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The Impact of COVID-19 on Nuclear Medicine Operations Including Cardiovascular Manifestations in the USA



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The pandemic of coronavirus 2019 disease (COVID-19) not only directly causes high morbidity and mortality of the disease, but also indirectly affects patients with pre-existing medical conditions, particularly cardiovascular diseases, with delayed or deferred outpatient care and procedure including nuclear medicine studies because of concerns about exposure to the virus. In this article, the impact of COVID-19 on hospital operation and nuclear medicine practice in the United States along with recommendations and guidance from major academic organizations are presented. Safe operation of specific nuclear medicine scans, such as lung scintigraphy and nuclear cardiac imaging, are reviewed in the context of balancing benefits to patients against the risk of exacerbating the spread of the virus. Thoughtful reintroduction of nuclear medicine services are discussed based on ethical considerations that maximize benefits to those who are likely to benefit most, taking into consideration baseline health inequities, and ensuring that all decisions reflect best available evidence with transparent communication. Finally, potential correlation between decreased volume of nuclear cardiac studies performed during the pandemic and corresponding increased deaths from ischemic and hypertensive cardiac disease is discussed. Semin Nucl Med 52:11-16 © 2021 Elsevier Inc. All rights reserved.

Introduction

The late 2019 witnessed an unprecedented outbreak emerging from Wuhan, China, which extended to the whole world by March 11, 2020 with the World Health Organization (WHO) declaring it a pandemic.¹ The spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing the coronavirus 2019 (COVID-19) disease affected billions of people across the globe and severely disrupted life, leaving long lasting social and economic despair, increasing strain on health care systems, shortage of medications and radiotracers, with dire survival consequences.

The first case of SARS-CoV-2 in the USA was identified in late January 2020. From January 21 through February 23, 2020, public health agencies detected 14 cases of COVID-19 in the United States, all related to travel from China.² The first community-spread case was confirmed on February 26, 2020 in a California resident who became ill on February 13.³ By mid-March, all 50 states in the United States had confirmed COVID-19 cases.

On March 13, 2020, the United States Government declared a national emergency to combat the spread of COVID-19 infectious disease. This led to a range of social distancing interventions across the country (including restrictions on social contact, large public gathering, and travel), sanitization, and use of personal protective equipment (PPE). Starting April 2020, the health-care industry began facing a true stress test of the industry with the eventual and overwhelming influx of COVID-19 patients.

In the United States, there were marked increases in deaths caused by ischemic heart disease and hypertensive heart disease since the onset of the COVID-19 pandemic, particularly in cities and states that experienced the initial surge of cases, such as New York.⁴ This may have been a consequence of additional stress from the pandemic, and marked disruption in cardiovascular diagnostic services including nuclear myocardial perfusion imaging, potentially impacting care for

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millions of patients who are at risk for or living with heart disease conditions (Fig. 1). 5

Impact of COVID-19 on Nuclear Medicine Practice

The record-breaking influx of patients due to the pandemic succumbed hospitals to challenges due to the extraordinary demand for intensive care beds, ventilators, and other support equipment for patients. Demand for PPE far exceeded its available supply, pushing healthcare workers to ration its use and prioritize front-line workers' protection.

The prioritization of COVID-19 related care, led to a cascade of consequences on non-pandemic related patient services. Governors and healthcare professionals postponed and de-prioritized routine and screening tests, elective surgeries and procedures, leading to significant delays in patient care and management. In addition, some patients stopped seeking care due to infection and spread concerns, and avoided hospitals from added fear of exposure.⁶

Over the course of a few weeks, the medical industry emerged and adopted strategies to accommodate for a neverbefore seen reality. Of note, hospitals and practices promoted both the use of ambulatory care and telehealth services for patients with less severe symptoms (to help relieve the pressure on emergency departments and protect both patients and staff through social distancing measures). In addition, to help triage patient flow into the hospitals, hospital administrators deployed efforts to educate the public about COVID-19 screening or testing processes to avoid patients entering the hospital if not advised under strict guidelines. In addition, government intervention was required in some instances, converting existing spaces like convention centers and schools into makeshift hospitals to separate COVID-19 patients and accommodate patient surge.

Although nuclear medicine departments were not recognized as the front line of the pandemic response, nonetheless, they experienced a dramatic change in their routine clinical practice. Diagnostic and therapeutic nuclear medicine procedures witnessed a progressive decline starting in the first quarter of 2020 due to adjusting their standard workflow to cope with the new era of COVID-19 pandemic. Similar to other departments, this was due to several changes and mitigations that were put in place to limit the spread of the disease and decrease the risk to patients with underlying conditions who require nuclear medicine studies and treatments. As such, many departments drastically reduced the number of appointments and deferred nonurgent studies. As an example, in the authors' institution, compared to the same time in 2019, the monthly volume of general nuclear studies (Fig. 2A), nuclear cardiac imaging (Fig. 2B) and oncology PET/CT (Fig. 2C) started dropping rapidly in March, reaching a nadir in the April. The drop of studies in March and April 2020 coincided with the rise of COVID-19 cases and deaths as reported by the CDC in the same time period. The number of studies caught up in June and remained somewhat stable throughout October 2020, except for a noticeable decline in August 2020, which also coincided with the second peak of newly diagnosed COVID-19 cases in late July and the rising deaths in August 2020. A slow and continued decline for all 3 modalities was also witnessed from November 2020 until February 2021. This decline is likely related to the increase in newly diagnosed COVID-19 cases and deaths for the same time period.

The pandemic decreased supply chains and disrupted distribution channels due to the imposed border lockdowns and subsequent grounding of non-essential cargo flights. For nuclear medicine specifically, these restrictions and lockdowns impacted the availability of necessary tracers such as ^{99m}Tc/⁹⁹Mo and ¹³¹I, which are required radiopharmaceuticals for the majority of conventional nuclear medicine studies. Indeed, there was decreased transport of radiotracers, such as Molybdenum-99, to the United States from Europe (Belgium and the Netherlands), South Africa and Australia, due to flight restrictions. However, the reduction in supply of such radiotracers was on large part matched by the decreased demand of non-invasive imaging in the United States. Conventional nuclear medicine studies that were dependent on ^{99m}Tc/⁹⁹Mo generators, such as cardiac, lung, thyroid, and bone scans were more significantly affected than those using cyclotron or generator produced PET radiotracers. Fortunately, since FDG PET/CT is used in the vast majority of patients for cancer diagnosis and staging, these studies were given higher priority in scheduling over traditional studies.

Changes in Nuclear Medicine Workflow

As a result of the pandemic, and in order to ensure the safety of both patients and staff, nuclear medicine departments had to modify their workflow based on phased opening and adequacy of supplies and resources.⁸ As a first and initial step, nuclear medicine departments and laboratories implemented scheduling changes due to lockdown measures that abided by national, state and local regulations. In addition, operating hours required adjustments based on staff availability, testing resources, and availability of PPE. In some cases, supply chain restrictions and availability of radioisotopes, also affected the frequency of certain tests.

Patient admission protocols were also adjusted in light of the pandemic. Prior to arrival, patients were reminded to come to the nuclear medicine department wearing a face mask and preferably unaccompanied by another family member or friend. Upon arrival, COVID-19 screening for presence of fever or other COVID-19 signs or symptoms, exposure to high-risk subjects, and recent travel to high risk areas, would occur. When suspected COVID positive patients were identified, the scheduled imaging procedure was cancelled and postponed. In addition, the patient (and accompanying person, if any) were separated and isolated and managed by the hospital's infectious diseases team.

COVID-19 testing, preferably by reverse transcription polymerase chain reaction (RT-PCR), was required whenever possible. However, it is imperative to point out that a



Figure 1 International impact of COVID-19 on the diagnosis of heart disease (Top panel) bar graph demonstrating reduction in procedure numbers for all stress studies in 758 facilities in 99 countries, who performed at least 1 modality of stress imaging. Individual modalities are also displayed showing reduction in each in March 2020, compared with March 2019, and a further reduction to April 2020. (Bottom panel) The world maps further illustrate these reductions for individual countries for stress electrocardiography (ECG), echocardiography (Echo), nuclear (combined single-photon emission computed tomography [SPECT] and positron emission tomography [PET]) imaging, and cardiac magnetic resonance (CMR) imaging between March 2019 and April 2020. Gray shading indicates data not available from the country or territory. (Reproduced from Einstein AJ, et al. J Am Coll Cardiol 2021:77;173-185 with permission).

negative test result may not rule out COVID-19 and all patients and their relatives could be considered asymptomatic carriers. Therefore, patients, nuclear medicine staff, and the department as a whole continued to follow strict preventive measures through physical distancing, PPE and increased cleaning routines. Hygiene and proper infection control of the scanners, surfaces and equipment were also strictly implemented. As such, scheduling of patients had to accommodate for the necessary cleaning protocol to be followed. When absolutely required, scanning a COVID-19 suspected patient were scheduled as the last appointment of the working day and, if possible, after



Figure 2 Monthly case volume trend for general nuclear medicine studies (A), nuclear cardiac studies (B) and oncologic PET/CT (C) from January 2019 to April 2021 in the authors' institution.

all other patients and non-essential staff members had left the nuclear medicine department.

While telehealth services emerged in United States in the late 1960s, its adoption throughout the healthcare industry significantly increased in light of the pandemic to reduce close contacts and mitigate risks of transmission.⁹ In March 2020, Centers for Medicare & Medicaid Services (CMS) expanded the use of telehealth, with virtual encounters covered the same way as in-person visits.¹⁰ This also included remote studies reporting via teleradiology.

Recommendations and Guidance From Academic Organizations for Nuclear Medicine Practices During the Pandemic

Lung V/Q Scan

Due to concern for aerosol leakage and the potential of contamination by the radiolabeled aerosol during the ventilation portion of the study,¹¹ the Society of Nuclear Medicine and Molecular Imaging (SNMMI) released a statement on March 19, 2020, reverting to a nonventilation approach for the evaluation of pulmonary embolus in order to reduce the risk of spread of COVID-19 to patients and staff despite the loss of important information about airway physiology.¹² Because many ventilation systems are difficult to completely disinfect, many institutions elected to eliminate entirely the ventilation portion of the lung V/Q study. When lung perfusion images show no evidence of pulmonary thromboembolism, acute pulmonary embolism is essentially ruled out, and no further studies are needed. While it was recognized that not performing paired ventilation images would eliminate important information about airway physiology, it was recommended

to practice the most judicious approach until the COVID-19 pandemic is under control.

With the improved testing and increased vaccinations against COVID-19, and subsequent decline in new cases in many regions across the country, the original SNMMI statement was updated in September 2020, and revised in March 2021 with considerations of resuming ventilation studies on a case-by-case basis,¹³ particularly when it aids in diagnosing lung disease, including vascular and airway disease. Of course, local health care facility and institutional COVID-19 policies should be the primary source of guidance as to the handling of patients with and without suspected COVID-19 infection.

Nuclear Cardiology Studies

Specific considerations and imaging protocols in nuclear cardiology were revised as well in order to minimize and/or prevent droplet exposure during exercise to the staff and other patients. The American Society of Nuclear Cardiology (ASNC) in coordination with the SNMMI issued a statement in late March 2020 regarding adapting nuclear cardiology practices during the COVID-19 crisis.¹⁴

For stress testing, pharmacologic vasodilator agents were recommended over exercise testing, in order to decrease droplet exposure risk, especially when the COVID-19 status of the patient is unknown. However, if exercise testing was deemed necessary, higher-level PPE for staff, and surgical mask or face covering for patients, were recommended. In addition, given the need to minimize time of interaction between nuclear medicine staff and patients and maximize distance of interaction, it was recommended to select the protocol with the shortest duration of scan time and exposure to staff. For example, considering stress first and single day imaging with rapid acquisition protocols. If the stress study is normal then additional imaging under resting condition would not be required. On the other hand, if the stress study is abnormal and additional rest imaging is required, outpatients were recommended to schedule the rest study on a different day. For inpatients, it was suggested that the radiotracer be injected in their room and subsequently the patient was brought down to the nuclear medicine department for imaging. Cardiac PET myocardial perfusion imaging, if available, would be preferred over SPECT imaging for a more rapid throughput and to help minimize exposure for patients and staff in the laboratory.

Later in October 2020, ASNC, SNMMI, the International Atomic Energy Agency (IAEA) and the Infectious Disease Society of America (IDSA), provided guidance to reestablishing non-emergent care in nuclear cardiology laboratories in the United States and worldwide.¹⁵ The North American Cardiovascular Societies issued similar guidance.¹⁶ It was recommended that urgent and symptomatic patients be tested first while monitoring the symptoms of all other patients, and change their status to urgent, as clinically indicated.

Potential Link Between Increased Ischemic Cardiac Deaths and Decreased Nuclear Cardiac Scans

A recent study using data from the National Center for Health Statistics analyzed the cardiovascular deaths after the onset of the pandemic in the United States, which showed a nationwide increase in deaths caused by ischemic heart disease and hypertensive disease after the onset of pandemic in 2020, compared with the deaths over the same time period in 2019.⁴ In contrast, deaths from heart failure, cerebrovascular disease or other circulatory system diseases have not significantly increased. This increased deaths caused by ischemic and hypertensive heart diseases were more prominent in states or cities experienced the first surge of the pandemic (eg, New York City). The findings suggested an indirect impact of the pandemic on patients with pre-existing cardiovascular diseases. Patients with acute coronary syndromes may have avoided emergent medical care and thus died at home (which is consistent with reports that deaths at home have increased in areas with the hardest hit by COVID-19).¹⁷ There is a potential link of the observed increased deaths of ischemic heart disease to the decreased nuclear cardiac studies performed during the same time period, as reflected in our institution results (Fig. 2). Although the data are not sufficient to show a direct causal link between the increased ischemic cardiac deaths and the decreased nuclear cardiac scans, it clearly suggests that the latter could be a factor that contributes to the cardiac death. A reduction in nuclear cardiac scan could lead to an under-detection of culprit vascular lesion and delayed appropriate revascularization. The findings highlight the importance to educate patients to receive urgent medical care for conditions such as coronary artery disease during the pandemic. In addition, there is also concern about increased occurrence of Takotsubo cardiomyopathy during the

pandemic due to increased mental stress.¹⁸ Takotsubo cardiomyopathy is a type of heart failure with characteristic wall motion of apical ballooning, usually precipitated by emotional stress.¹⁹ Nuclear cardiac ¹²³I-metaiodobenzylguanidine (*m*IBG) scan which targets cardiac sympathetic tone, could be a major tool for exploring the underlying etiology of the disease.^{20,21} Clinicians should be aware of potential increased cases of Takotsubo cardiomyopathy during the pandemic.

Current Status and Preparation for Future Outbreaks

Learning from the current pandemic, it is crucial to prepare for future outbreaks. Culprit pathogens must be managed as eradication is rarely realized. As outlined in prior sections, the pandemic has pushed nuclear medicine departments to adjust their usual operational workflow. While re-establishment of nonemergent care is getting back to normal, departments should continue to adopt current measures as a new norm of operation.

First, preventive social and hygienic measures, along with pertinent testing and increasing vaccinations against COVID-19 should continue to be adopted according to the CDC guidelines and local infectious policies. As of May 2021, The US Food and Drug Administration (FDA) has approved three COVID-19 vaccines for emergency use. As such, departments should continue vaccinating all staff. In addition, careful screening of staff and patients, thorough cleaning protocols including disinfection of equipment and rooms, and appropriate use of PPE should be maintained.²²

Secondly, teleradiology and teleconsultation must be more formally integrated into departments' policies. These technologies enable and empower departments to both protect faculty, staff, physicians, and patients providing the opportunity to sustain and increase studies performed. Meetings that cannot be virtual, must either be prioritized, rescheduled, or canceled when possible.

Thirdly, in the current era, diagnosis and treatment of various human conditions and diseases are increasingly being defined by underlying molecular and genomic aberrations rather than by clinical signs and symptoms alone.²³ Thus, nuclear medicine and molecular imaging is uniquely primed to exploit the targeting of expressed cell-surface molecules and intracellular processes of various tissues and organs.^{24, 25} Such information can potentially allow more effective choice of medical or therapeutic intervention, and individualized monitoring of response to treatment.^{26, 27} Although SARS-CoV-2 is considered a biosafety level 3 or 4 (BSL3/4) threats, the application of cellular and molecular functional imaging and targeted radionuclide therapy may lead to promising experimental research in the field of nuclear medicine.²⁸ Examples of molecular targets include the angiotensin converting enzyme 2 receptor, the cell entry tropism of SARS-CoV2, and $\alpha_{\rm v}\beta_6$, an epithelium-specific cell surface receptor which is upregulated in diseased lung; ¹⁸F- $\alpha_{\rm v}\beta_6$ -BP PET/CT can aid with diagnosis and monitoring of lung damage.²⁹⁻³² In addition, experimental antiviral drugs and tumors treatment like

radiotherapeutic Auger emitters to potentially treat patients with active COVID-19 infection are also being evaluated.³³

Conclusions

To minimize disease spread during the pandemic of the COVID-19, nuclear medicine departments in the United States strictly follow up the recommendations and guidance of the government, hospital administrative, and academic organizations such as the SNMMI and ASNC, to modify imaging protocols and to adjust daily volume loading, reflecting the best evidence of benefits and risks. However, there is a potential link of increased ischemic cardiac deaths to a decreased volume of nuclear cardiac studies during the peak of the pandemic.

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