 (22)	.23
Death or removal on waiting list	14 (41)	16 (32)	5 (28)	.56
Transplanted	14 (41)	31 (62)	12 (67)	.101
Sarcopenia by SMI at L3	23 (70), n=33[c]	30 (60)	3 (17)	<.001[b]
Sarcopenia by PMI at umbilicus	2 (8), n=24[c]	6 (15), n=39[c]	2 (15), n=13[c]	.70

Abbreviations: NHOPI, Native Hawaiian and Other Pacific Islander; SD, Standard deviation; BMI, Body mass index; MELD, Model for End-Stage Liver Disease; NASH, Non-alcoholic steatohepatitis; SMI, Skeletal muscle index; PMI, Psoas muscle index.
[a] Count and percent presented except where denoted by the asterisk.
[b] Subgroup analysis showed there was no difference between whites and Asians (*P*=.49).
[c] n is number of patients. These differences are based on the availability of cross-sectional images.

Table 2. Odds Ratios for Patient Characteristics, Chronic Liver Disease Etiologies, and Waiting List Complications among Asians and Native Hawaiians and Other Pacific Islanders Compared to Whites

	Asian OR (95% CI)	NHOPI OR (95% CI)
Female	1.21 (0.46-3.23)	1.14 (0.31-4.19)
Obesity, BMI ≥30	1.08 (0.37-3.30)	9.23 (2.18-49.23)[a]
Ascites	0.66 (0.21-1.93)	0.80 (0.19-3.78)
Hepatic encephalopathy	0.31 (0.10-0.88)[a]	0.49 (0.12-2.02)
Variceal bleeding	0.74 (0.26-2.15)	0.43 (0.07-1.99)
Hepatitis B	9.13 (1.21-411.71)[a]	9.43 (0.97-92.07)
Hepatitis C	0.55 (0.20-1.49)	0.64 (0.16-2.39)
Alcoholic liver disease	0.25 (0.81-0.74)[a]	0.23 (0.05-0.92)[a]
NASH	3.94 (0.76-39.51)	3.12 (0.32-41.04)
Liver cancer	1.55 (0.55-4.64)	2.19 (0.56-8.67)
Multiple waiting list events	0.38 (0.01-1.37)	0.80 (0.15-3.55)
Death or removal on waiting list	0.68 (0.25-1.84)	0.56 (0.13-2.17)
Transplanted	2.31 (0.88-6.25)	0.36 (0.09-1.33)
Sarcopenia by SMI at L3	0.66 (0.23-1.81)	0.09 (0.01-0.42)[a]
Sarcopenia by PMI at umbilicus	1.98 (0.32-21.80)	0.51 (0.03-7.92)

Abbreviations: NHOPI, Native Hawaiian and Other Pacific Islander; OR, Odds ratio; 95% CI, 95% confidence interval; BMI, Body mass index; NASH, Non-alcoholic steatohepatitis; SMI, Skeletal muscle index; PMI, Psoas muscle index.
[a] P<.05

Table 3. Logistic Regression for Sarcopenia by SMI at L3 by Patient Characteristics, Chronic Liver Disease Etiologies, and Waiting List Complications

	OR	95% CI	*P*-value
Overall	12.0	1.22-118	.033
Age ≥ 60	2.02	0.42-9.61	.38
Sex	0.25	0.05-1.28	.096
BMI ≥ 30	0.01	0.002-0.09	<.001
Ascites	0.975	0.16-5.90	.98
Variceal bleeding	0.87	0.16-4.50	.86
Multiple waiting list events	1.69	0.19-15.3	.64
Hepatic encephalopathy	5.83	0.98-34.9	.053
SBP	0.63	0.11-3.72	.61
Hemodialysis status	2.50	0.10-63.8	.58
HCC	13.9	1.33-145	.028
Alcoholic liver disease	0.89	0.16-5.06	.90
Hepatitis B	1.02	0.11-9.35	.98
Hepatitis C	0.08	0.009-0.76	.027
NASH	0.04	0.003-0.540	.016
Asian	0.46	0.10-2.19	.33
NHOPI	0.08	0.009-0.81	.032

Abbreviations: OR, Odds ratio; 95% CI, 95% confidence interval; BMI, Body mass index; SBP, Spontaneous bacterial peritonitis; HCC, Hepatocellular carcinoma; NASH, Non-alcoholic steatohepatitis; NHOPI, Native Hawaiian and Other Pacific Islander.
Area under the curve of a receiver operating characteristics curve for this model was 0.937 (95% CI: 0.885-0.989).

Table 4. Logistic Regression for Death or Removal on Liver Transplant Waiting List for Patient Characteristics, Chronic Liver Disease Etiologies, and Waiting List Complications

	OR	95% CI	*P*-value
Overall	0.00002	0.00000001-0.05	<.01
Age≥60	1.08	0.97-1.20	.168
Sex	0.216	0.04-1.21	.081
BMI≥30	27.9	1.05-739	.047
MELD score at wait listing	1.07	0.95-1.20	.27
Ascites	5.55	0.76-40.7	.092
Variceal bleeding	0.834	0.16-4.36	.83
Multiple waiting list events	0.139	0.02-0.93	.042
Hepatic encephalopathy	3.83	0.81-18.1	.090
SBP	0.456	0.08-2.75	.39
Hemodialysis status	2.99	0.15-61.5	.48
Fulminant liver failure	674000	0-infinite	.99
HCC	1.49	0.18-12.7	.72
Alcoholic liver disease	0.05	0.005-0.48	.010
Hepatitis B	0.701	0.10-4.93	.72
Hepatitis C	0.558	0.05-6.21	.64
NASH	0.453	0.05-4.41	.50
Sarcopenia by SMI at L3	84.6	2.12-3380	.018

Abbreviations: OR, Odds ratio; 95% CI, 95% confidence interval; BMI, Body mass index; MELD; Model for End-Stage Liver Disease; SBP, Spontaneous bacterial peritonitis; HCC, Hepatocellular carcinoma; NASH, Non-alcoholic steatohepatitis; SMI, Skeletal muscle index.
The area under the curve of a receiver operating characteristics curve for this model was 0.873 (95% CI: 0.793-0.953).

Discussion

Although the term "sarcopenia" has been used with increasing frequency in the literature, there is no universally accepted metric with well-tested cutoff values for sarcopenia. While groups have attempted to define sarcopenia by sex,[8,17] there is a paucity of data on whether various cutoff values will be applicable to all races. Rush, et al, (2009) in an analysis of 933 Europeans, Asian Indians, and Pacific Islanders showed that racial differences in fat distribution, muscularity, bone mass, and leg length suggest universal BMI cutoffs may not be appropriate.[21] This conclusion also suggests that racial differences in muscle mass could affect the definition of sarcopenia. Studies done in Asia have delineated different cutoffs for SMI than the US-based studies.[17,22,23] A UK-based study of 600 hemodialysis patients consisting of 281 whites, 167 Asians, 149 blacks, and 3 others noted Asians to have a greater prevalence of sarcopenia than whites, though this study utilized appendicular skeletal muscle mass rather than SMI.[24] There may even be regional differences in baseline muscle mass as suggested by a group who described this phenomenon in various parts of Mexico.[25] In our study with a large proportion of Asians and NHOPIs, there was no difference in the incidence of sarcopenia between Asians and

whites, but NHOPIs were less likely to be sarcopenic with the cutoffs for SMI as defined by Carey, et al, (2017).[17] Although we attempted to define cutoffs for sarcopenia using the receiver operating curve, small sample size limited the accuracy of area under the curve. Further, the definition of sarcopenia by race is important, especially if sarcopenia will be used as a tool for determining candidacy or allocation for liver transplantation in the future. Interestingly, a lower proportion of whites received a liver transplant (whites: 41%, Asians: 62%, and NHOPIs: 66%), yet this was not statistically significant (*P*=.10).

While BMI is commonly used to define obesity, it is not reliable for estimating muscle mass. Increasing numbers of patients are found to have "sarcopenic obesity" or the presence of low muscle mass and high fat mass. This finding has clinical significance in multiple disease conditions as sarcopenic obesity is associated with an increased the risk of falls in women[26] and poor outcomes in cardiovascular conditions,[27,28] pancreatic cancer surgery,[29] and gastric cancer surgery.[30] With respect to liver disease, sarcopenic obesity was associated with worse survival in those with cirrhosis,[31] and obesity was a predictor of sarcopenia in pretransplant NASH patients.[32] NHOPIs are known to have a high prevalence of obesity, as 8 of the top 10 most obese countries in the world are Pacific Islands where more than 90% of the population has a BMI above 30.[33] However, it is important to note that BMI definitions for being overweight and obesity may differ by race.[21] In this study, NHOPIs had a much higher prevalence of obesity, but were less likely to be sarcopenic according to the current definition which was calculated in a Caucasian-dominant population.[17] Consequently, it is unclear if NHOPIs truly have less sarcopenia or if racial variations in muscle mass simply result in fewer NHOPIs having sarcopenia as defined by US standards.

Sarcopenia has been shown to be intimately associated with complications of cirrhosis, especially hepatic encephalopathy due to the role of muscle in ammonia detoxification.[34] A recent meta-analysis of 1795 patients with cirrhosis in 6 studies showed a significant association between sarcopenia and hepatic encephalopathy. However, the 6 studies that were analyzed had variable definitions of sarcopenia, 3 different ways of assessing hepatic encephalopathy and were done in different cohorts of patients with cirrhosis (inpatients, liver transplant candidates, and patients awaiting transjugular intrahepatic portasystemic shunts). They did not find any association between ammonia level and sarcopenia.[35] In this study, NHOPIs were less likely to have sarcopenia than Asians or whites but had a similar incidence of hepatic encephalopathy. As a result, there was a higher proportion of NHOPIs without sarcopenia who developed hepatic encephalopathy. It is unclear if NHOPIs inherently have more encephalopathy or if higher baseline muscle mass potentially misclassifies them non-sarcopenic with the current definition. Perhaps the loss of muscle mass over time may be a more relevant indicator of sarcopenia and disability.

Differences in sarcopenia by disease etiology may potentially contribute to ethnic variations. Although this has not been explored definitively, in a study of 265 patients with cirrhosis being evaluated for liver transplant, 47% of those with alcoholic liver disease had sarcopenia compared to 22% of those with NASH.[36] In addition, patients with cirrhosis and lower skeletal muscle attenuation due to fat deposition have been shown to have increased the risk of developing HCC.[37] Hawai'i has a high burden of HCC and 34% of state transplant candidates carry this diagnosis. While there were differences in disease etiology by race with more alcoholic liver disease seen in whites and more hepatitis B present in Asians and NHOPIs, there was no difference in the incidence of hepatitis C or HCC between the races. Despite differences in disease etiology, the presence of HCC was the strongest predictor of sarcopenia (OR: 13.9, 95% CI: 1.33-145); meanwhile, NHOPIs, and those with obesity, NASH, and hepatitis C were independently associated with decreased risk of sarcopenia.

The presence of sarcopenia has been associated with complications in cirrhosis, waiting list mortality, and poor outcome after liver transplant. However, this is controversial as some have reported that sarcopenia did not increase mortality[38,39] and that frailty may be more important than sarcopenia.[36] Furthermore, the definitions for sarcopenia have varied in these studies. Ebadi, et al, (2018) suggested that PMI had poor performance in predicting waitlist mortality in comparison to SMI.[40] This may be because the psoas muscle represents only a portion of the total muscle mass at the level of evaluation and may be susceptible for change in non-hepatic disease conditions.[40,41] Even the use of a MELD-Sarcopenia score has been debated as some have purported that this is superior to MELD score at predicting waitlist and post-operative mortality,[10] while others suggest that it had limited value in predicting waiting list mortality.[40] This study showed that while alcoholic liver disease (OR: 0.05, 95% CI: 0.005-0.48), obesity (OR: 27.9, 95% CI: 1.05-739) and multiple waiting list events (OR: 0.139, 95% CI: 0.02-0.93) were important risk factors, sarcopenia (OR: 84.6, 95% CI: 2.12-3380) was the strongest predictor of death or removal from the waiting list.

This study is limited in that it occurred in a single facility study and was performed retrospectively at a relatively low-volume transplant center. The sample size was also limited because we excluded patients without cross-sectional imaging at our center in order to minimize differences in imaging equipment and technique and to keep the measurements as uniform as possible. We also excluded patients who were of black race or Hispanic ethnicity as these groups were too small for adequate comparison. Finally, sarcopenia was measured manually by a single investigator instead of a computer-based algorithm with multiple investigators. Although training in measuring skeletal muscle area was provided by a radiologist, the investigator did not have formal clinical radiology training. These factors may have potentially overestimated the presence of sarcopenia.

In conclusion, this study is similar to many studies in that we show that HCC is associated with sarcopenia and sarcopenia is associated with death and removal from the transplant waiting list. However, there are distinct differences in the prevalence of sarcopenia by race using conventional definitions. NHOPIs had much less sarcopenia and yet had similar frequency of complications of ascites, hepatic encephalopathy, hospital admissions, multiple waiting list events and removal/death on the waiting list compared to whites and Asians. Perhaps a higher baseline muscle mass in NHOPIs accounts for this difference. Larger studies of patients with varying ethnicities are needed to develop a universally applicable definition of sarcopenia before we use this for liver transplant listing and allocation.

Conflict of Interest

None of the authors identify a conflict of interest.

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ʻO ka ʻŌlelo Ke Ola (Language Is Life): Language Access and the Office of Language Access (OLA)

Aphirak Bamrungruan JD

Insights in Public Health is a monthly solicited column from the public health community and is coordinated by HJH&SW Contributing Editor Tetine L. Sentell PhD from the Office of Public Health Studies at the University of Hawai'i at Mānoa and Contributing Editor Michele N. Nakata JD from the Hawai'i Department of Health.

Introduction

Hawai'i is one of the most culturally diverse states with 1 of the highest proportions of non-English speakers in the nation. According to the US Census Bureau, Hawai'i's total population aged 5 years and older is 1 337 965 with roughly 344 880 (25.8%) speaking a language other than English at home[5] and 152 618 (11.4%) indicating that they speak English "less than very well,"[6] classifying them as limited English proficient (LEP).

Under Hawai'i's Language Access Law,[7] the term LEP refers to an individual who, on account of national origin, does not speak English as the person's primary language and self identifies as having a limited ability to read, write, speak, or understand the English language. Hawai'i ranks sixth in the nation per capita for LEP.[8] The top 10 languages spoken by individuals with LEP in Hawai'i are: Ilocano, Tagalog, Japanese, Chinese, Korean, Spanish, Vietnamese, Samoan, Marshallese, and Trukese (Chuukese).[9]

The lack of English proficiency has a strong impact on people's economic and social activities, health literacy and wellness, access to education, employment, and important public assistance, benefits, programs and services. According to the Hawai'i Department of Business, Economic Development and Tourism (DBEDT), 56.7% of all non-English speakers have a less than high school educational level.[10] Additionally, the median earnings of non-English speakers are lower than English-only speakers.[11] Language access continues to be a significant barrier for individuals with LEP both educationally and economically in accessing important benefits or services, understanding and exercising important rights, complying with applicable responsibilities, and understanding complex information provided by government and government-funded programs and activities.

Legal Mandates for Language Access

Language access is a civil right. This right derives from Title VI of the Civil Rights Act of 1964 which provides that, "[n]o person in the United States shall, on the ground of race, color, or national origin, be excluded from participation in, be denied the benefits of, or be subjected to discrimination under any program or activity receiving Federal financial assistance."[12] This means that any government agency receiving federal financial assistance—either directly or indirectly—is required to comply with Title VI.

On August 11, 2000, President Clinton signed Executive Order No. 13166, entitled "Improving Access to Services for Persons with Limited English Proficiency" (EO 13166) requiring each federal agency to prepare a plan to improve access to its federally conducted programs and activities by eligible persons with LEP,[13] consistent with the compliance standards set forth by the US Department of Justice (DOJ) LEP guidance[14] issued on the same day. EO 13166 requires recipients of federal financial assistance to ensure that persons with LEP have "meaningful access" to their programs and services. Meaningful access means "language assistance that results in accurate, timely, and effective communication at no cost to the LEP individual." For individuals with LEP, meaningful access denotes "access that is not significantly restricted, delayed or inferior as compared to programs or activities provided to English proficient individuals."

While the legal mandates under Title VI and EO 13166 provide language access to any program or activity receiving federal financial assistance, there are many programs and activities in the State of Hawai'i that are operated solely on state funds. As a result, the 2006 Hawai'i State Legislature passed the Hawai'i Language Access Law (codified as chapter 321C, Hawai'i Revised Statutes) to address affirmatively, on account of national origin, the language access needs of LEP persons.[15] This made Hawai'i the first state in the nation to pass a comprehensive language access law. Chapter 321C, HRS, applies to all state agencies and covered entities.

The key requirements of the Hawai'i Language Access Law

are the provision of oral and written language services, free of charge, to persons with LEP.[16] Under Hawai‘i Language Access, oral language services means the free provision of oral information necessary to enable persons with LEP to access or participate in services, programs, or activities of a state agency or covered entity.[17] This type of service is commonly known as an interpretation service. Written language services mean the free provision of written information necessary to enable persons with LEP to access or participate in services, programs, or activities of a state agency or covered entity,[13] commonly known as a translation service.

What Is the Office of Language Access?

The Office of Language Access (OLA) was established to implement the Hawai‘i Language Access Law to ensure meaningful access to services, programs, and activities offered by the executive, legislative, and judicial branches of state government, including departments, offices, commissions, boards, or other agencies, and all covered entities for persons with LEP.[14] OLA's overall purpose is to address affirmatively the language access needs of individuals with LEP by providing oversight and central coordination to the executive, legislative, and judicial branches of Hawai‘i's state government, and technical assistance to state-funded agencies in developing and implementing of language access requirements as required by law. OLA also works to establish statewide goals and objectives relating to improving access by individuals with LEP to programs, services, and activities of state and state-funded agencies, monitors and reviews state agencies for compliance, and provides language access complaint resolution.

OLA is headed by the executive director, who is appointed by the governor.[15] The executive director coordinates, supervises, and oversees the work, activities, and programs of OLA. The Hawai‘i Language Access Law also established a 17-member Language Access Advisory Council ("LAAC") which assists the executive director by providing input on: implementation and compliance with the Hawai‘i language access laws; the quality of oral and written language services provided under the law; and the adequacy of a state agency or covered entity's dissemination and training of its employees likely to have contact with persons with LEP, its policies and procedures for language services, its competency in working effectively with in-person and telephone interpreters, and its understanding of the dynamics of interpretation between clients, providers, and interpreters.[16]

What Does OLA Do?

OLA is comprised of 2 organizational segments — Monitoring and Compliance (MC) and the Language Access Resource Center (LARC). MC is responsible for providing technical assistance to state-funded agencies in the development of their language access plans and on matters related to the provision of language access assistance to persons with LEP. The primary functions of MC include: conducting research and analysis on questions regarding the application and implementation of state and federal laws governing persons with LEP; formulating and implementing compliance monitoring strategies; conducting on- and off-site visits; reviewing and evaluating plans, data, reports, and other related information; providing feedback on implementation of language access plans; and investigating, making recommendations, and tracking the resolutions of language access complaints.

LARC is responsible for addressing the need for a centralized resource that meets the specific language service needs of government agencies and state-funded entities. The major tasks of LARC are: maintaining and updating the online roster of interpreters and translators; conducting outreach activities to encourage interested individuals to become interpreters and translators; producing and translating outreach and other educational materials; establishing a training program for state and state-funded agencies on how to utilize and work with interpreters; establishing a training program for interpreters and translators to improve their skills; identifying a process to test and certify interpreters and translators and promoting use of the process to ensure the quality and accuracy of their services; and establishing an online library of resources on language access.

Collaborations Between OLA and Other Agencies

In 2017, OLA began a collaboration with the Office of Equality and Access to the Courts (OEAC), the Hawai‘i State Judiciary, and the Hawai‘i Language Roadmap (Roadmap) at the University of Hawai‘i at Mānoa to focus on developing shared understandings and best practices for language use that addresses language access for those with LEP, use of bilingual/multilingual skills on the job, and certification of language proficiency. In September 2017, OLA, in collaboration with Roadmap, hosted a symposium at the University of Hawai‘i East-West Center titled, "The Multilingual Match: Meeting the Needs of Hawai‘i's Workforce through Career-based Pathways to Linguistic Proficiency." The purpose of this symposium was to identify and address the needs, challenges, and pathways of ensuring quality and accurate language services for those in need.

Following this successful symposium, OLA partnered with Roadmap and the Hawai‘i Department of Education (DOE) to organize the State of Hawai‘i's first Multilingual Career Development Day in March 2018. This event raised student awareness about the value of language skills and encouraged the continued development of language skills when using these in their daily life, in their communities, and in our local workforce. The second Multilingual Career Development Day was held in April 2019 and about 100 students from the DOE and the University of Hawai‘i system represented the Class of 2019 Seal of Biliteracy candidates. The Seal of Biliteracy is

an award given by a school, district, or state in recognition of students who have studied and attained proficiency in 2 or more languages by high school graduation.[17] OLA and its partners are planning to host the next Multilingual Career Development Day in Spring 2020.

In November 2019, OLA again partnered with Roadmap to host the Symposium on Building a Multilingual Workforce for Hawai‘i at the University of Hawai‘i at Mānoa campus. The symposium brought together leaders from education, business, government, and non-profit organizations and provided participants with an opportunity to talk story about our state's multilingual heritage, how it strengthens our workforce, and how it presents challenges in our daily workplace interaction.

Since 2018, OLA has also partnered with the Hawai‘i State Judiciary to conduct the annual state-wide Basic Orientation Workshops, which are held as 3 sessions on Oahu and 4 sessions on other islands per year, for interested language interpreters. The purpose of these workshops is to provide training to increase the number and availability of qualified language interpreters in order to advance meaningful access for persons with LEP at judicial hearings. The next workshop will be held at the Hawai‘i Supreme Court in September 2020.

In 2020, OLA and the Conference Planning Committee will be holding the 2020 Hawai‘i Conference on Language in August 2020. This conference will provide an opportunity for participants to attend informational sessions presented by subject matter experts on various language access topics. An audience of 250 people, comprising state and local government personnel, service providers from the non-profit and private sectors, medical institutions, social services agencies, cultural organizations, community advocates/leaders, interpreters, translators, and the limited-English proficient community is anticipated. These collaborations of the Executive Branch through OLA with the Judiciary Branch through OEAC and educational departments through Roadmap and DOE reflect the growing recognition of the language access needs for our multilingual population.

Conclusion

Although the State of Hawai‘i passed the Language Access Law in 2006, Hawai‘i's LEP community continues to be challenged both educationally and economically in accessing and participating in social, health, educational, and employment opportunities due to their limited English proficiency. OLA believes language should cease to be a barrier in Hawai‘i and instead be used as a tool to connect people together. Providing language access is a shared responsibility for everyone in the Aloha State. Ensuring Hawai‘i's LEP community meaningful access will strengthen their connections in all aspects of local life.

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University of Hawaiʻi Cancer Center: Collaboration Through Partnership with the National Cancer Institute

Jared D. Acoba MD and Jeffrey L. Berenberg MD

The Cancer Center Connection is a standing column from the University of Hawai'i Cancer Center and is edited by HJM&PH Contributing Editor Shane Y. Morita MD, PhD.

The University of Hawaiʻi Cancer Center (UHCC) is the only National Cancer Institute (NCI)-designated Cancer Research Center serving Hawaiʻi and the Pacific. This past year, UHCC successfully attained renewal of its Minority/Underserved NCI Community Oncology Research Program (M/U NCORP) grant. The NCORP and its predecessor, the Minority Based-Community Clinical Oncology Program (MB-CCOP) have provided funding to support cancer clinical trials infrastructure in the state of Hawaiʻi since 1994. We will describe the history of the NCI-sponsored clinical trial program, specifically how it relates to Hawaiʻi. We will also provide numerous examples of clinical trials that are particularly relevant to the people of Hawaiʻi that have been made available through the CCOP and NCORP mechanisms.

The History of NCI-sponsored Cancer Clinical Trials at Community Cancer Centers

Recognizing that 85% of cancer patients are treated in the community setting, the NCI established the Community Clinical Oncology Program (CCOP) to provide opportunity for participation on NCI-sponsored clinical trials in the community and to help increase accrual to cancer research studies nationwide. To ensure that clinical trial participation was available to patients of racial minority groups, the NCI created a parallel program of centers that care for a large portion of racial minority patients called the Minority Based CCOP (MB-CCOP). The University of Hawaiʻi Cancer Center was awarded its first MB-CCOP grant in 1994 under the direction of Dr. Brian Issell.

The NCI created the National Community Cancer Centers Program (NCCCP) in 2007 to focus on improving the quality of cancer care delivered at community cancer clinics throughout the United States (US). The Queen's Medical Center was selected as an NCCCP participant in 2010 with Dr. Paul Morris serving as principal investigator (PI).

In 2014, the NCI created the NCI Community Oncology Research Program (NCORP) that combined the research focus of the CCOP and the cancer care delivery and health care disparities emphasis of the NCCCP. The University of Hawaiʻi was one of the first 12 sites to be awarded a Minority/Underserved NCORP (M/U NCORP) grant with Dr. Jeffrey Berenberg as contact PI. Dr. Morris served as co-PI in charge of overseeing Cancer Care Delivery Research. The most recent round of NCORP grants were awarded this year to 53 sites (including UH and 13 other M/U NCORP sites) and covers patients in 44 states, Puerto Rico, and Guam.

In its initial grant period from 2014-2019, the NCORP program has succeeded in enrolling more than 37000 patients in cancer studies across 49 sites. These include studies involving all aspects of cancer medicine: screening, prevention, symptom control, cancer care delivery, and treatment trials. Achievements included addressing clinical problems such as chemotherapy induced nausea and vomiting (CINV). A study of olanzapine to prevent CINV in patients treated at the Hawaiʻi M/U NCORP and other NCORP sites demonstrated that olanzapine significantly reduced the risk of CINV and altered the standard of care.

The studies presented below provide examples of the work done at the UH Cancer Center.

NCI Cancer Clinical Trials in Hawaiʻi and Soon Guam

The Hawaiʻi M/U NCORP provides the financial and personnel infrastructure to facilitate cancer clinical trial participation in Hawaiʻi, supporting over two-thirds of the cancer patients in the state each year. The 6-year $8 million grant awarded to the Hawaiʻi M/U NCORP provides the people of Hawaiʻi access to NCI sponsored cancer clinical trials. Dr. Berenberg is the contact PI for the NCORP grant for this most recent award cycle, and Drs. Jared Acoba and Randall Holcombe serve as Multiple-PIs.

To deliver clinical trial opportunities across the state, the Hawaiʻi M/U NCORP partners with large private hospital systems including The Queen's Medical Center, Hawaiʻi Pacific Health,

Kuakini Medical Center, as well as Tripler Army Medical Center and the largest private radiation and medical oncology practices on O'ahu, the Cancer Center of Hawai'i, Hawai'i Cancer Care, and Hawai'i Oncology Incorporated. In addition, the new grant provides the opportunity for patients in Guam to have access to the NCI clinical trials for the first time. This effort is led by Dr. Berenberg and Virginia McMahon in Hawai'i and Dr. Samir Ambrale in Guam. For patients in Hawai'i and Guam, the importance of having clinical trial opportunities close to home cannot be underscored enough, as the next nearest site for cancer clinical trials is nearly 2500 miles away.

Trials for People at Risk for Cancer, Cancer Patients, and Cancer Survivors in Hawai'i

There are many examples of NCORP clinical trials that are specifically applicable to the people of Hawai'i. Breast cancer is the most common malignancy among women in Hawai'i. Screening mammograms help to detect breast cancer at an early stage when it is easiest to treat. Recently, a newer imaging technique, digital breast tomosynthesis, has become available in Hawai'i. Retrospective data suggest that, compared with standard digital mammography, tomosynthesis offers better detection of invasive breast cancers and leads to fewer additional imaging studies for false-positives (lesions that appear to be cancer but are actually benign).[1] However, this benefit has not yet been confirmed in a prospective study, and tomosynthesis does come with a higher financial cost as well as a modest increase in radiation dose.[2] The national Tomosynthesis Mammographic Imaging Screening Trial (TMIST) is a prospective randomized study that will compare the utility of digital mammography versus tomosynthesis in detecting advanced breast cancers. TMIST is open in Hawai'i through the Hawai'i M/U NCORP as well as The Queens Medical Center and allows women in Hawai'i to participate in this potentially paradigm-changing study to determine the most effective breast cancer screening test. UH is partnering with the NCI to increase participation of Micronesian women in Hawai'i.

Hawai'i has one of the highest rates of cholangiocarcinoma in the US, and this has led the Hawai'i State Legislature to grant $350,000 to the UH Cancer Center to investigate cancers in the hepatobiliary tract such as cholangiocarcinoma. Many patients with cholangiocarcinoma present with advanced disease for which chemotherapy is the optimal treatment option. SWOG 1815 is an NCORP clinical trial comparing the standard chemotherapy regimen of cisplatin and gemcitabine with the novel combination of cisplatin, gemcitabine, and nab-paclitaxel, a combination that has displayed an excellent response rate and will hopefully improve survival. The Hawai'i M/U NCORP has accrued the most patients to this study thus far among all community cancer centers in the US.[3]

Other clinical trials available through the NCORP that are particularly relevant to the population of the state include studies on older adults and obese patients. Hawai'i ranks as the 16th oldest state with 13.3% of the population over 65 years of age. The Hawai'i M/U NCORP opened a clinical trial, URCC13059, that aims to decrease the morbidity of older adults undergoing cancer treatment through use of a modified geriatric assessment. Native Hawaiians have an increased cancer mortality rate attributed in part to higher rates of obesity and hypertension, as well as other genetic and life-style risk factors. In response, A011401 (BWEL) trial was opened to address this problem. This trial is a 2-year diet and life-style modification study to improve breast cancer outcomes among obese women.

NCORP participation has also made trials available to cancer survivors. For example, one trial aims to improve quality of life for head and neck cancer survivors, and another trial aims to decrease the risk of cancer recurrence for colon cancer survivors in Hawai'i. Head and neck cancer survivors often suffer from radiation-induced xerostomia – persistent dry mouth as a consequence of their radiation therapy. These patients may be eligible for an NCORP study, sponsored by the Wake Forest research base, that offers acupuncture as a therapy to increase saliva production. In part because acupuncture is a widely accepted treatment among the people of this state, the Hawai'i M/U NCORP has been one of the highest accruing sites for this trial. Colon cancer is the second leading cause of cancer death in Hawai'i. SWOG 0820 is a clinical trial for colon cancer survivors that is utilizing the combination of sulindac and eflornithine as a treatment to prevent the occurrence of new colon cancers and precursor polyps.

Cancer Care Delivery Research: Studies Aimed to Improve the Patient Experience

As an extension of the NCCCP program, the NCORP includes Cancer Care Delivery Research (CCDR) studies that aim to improve clinical outcomes and patient well-being by intervening on patient, clinician, and organizational factors that influence care delivery with an emphasis on diagnosis, treatment, survivorship, and end-of-life care. One example of a CCDR trial is A231701CD, a study for women undergoing surgery for breast cancer. The goal of the study is to use a decision aid to increase patient engagement in decision making for patients with newly diagnosed stage 0-III breast cancer. The study specifically assesses barriers faced by socioeconomically disadvantaged patients. Through the coordination of efforts of research staff at UHCC and Hawai'i Pacific Health, 26 patients have been enrolled into this trial.

NCORP Trials Shaping Cancer Medicine into the Future

Between 1980-2017, 43% of all NCI-sponsored trials influenced the practice of clinical oncology. An estimated 3.3 million years of life have been gained as a result of these studies at a reasonable cost of $125 per life-year gained.[4] Having access to these trials is extremely important to patients as it offers them access to up-to-date treatment strategies and novel medications. The Hawai‘i M/U NCORP has been offering access to these trials to the people of Hawai‘i for the last 25 years. Through collaboration with its clinical partners, the NCORP will continue to provide this critical service for the next several years and beyond.

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Hawai'i Journal of Health & Social Welfare (HJH&SW)

Guidelines for Publication of HJH&SW Supplements

The Hawai'i Journal of Health & Social Welfare (HJH&SW) partners with organizations, university divisions, and other research units to produce topic-specific issues of the journal known as supplements. Supplements must have educational value, be useful to HJH&SW readers, and contain data not previously published elsewhere. Each supplement must have a sponsor(s) who will work with the HJH&SW staff to coordinate all steps of the process. Please contact the editors at hjhsw@hawaii.edu for more information if you would like to pursue creating a supplement.

The following are general guidelines for publication of supplements:

1. Organizations, university divisions, and other research units considering publication of a sponsored supplement should consult with the HJH&SW editorial staff to make certain the educational objectives and value of the supplement are optimized during the planning process.

2. Supplements should treat broad topics in an impartial and unbiased manner. They must have educational value, be useful to HJH&SW readership, and contain data not previously published elsewhere.

3. Supplements must have a sponsor who will act as the guest editor of the supplement. The sponsor will be responsible for every step of the publication process including development of the theme/concept, peer review, editing, preliminary copy editing (ie, proof reading and first round of copy editing), and marketing of the publication. HJH&SW staff will only be involved in layout, final copy editing and reviewing final proofs. It is important that the sponsor is aware of all steps to publication. The sponsor will:

a. Be the point of contact with HJH&SW for all issues pertaining to the supplement.
b. Solicit and curate articles for the supplement.
c. Establish and oversee a peer review process that ensures the accuracy and validity of the articles.
d. Ensure that all articles adhere to the guidelines set forth in journal's Instructions to Authors page, especially the instructions for manuscript preparation and the statistical guidelines.
e. Obtain a signed Copyright Transfer Agreement for each article from all authors.
f. Comply with all federal, state, and local laws, rules, and regulations that may be applicable in connection with the publication, including ensuring that no protected health information appears in any article.
g. Work with the editorial staff to create and adhere to a timeline for the publication of the supplement.
h. Communicate any issues or desired changes to the HJH&SW staff in a timely manner.

4. Upon commissioning a supplement, the sponsor will be asked to establish a timeline for the issue which the sponsor and the HJH&SW editor(s) will sign. The following activities will be agreed upon with journal publication to take place no later than 24 months after signing. Extensions past the 24 months will be subject to additional fees based on journal publication rates at that time:

- Final date to submit a list of all articles, with working titles and authors
- Final date for submitting Word documents for copy editing
- Final date for submitting Word documents for layout
- Final date to request changes to page proofs (Please note that changes to page proofs will be made only to fix any errors that were introduced during layout. Other editing changes will incur an additional fee of $50 per page.)

5. The cost of publication of a HJH&SW supplement is $5,000 for an 8-article edition with an introduction from the sponsor or guest editor. Additional articles can be purchased for $500 each with a maximum of 12 articles per supplement. This cost covers one round of copy editing (up to 8 hours), layout, online publication with an accompanying press release, provision of electronic files, and indexing in PubMed Central, SCOPUS, and Embase. The layout editor will email an invoice for 50% of the supplement to the designated editor for payment upon signature of the contract. The remaining will be due at the time of publication. Checks may be made out to UCERA.

6. The sponsor may decide to include advertisements in the supplement in order to defray costs. Please consult with the HJH&SW advertising representative Michael Roth at 808-595-4124 or email rothcomm@gmail.com for assistance.

7. Supplement issues are posted on the HJH&SW website (http://www.hawaiijournalhealth.org) as a full-text PDF (both of the whole supplement as well as each article). An announcement of its availability will be made via a press release and through the HJH&SW email distribution list. Full-text versions of the articles will also be available on PubMed Central.

8. It is the responsibility of the sponsor to manage all editorial, marketing, sales, and distribution functions. If you need assistance, please contact the journal production editor. We may be able to help for an additional fee.

9. The editorial board reserves the right of final review and approval of all supplement contents. The HJH&SW will maintain the copyright of all journal contents.

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Sample Workflow and Timeline for a Supplement

1. The sponsor contacts the HJH&SW editors (hjhsw@hawaii.edu) to discuss the supplement topic, estimated timeline, length and cost. HJH&SW staff will review the journal requirements for articles and share our review process with the sponsor. **Time frame: 2 weeks**

2. The sponsor will complete the draft contract and pay a non-refundable deposit of $2500 or half the contract value. **Time frame: 3 days**

3. The sponsor will solicit articles for the supplement. **Time frame: 3-6 months**

Articles must comply with:

- Instructions for Manuscript Preparation and Submission of Research Articles
- Instructions for Manuscript Preparation and Submission of Columns
- HJH&SW Statistical Guidelines
- HJH&SW Style Guide for Native Hawaiian Words and Phrases
  AMA Manual of Style A free summary can be found here.

4. The sponsor will oversee the article selection, peer review, and editing process. We recommend that time be allowed for at least two rounds of reviews for each article. **Time frame: 3-6 months**

- Ensure that each article includes Institutional Review Board (IRB) review and approval, and a statement disclosing any conflicts of interest.
- Obtain a Copyright Transfer Agreement signed by all authors for each article.

5. *Optional*: During this time, the sponsor can solicit advertisements for the supplement to help defray costs for publication and/or printing. To initiate this process, the sponsor will work the HJH&SW advertising representative Michael Roth at 808-595-4124 or rothcomm@gmail.com.

6. The sponsor or their designee will conduct a final review of each article to ensure adherence to HJH&SW guidelines and AMA style. **Time frame: 2 weeks**

7. For each article, the sponsor will submit the final Word document and Copyright Transfer Agreement to the HJH&SW journal production editor. The journal production editor will send the articles to the copy editor for final journal style review. Copyediting will be 8 hours per edition plus 1 hour per article for additional articles purchased. Any additional hours will be billed at $100 per hour. **Time frame: 2 weeks**

8. The sponsor will submit the final articles to the layout editor for formatting. **Time frame: 1 month**
Acting in the role of guest editor, the sponsor will include a column introducing the supplement.
IMPORTANT: All articles submitted for layout should be in their finalized form. Page proofs will be returned to the sponsor for their review and approval, but changes will only be made to fix any errors that were introduced during the layout process. Any editing or changes to the text or figures after the initial copy layout will incur a fee of $50 per page.

9. The sponsor will review the electronic copy from the layout editor and submit any final corrections. **Time frame: 5 working days**

10. The layout editor will make the final corrections and provide a finished electronic copy of the supplement to the sponsoring editors to allow time for printing.

11. The managing editor will work with the sponsor to draft a press release. Sponsors should contact the managing editor at least 30 days prior to the date of publication to plan and script the press release. Sponsors are encouraged to submit 1-2 photos to accompany the press release. Note that obtaining signed photo releases is the responsibility of the sponsor.

12. The supplement will be published online along with the press release. An electronic copy will be sent to our subscribers and circulation lists, and the edition will be forwarded to the National Library of Medicine for indexing and made available for no cost access to the public.

Revised 2/6/20

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