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ABOUT COVER

Joao Mesquita, DVM, MSc, PhD, Professor, Epidemiology Reseach Unit, Polytechnic Institute of Viseu; Public Health Institute of the University of Porto, Porto 3500-606, Portugal. jrmesquita@icbas.up.pt

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MINIREVIEWS

Life after recovery from SARS, influenza, and Middle East respiratory syndrome: An insight into possible long-term consequences of COVID-19

Amir Masoud Afsahi, Alecio F Lombardi, Sara Valizadeh, Ali Gholamrezanezhad

ORCID number: Amir Masoud Afsahi 0000-0002-8906-7767; Alecio F Lombardi 0000-0002-6820-1779; Sara Valizadeh 0000-0003-0383-7722; Ali Gholamrezanezhad 0000-0001-6930-4246.

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Amir Masoud Afsahi, Alecio F Lombardi, Department of Radiology, UCSD, La Jolla, CA 92093, United States

Sara Valizadeh, Department of Restorative Dentistry, School of Dentistry, Tehran University of Medical Sciences, Tehran 1439955991, Iran

Ali Gholamrezanezhad, Department of Radiology, Keck School of Medicine of USC, Los Angeles, CA 90033, United States

Corresponding author: Ali Gholamrezanezhad, MD, Assistant Professor, Doctor, Department of Radiology, Keck School of Medicine of USC, 1975 Zonal Ave, Los Angeles, CA 90033, United States. ali.gholamrezanezhad@med.usc.edu

Abstract

Viral infectious diseases have become an increased public health issue in the past 20 years. The outbreaks of severe acute respiratory syndrome coronavirus (SARS-CoV-1) in 2002, influenza H1N1 in 2009, Middle East respiratory syndrome-CoV in 2012, and the current new coronavirus SARS-CoV-2 have shown that viral infectious diseases are a major concern in the 21st century. As the world lives under the pandemic of a new coronavirus (COVID-19), knowing the clinical characteristics from those past diseases and their long-term outcomes is important to understand the current coronavirus pandemic and its complications and consequences better and plan for possible future outbreaks. Several long-term complications have been described with these respiratory viral diseases, such as decreased pulmonary function, pulmonary fibrosis, chronic fatigue syndrome, avascular necrosis of bone, polyneuropathy, encephalitis, posttraumatic stress disorder, depression, and anxiety. This article summarizes several studies describing chronic complications and long-term outcomes of patients recovered from these viral syndromes.

Key Words: COVID-19; Long-term; Consequences; SARS; Middle East respiratory syndrome; Influenza

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Core Tip: As the world now lives more under the acute burden of this pandemic, very soon possible long term and late consequences of this disaster will appear and the globe will be challenged by those little known before and probably unknown complications. These late complications can potentially be due to the disease itself and/or the side effects of medications or medical interventions applied. Our task as health care professionals is to have a high suspicion upon approaching patients with history of this disease. We believe that by reviewing the recent outbreaks' long-term complications, we will have a better understanding of these potential complications.

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INTRODUCTION

The widespread infectious diseases became a significant public health issue globally in the past 20 years. There have been four major viral contagious outbreaks in the 21st century: The severe acute respiratory syndrome (SARS) in 2002, the H1N1 influenza pandemic in 2009, the Middle East respiratory syndrome (MERS) in 2012 and the current novel coronavirus (COVID-19) in 2019-2020. In between, every year, thousands of people die from complications of seasonal influenza around the world. Besides their high mortality rates, these viral infectious diseases proved to cause long-term outcomes for those who survive. Pulmonary lung dysfunction and residual parenchymal/imaging abnormalities can persist several years after hospital discharge. Many patients can develop avascular necrosis of bone due to the high doses of corticosteroids used in treatment. Several studies reported chronic fatigue syndrome with neuromuscular dysfunction as complications of these viral syndromes. The psychological and mental burden has also been proved in patients and health care workers involved in the treatment and coordination of these pandemics. Acute neurologic complications may cause long-term disability, which can have a significant impact on the health care system and the quality of life of those affected. This article aims to review studies describing long-term multi-system clinical outcomes in patients affected by SARS, MERS, and Influenza following the most recent outbreaks. A summary of main complications and long-term outcomes in patients affected by these outbreaks is shown in Table 1.

RESPIRATORY SYSTEM

SARS

The first cases of a new severe lower respiratory tract infection were reported in early 2003 in Guangdong, China, rapidly spreading throughout Asia and Canada in the following months. Later in that year, this infection became known to be caused by a new coronavirus, named SARS-CoV, that spread through 29 countries from January to September 2003, infecting a total of 8098 patients and causing 774 deaths, with a mortality rate of 9.5%[1]. SARS-CoV is a single-stranded positive RNA virus that belongs to the coronavirus genus and can be spread through the respiratory system, droplets, aerosol, and contaminated surfaces. Young adults between 20-50 years old were the most affected population. Most patients presented initially with fever, headache, joint pain, and dyspnea and could progress to pneumonia and spread to other systems with recovery or death.

Pulmonary involvement of SARS is described to occur in three distinct phases: From 1-7 d of infection (initial phase) mild unilateral ground-glass opacities predominates, from 7-14 d of infection (progression phase) there is an expansion of the ground-glass opacities that becomes multi-focal, bilateral and can progress to consolidations, finally after 2-3 wk of symptom onset the recovery phase begins, with the absorption of the lesions. Some patients may develop interstitial, lobular, and lobar thickening,

Table 1 General complications and long-term manifestations associated with SARS, Middle East respiratory syndrome, and influenza

System	Clinical and Image manifestation
Respiratory system	CT Ground-glass opacities and interstitial thickening
	Reduced lung function
	Low DLCO, VC and FVC
Musculoskeletal system	Chronic fatigue
	Myalgias
	Avascular necrosis of the hip
Neurologic system	Guillain-barré syndrome
	Miller fisher syndrome
	Gustatory and olfactory dysfunction
	Neurologic disease exacerbation
Mental disorders	PTSD
	Depression
	Anxiety
	Burnout

CT: Computed tomography; DLCO: Diffusion capacity of carbon monoxide; VC: Vital capacity; FVC: Functional vital capacity; PTSD: Post traumatic stress disorder.

honeycomb manifestations and traction bronchiectasis characterizing pulmonary fibrosis[1].

Chronic complications of SARS have been described in the following years of the outbreak. The respiratory system is the most affected, characterized by pulmonary fibrosis and decreased lung function. A recent systematic review and meta-analysis by Ahmed *et al*[2] showed that critically ill patients recovered from SARS presented with significant pulmonary function impairment and reduced exercise tolerance 3 to 6 mo post disease recovery[2]. These patients had also reduced diffuse capacity of the lung for Carbon monoxide (DLCO), vital capacity (VC), and forced vital capacity (FVC), which according to the authors, might have impacted aerobic capacity, general physical conditioning and exercise tolerance. The authors also describe that although many patients had improvement in lung function, the meta-analysis has shown that reduction in DLCO and lung fibrosis may persist for years in some patients[2].

Ng *et al*[3] studied the pulmonary function and persistent pulmonary CT abnormalities in patients recovered from SARS in Hong Kong, six months after hospital discharge. The investigators found that 43 out of 57 patients had some pulmonary function abnormality (with the mild obstructive defect as the most common finding), 20 patients had reductions in the carbon monoxide transfer factor (TLCO), 17 patients had abnormal total lung capacity, and four patients had abnormal FVC. Radiological abnormalities were also found in 43 patients out of 57: The median number of segments involved were three in the upper and lower lobes, and the use of corticosteroids was associated with the persistent findings[3].

The most common image findings in high-resolution pulmonary CT in the late stage of acute respiratory distress syndrome (ARDS) caused by SARS were ground-glass opacification, interstitial thickening, and consolidation, according to a study by Joynt *et al*[4]. Other findings were lung fibrosis, cysts, and even pneumothorax, which could be associated with mechanical ventilation, according to the authors. The use of mechanical ventilation or duration of treatment did not appear to have influenced imaging findings[4]. Wu *et al*[5] studied lung function and high-resolution CT image of the chest in 11 patients recovered from SARS at six and 84 mo after hospital discharge[5]. The investigators found that eight patients (72.7%) presented reticulation and interlobular thickening at 84 mo follow-up, two patients (18.2%) showed ground-glass opacification and only 1 had no lung abnormality. Traction bronchiectasis was found in six patients. As for the lung function, at 84 mo follow-up nine (81.8%) from the eleven patients had a low DLCO, eight (72.7%) had mild lung function damage, and 1 (9.1%) had moderate lung function damage[5].

SARS may show a clinical presentation similar to ARDS in the acute phase and shares with ARDS some imaging characteristics and long-term sequela represented by pulmonary interstitial thickening and ground-glass opacities[6].

Chan *et al*[7] described a series of patients treated from SARS in China in which 20% were found to have mild restrictive pulmonary defect six weeks after discharge[7]. The investigators also described other case series that showed reduced lung inspiratory and expiratory pressures, low DLCO, reduced FVC, and muscle fatigue that could partially explain restricted function lung defects in some patients[7].

Zhang *et al*[8] studied 71 health care workers that contracted and recovered from SARS during the outbreak in 2003 in China for 15 years, from August 2003 to March 2018[8]. Most of the patients had a diminished percentage of pulmonary lesions on CT scans (9.4% to 3.2%) from 2003 to 2004 that remained stable until 2018[8]. Image abnormalities most described were residual ground-glass opacities and interstitial thickening. Pulmonary function was the same between 2006 and 2018, and patients showed a mild decline in diffusion capacity from 2006 to 2018[8].

MERS

MERS is an ongoing coronavirus outbreak caused by the MERS-CoV which had the first case diagnosed in 2012 in Saudi Arabia. According to the most recent report from the World Health Organization, a total of 2494 cases of MERS, including 858 deaths (case-fatality rate: 34.4%), were reported globally in 27 countries. The clinical presentation is comprised of fever, chills, malaise, anorexia cough and dyspnea, nausea and vomiting that can progress to severe lower respiratory tract disease, ARDS, acute kidney injury and multi-organ failure, frequently requiring mechanical ventilation and intensive care hospital treatment[9]. The risk of transmission is increased with direct or indirect contact with dromedary camels and patients infected with MERS-CoV. People from 30 to 50 years are the most commonly affected, but higher mortality rates occur among patients 50-79 years, according to the WHO[10].

Batawi *et al*[11] studied the quality of life reported by survivors from MERS that required hospitalization in Saudi Arabia after one year of the diagnosis[11]. Average scores were low for physical functioning, general health, emotional role, and were worst among those patients that required intensive care unit (ICU) treatment compared with patients treated in the non-ICU environment.

Image findings in MERS are nonspecific, with ground-glass opacities and consolidation being the most commonly reported[12]. Lung fibrosis, ground-glass opacities, and pleural thickening are the most common chronic radiographic findings, with more abnormalities being associated with higher days of ICU treatment and older age upon diagnosis[13]. Some patients can develop traction bronchiectasis and fibrosis, along with subpleural bands and architectural distortion[14,15]. In one study with 14 critically ill patients diagnosed with MERS in 2014, nine patients died, and those who survived had good clinical outcomes after one year. However, the authors did not detail the pulmonary function status or image findings[16].

Influenza

Influenza viruses are negative-sense, segmented RNA viruses from the Orthomyxoviridae family that cause annual seasonal epidemics worldwide, and under some circumstances, can go through reassortment of its segmented genetic material, giving origin to different strains causing pandemics[17,18]. According to the centers for disease control and prevention (CDC), there were five influenza pandemics in the twentieth century (1918, 1930, 1957, and 1968) and one in the 21st century (2009 H1N1). The most recent one, caused by the H1N1pdm09 Flu Virus, caused 12469 deaths in the United States from April 2009 to April 2010 and has circulated seasonally throughout the country[19].

The most common acute and subacute respiratory and overall complications of seasonal and epidemic influenza are primary viral pneumonia, secondary bacterial pneumonia, pneumonia caused by opportunistic agents and exacerbation of chronic obstructive pulmonary disease, and asthma. However, during epidemics, infections tend to be more serious, usually requiring ICU treatment, presenting with a higher mortality rate than the seasonal disease[20,21].

Chen *et al*[22] reported chronic pulmonary complications from influenza A (H7N9) during two years after discharge from the hospital and showed interstitial abnormalities and fibrosis on lung image after six months, along with restrictive and obstructive lung function throughout the follow-up period[22].

Luyt *et al*[23] studied a total of 24 patients recovered from influenza A (H1N1) infection treated in ICUs with and without extracorporeal lung assist (ECLA) one year after hospital discharge and found that 50% of the patients in the group treated with

ECLA and 40% of them not treated with ECLA reported significant exertion dyspnea, and 75% and 64% of the patients in each group respectively had decreased diffusion lung capacity across the blood-gas barrier[23]. Both groups also had reduced exercise capacities and reported lower health-related quality of life compared with a group from the healthy population [23].

Li *et al*[24] showed in a study with children recovered from SARS that 34% had high-resolution CT residual abnormalities: Ground-glass opacities (31.2%), air trapping (8.5%), and combination of ground-glass and air trapping (18.8%). The investigators also found mild decreased pulmonary function in four out of 38 patients[24].

A summary of the main chronic clinical and imaging manifestations of SARS, MERS and Influenza is described on Table 2.

Musculoskeletal system

Avascular necrosis (AVN) of bone has been described as a significant complication of SARS, as critically ill patients frequently require high doses of corticosteroid treatment. Hong *et al*[25] described an incidence of 28 patients with AVN among 67 patients diagnosed with SARS, and that presented joint pain between March and May 2003[25]. The mean time from SARS diagnosis and development of AVN was 119 days, and all patients received a total dose of corticosteroid above 700 mg[25]. The most common affected sites were femoral head and knees. Magnetic resonance imaging (MRI) played an essential role in the diagnosis since no abnormalities were found on the radiographs. Later the investigators described in another study that Diffusion-weighted MRI could be used to reliably diagnose AVN in patients treated from SARS with corticosteroid[26].

Another study by Sun *et al*[27] investigated the possible role of anticardiolipin antibodies in the etiology of AVN in 62 patients diagnosed with post-SARS osteonecrosis and found that 33.9% of patients had at least one type of anticardiolipin antibodies (IgA, IgG, and IgM) compared to 7.7% in the control group. They concluded that these antibodies might play a role in the pathogenesis of post-SARS osteonecrosis[27].

The incidence of AVN after SARS varies among studies. Shen *et al*[28] described a 3% incidence in a group of 84 health care workers diagnosed with SARS and treated with different dosages of corticosteroids[28]. Li *et al*[29] found an incidence of 30% among a cohort of 40 patients diagnosed with SARS and treated with corticosteroids[29].

Lv *et al*[30] conducted a longitudinal study with 71 patients treated with corticosteroids for SARS over 36 mo after diagnosis. They showed that 29% of the patients developed AVN of the hips within 3-4 mo after treatment, two patients developed AVN after one year of the diagnosis and 11 patients after three years of observation outlining the long-term adverse effects[30].

Zhao *et al*[31] studied 190 hips from 117 patients that developed post-SARS AVN during seven years from diagnosis and found that 66 hips progressed in symptoms, 55 hips collapsed, and ten hips showed lesion regression[31]. According to the authors, the progression of symptoms and the bone collapse was associated with lesions with higher dimensions and lower viable lateral columns in the femoral heads. The mean time from the administration of corticosteroids and the development of AVN was 6.26 mo, and the mean time from the corticosteroid use and the development of symptoms was 18.39 mo[31]. In the 15-year follow-up study by Zhang *et al*[8], though, patients diagnosed with femoral head necrosis after treatment of SARS showed decreased AVN volume from 2005 to 2013 and plateaued until 2018[8].

Several patients that recovered from SARS were presented late with musculoskeletal pain, weakness, fatigue, shortness of breath, psychological distress, and significant sleep problems, known as the post-SARS syndrome. A retrospective study by Moldofsky *et al*[32] showed that chronic post-SARS syndrome was characterized by persistent fatigue, diffuse myalgia, weakness, depression, and nonrestorative sleep with associated REM-related apneas/hypopneas[32]. The authors suggested that this may be caused by the direct viral invasion of the central nervous system and peripheral tissues resulting in chronic post-inflammatory CNS pathology.

In a case-series by Stainsby *et al*[33], three patients diagnosed with SARS presented with a variety of neurological, muscular and joint findings that improved after conservative treatment, which according to the authors, could be caused by a viral myositis or from the use of corticosteroids in the treatment of the patients. The acute inflammatory condition with increased cytokines, platelet-activating factors, free radicals, and proteases was also raised as possible causes[33]. Table 3 summarizes the main chronic musculoskeletal findings in patients treated for SARS.

Table 2 Common respiratory system long-term manifestations associated with severe acute respiratory syndrome, Middle East respiratory syndrome, and influenza

Diagnosis	Clinical Manifestation
SARS	Interstitial thickening, traction bronchiectasis[1]
	Decreased exercise tolerance[2]
	Pulmonary ground-glass opacities, consolidations, pulmonary fibrosis[4,5]
MERS	Pulmonary ground-glass opacities, consolidation and pulmonary fibrosis[12,13]
Influenza	Lung interstitial abnormalities and fibrosis, restrictive and obstructive function patterns[21]
	Reduced exercise capacity[23]

MERS: Middle East respiratory syndrome; SARS: Severe acute respiratory syndrome.

Table 3 Common chronic musculoskeletal disorders associated with severe acute respiratory syndrome

Diagnosis	Clinical manifestation
SARS	Avascular necrosis of the hip and knee[25,28-31]
	Diffuse myalgia[32]
	Weakness
	Persistent fatigue[33]
	Non-restorative sleep

SARS: Severe acute respiratory syndrome.

Neurologic system

Coronaviruses can invade the nervous system by several routes, including transsynaptic transfer, direct invasion *via* the olfactory nerve, or migration across the blood-brain barrier, spreading to different central nervous system locations, including the brain, basal ganglia, midbrain, where neuronal death can occur[34], causing a wide range of neurological complications[35]. Immunologic process are also suggested as possible contributors to neurologic complications in these patients[36]. Patients with preexisting neurological disorders are at risk of developing complications from coronaviruses diseases in association with neurological disease exacerbation, especially those with previous diagnosis of dementia and Parkinson's disease[37]. Clinicians should be aware of this risk of exacerbation of neurologic disorders to take early preventive measures and long-term follow-up.

Most of the neurologic complications found in patients with viral infections like SARS, MERS, and Influenza are acute, with headache, anosmia, seizures, and encephalitis as the most common. Encephalitis and Guillain-Barre syndrome have been reported 2-3 wk after the acute symptoms of MERS and are diseases with the potential to cause long-term sequelae[38].

Recent case reports have linked SARS coronavirus to rapid-onset Guillain-Barré syndrome that evolved to tetraparesis or tetraplegia over a period of 36 h to 4 d and necessitated mechanical ventilation; and Miller-Fisher syndrome, presenting with ageusia, oculomotor palsy, ataxia, areflexia[39,40]. One patient presented with increased serum immunoglobulin antibodies and treatment with intra-venous immune globulin resulted in complete recovery.

It is important to mention the gustatory and olfactory dysfunction referred by patients after infection by COVID-19[41], that needs further long-term investigation and follow-up considering its potential to cause low quality of life.

Mental / psychiatric abnormalities

Psychiatric symptoms were common in patients affected by SARS and MERS and in health care workers involved in the frontlines of treatment. A study with 90 patients that survived the SARS outbreak showed 58.9% incidence of psychiatric disorders and 33.3% prevalence of any mental disorder after 30 mo[42]. Depression, anxiety, and

posttraumatic stress disorder (PTSD) were the most commonly diagnosed, and the symptoms were worst in health care workers affected by the disease[42].

In another study with patients recovered from SARS in Hong Kong, about 35% of the patients reported "moderate to severe" or "severe" anxiety and depressive symptoms, which were more prevalent in those who had family members killed by the disease or were health care workers[43]. PTSD symptoms have been found in 4% of patients one month after hospital discharge for SARS and 5% after three months of discharge in a cohort of 131 patients[44]. Park *et al*[45] evaluated survivors of MERS in a prospective cohort study at multiple centers throughout Korea, assessing PTSD and depression 12 mo after hospital discharge and found a 42.9% prevalence of PTSD symptoms and 27% prevalence of depression[45].

Another follow-up study from Lam *et al*[46] showed that even four years of hospital discharge patients affected by SARS had active psychiatric illnesses (40% prevalence) and chronic fatigue symptoms (40.3% prevalence)[46]. The quality of life of patients recovered from MERS and SARS has been assessed in a study by Batawi *et al*[11] one year after diagnosis showing similar results in both groups, but lower scores for those patients admitted to ICU during treatment[11].

Health care workers comprise a group especially sensitive to mental health problems during infectious disease outbreaks. The long-term impact 13 to 26 mo after the SARS outbreak in 769 health care workers has been assessed and showed significantly higher levels of burnout, psychological distress, and posttraumatic stress[47]. According to the investigators, personal variables that contributed to adverse outcomes were maladaptive coping by avoidance, hostile confrontation, self-blame contributed, and attachment anxiety[47].

An interesting topic that emerged during the COVID-19 pandemic is the widespread use of telemedicine, not only in clinical specialties but also in surgery specialties[48], which could be an option in the future to help underserved patients and reduce health care workers burden by consulting less-severe patients that should not go to a hospital through online counseling. Table 4 gives a summary of the main neurologic and mental chronic disorders associated with SARS, MERS and Influenza.

CONCLUSION

Viral infections and especially the recent SARS, MERS, and Influenza, can affect different systems with potential long-term clinical outcomes that may reduce the quality of life and impair the work capacity of the patients. A high prevalence of mental and psychiatric symptoms has been associated with SARS, and MERS recovered patients and health care workers involved in treatment. Chronic fatigue and neurologic sequelae were common complications among patients with SARS and influenza. Avascular necrosis of the hip and joint pain has also been described as a common complication from the high doses of corticosteroid treatment necessary in critically ill patients.

Table 4 Neurologic and mental chronic manifestations associated with severe acute respiratory syndrome, Middle East respiratory syndrome, and influenza

Diagnosis	Clinical manifestation
SARS/COVID-19	Gustatory and olfactory dysfunction[41]
	Miller-fisher syndrome
	Exacerbation of neurologic diseases
	Depression, anxiety, PTSD[42]
	Chronic fatigue[46]
	Burnout, psychological distress[47]
MERS	Encephalitis and guillain-barre syndrome[38]
Influenza	Encephalitis, seizures, headache

COVID-19: Coronavirus disease 2019; MERS: Middle East respiratory syndrome; PTSD: Post traumatic stress disorder; SARS: Severe acute respiratory syndrome.

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CASE REPORT

Stenotrophomonas maltophilia, an emerging pathogen in newborns: Three case reports and a review of the literature

Bijaylaxmi Behera

ORCID number: Bijaylaxmi Behera 0000-0001-9061-7677.

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Bijaylaxmi Behera, Department of Pediatrics & Neonatology, Chaitanya Hospital, Chandigarh 160044, India

Corresponding author: Bijaylaxmi Behera, MD, Chief Physician, Department of Pediatrics & Neonatology, Chaitanya Hospital, Sector 44, Chandigarh 160044, India.
jollybubu2008@gmail.com

Abstract

BACKGROUND

Stenotrophomonas maltophilia (*S. maltophilia*) is a rare cause of neonatal sepsis with significant morbidity and mortality and has extensive resistance to several antibiotics leaving few options for antimicrobial therapy. Only a few cases have been reported in neonates from developing countries. We report three cases of critically ill, extramural babies with neonatal *S. maltophilia* sepsis. All three babies recovered and were discharged.

CASE SUMMARY

All three cases were term extramural babies, who were critically ill at the time of presentation at our neonatal intensive care unit. They had features of multiorgan dysfunction at admission. Blood culture was positive for *S. maltophilia* in two babies and one had a positive tracheal aspirate culture. The babies were treated according to the antibiogram available. They recovered and were subsequently discharged.

CONCLUSION

Although various authors have reported *S. maltophilia* in pediatric and adult populations, only a few cases have been reported in the newborn period and this infection is even rarer in developing countries. Although *S. maltophilia* infection has a grave outcome, our three babies were successfully treated and subsequently discharged.

Key Words: Ceftriaxone; Multidrug resistant; Neonatal sepsis; *Stenotrophomonas maltophilia*; Cotrimoxazole; Tigecycline

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Core Tip: *Stenotrophomonas maltophilia* is a rare cause of neonatal sepsis with significant morbidity and mortality and has extensive resistance to several antibiotics leaving few options for antimicrobial therapy. Although there have been reports in the adult population, only a few cases have been reported in neonates from developing countries. The majority of babies have succumbed to this deadly infection. We present three cases of out-born babies with neonatal sepsis, who were critically ill. All three babies recovered and were subsequently discharged.

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INTRODUCTION

Stenotrophomonas maltophilia (*S. maltophilia*) was previously known as *Pseudomonas maltophilia* or *Xanthomonas maltophilia*[1]. It is currently an important multi-drug resistant, gram-negative, oxidase-negative, and catalase-positive, non-fermenting nosocomial pathogen associated with significant mortality[1]. *S. maltophilia* is the only species of *Stenotrophomonas* known to infect humans. It ranks third amongst the four most common pathogenic non-fermenting *Gram negative bacilli* (*NFGNBs*), the others being *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Burkholderia cepacia* complex[2]. *S. maltophilia* may have varied manifestations such as bacteremia, pneumonia, urinary tract infection, meningitis, endocarditis *etc*[3]. It is found in water, sewage, soil, plants, animals and in hospital settings, and may also be isolated from washbasins, respirators, antiseptics, and medical devices leading to device-associated infections such as catheter-associated bloodstream infections, urinary tract infections, and ventilator-associated pneumonia[4,5]. The treatment of *S. maltophilia* infection is very difficult as it is intrinsically resistant to the majority of commonly used drugs, such as all Carbapenems, and Levofloxacin[6-9]. Strains are usually susceptible to Trimethoprim-Sulfamethoxazole, but this combination is not used in neonates due to adverse effects. Strains have variable susceptibility to Ceftazidime[6,7]. *S. maltophilia* has a contrasting antibiotic susceptibility pattern to other *NFGNBs* such as *A. baumannii*, *P. aeruginosa* and *Burkholderia cepacia*, and the correct identification of *S. maltophilia* is very important, as it has to be differentiated from these other organisms. However, it is very challenging for a routine laboratory to identify *S. maltophilia*, due to its inert biochemical profile and difficulty in the interpretation of phenotypic characteristics. Subsequently, its correct identification is essential as no single drug is effective against all *NFGNBs*, which hinders initiation of appropriate empirical treatment resulting in increased morbidity and mortality[10].

CASE PRESENTATION

Case 1

Chief complaints: An out-born baby, delivered to a primigravida mother at 38 wk, with a birth weight of 3000 g *via* a lower segment caesarean section (LSCS) due to fetal distress, cried immediately after birth, but developed severe respiratory distress in the form of retractions and grunting with pulse oxygen saturation of 84%.

History of present illness: The baby was started on oxygen by hood, and received intravenous fluids, Cefotaxime, Amikacin and Vitamin K. On day two of life, the baby's respiratory distress worsened with chest X-ray suggestive of right lung pneumothorax and was referred to our hospital.

Physical examination: On admission, the baby had severe respiratory distress with a Downes score of 6/10 and features of shock such as weak pulse, prolonged capillary refill time (CFT), heart rate (HR) of 190 bpm, blood pressure (BP) of 40/28 mmHg and peripheral oxygen saturation (SpO_2) of 82%. Right side air entry was decreased compared to the left side.

Laboratory examinations: A sepsis screen sent on admission was positive with procalcitonin (PCT) of 15.43 ng/mL, μESR of 12 mm, total leucocyte count (TLC) of 20300 and an IT ratio of 0.22. Blood culture sent on admission showed growth of *S. maltophilia* (multi-drug resistant) (Table 1). Lumbar puncture (LP) was negative for meningitis.

Imaging examinations: Imaging showed right lung pneumothorax with left side consolidation.

Case 2

Chief complaints: A term, 37 wk out-born baby, weighing 2600 g, delivered by LSCS due to previous LSCS, cried immediately after birth but developed respiratory distress soon after birth.

History of present illness: The baby was started on oxygen and *i.v*. antibiotics. On day three of life, the baby's respiratory distress worsened and the child was referred to our hospital.

Physical examination: On admission, the child had severe respiratory distress with a Downes score of 7/10 and had features of poor perfusion such as tachycardia (HR: 185/min), CFT of more than 3 s, extremely weak pulse and unrecordable BP and SpO_2.

Laboratory examinations: A sepsis screen sent on admission was positive with PCT of 25.3 ng/mL, μESR of 10 mm, TLC was 21200, platelet count was 44000 and IT ratio was 0.22. Prothrombin time (PT) was 22 s, INR was 1.8 and partial activated partial thromboplastin time (aPTT) was 64 s. Blood culture sent on admission grew *S. maltophilia*, and the sensitivity pattern is provided in Table 1. LP was negative for meningitis.

Imaging examinations: Chest X-ray on admission was suggestive of white out lungs.

Case 3

Chief complaints: A term 38 wk out-born baby boy was referred to our hospital with symptomatic hypoglycemia and respiratory failure.

History of present illness: A term 38 wk 2600 g, out-born male baby was delivered by LSCS due to non-progression of labor, to a 25-year-old primigravida mother who was leaking per vagina for 20 h. Antenatal history was uneventful. The child developed symptomatic hypoglycemia at 10 h of life with lethargy and one episode of seizures. A sepsis screen revealed C-reactive protein of 10.9 mg/L and the baby was started on Cefotaxime and Amikacin. He developed severe respiratory distress on day four of life and was intubated and then referred to our hospital on manual ventilation.

Physical examination: On admission, the baby was in shock with prolonged CFT, tachycardia (HR: 192/min, weak pulse, BP of 36/22 mmHg), posturing, and a SpO_2 of 95% on manual ventilation.

Laboratory examinations: A sepsis screen revealed PCT of 16 ng/mL, μESR was 12 mm and IT ratio was 0.20, platelet count was 23000 with a deranged coagulogram (PT: 29 s, INR: 2, aPTT: 78 s). Arterial blood gas revealed mild metabolic acidosis. Blood culture isolated *Staphylococcus epidermidis*; which was sensitive to Cotrimoxazole, Nitrofurantoin, Linezolid, Daptomycin, Teicoplanin and Vancomycin. Tracheal aspirate sent on admission grew *S. maltophilia* which was sensitive to Ceftriaxone and had intermediate sensitivity to Colistin, Aztreonam, Ceftazidime, Moxifloxacin and was resistant to Ampicillin, Amikacin, Gentamicin, Cefotaxime, Cefepime, Meropenem, Augmentin, Cefuroxime, Cefoxitin, Ciprofloxacin, Levofloxacin and Cotrimoxazole (Table 1).

Imaging examinations: Chest X-ray was suggestive of pneumonia. Cranial ultrasonography was suggestive of cerebral edema with chinked ventricles.

FINAL DIAGNOSIS

Case 1

Term/38 wk/AGA/*S. maltophilia* sepsis/septic shock/pneumonia/right side

Table 1 Antibiograms of the three cases included in this report

Case No.	Cefotaxime	Ceftriaxone	Cefepime	Ceftazidime	Cefu	Amik	Gent	Amp	Mero	Cipro	Levo	Moxi	Amox	S-T	Colis	Tigecy	Aztreo
1	R	R	R	R	R	R	R	R	R	R	S	R	R	R	S	T	R
2	R	R	R	S	R	R	R	R	R	S	S	S	R	S	R	S	NA
3	R	S	R	IS	R	R	R	R	R	R	R	IS	R	R	IS	NA	IS

Cefu: Cefuroxime; Amik: Amikacin; Gent: Gentamicin; Amp: Ampicillin; Mero: Meropenem; Cipro: Ciprofloxacin; Levo: Levofloxacin; Moxi: Moxifloxacin; Amox: Amoxicillin; S-T: Sulfamethoxazole-trimethoprim; Tigecy: Tigecycline; Aztreo: Aztreonam.

pneumothorax.

Case 2

Term/37 wk/AGA/*S. maltophilia* sepsis/septic shock/pneumonia/disseminated intravascular coagulation (DIC)/pulmonary arterial hypertension (PAH).

Case 3

Term/38 wk/AGA/*Staphylococcus epidermidis* and *S. maltophilia* sepsis/septic shock/pneumonia/meningitis/DIC.

TREATMENT

Case 1

On admission, the baby had severe respiratory distress with a Downes score of 6/10 and features of shock. The child was intubated and was started on synchronized intermittent mandatory ventilation (SIMV) mode with settings of 13/04/60/100% and a pneumothorax was drained using an intercostal drainage tube. A normal saline bolus was followed by ionotropic support with Dopamine and Adrenaline and *i.v.* antibiotics Vancomycin and Meropenem were started. Colistin was added on day three after admission, as there was no significant clinical improvement. On the fourth day of life, the chest tube was clamped and removed. The baby was extubated on day five of NIMV mode with settings of 16/05/40/21% and gradually changed to nasal continuous positive airway pressure (CPAP). Subsequently, the baby was weaned to nasal prongs and finally oxygen support was stopped on the eighth day of life. Vancomycin, Meropenem and Colistin were given for a total duration of 14 d. Ionotropes were slowly tapered and finally stopped on day five of life. The baby was started on measured tube feeding and then gradually to spoon feeding and breastfeeding by day ten of life.

Case 2

A term, 37 wk out-born baby, weighing 2600 g, delivered by LSCS due to previous LSCS, cried immediately after birth but developed respiratory distress soon after birth and was started on oxygen and *i.v.* antibiotics. On day three of life, respiratory distress worsened and the baby was referred to our hospital. On admission, the child had severe respiratory distress with a Downes score of 7/10 and was in shock, the child was intubated and started on conventional ventilation but was changed to high frequency ventilation with a maximum setting of mean airway pressure of 18, inspired oxygen fraction of 100%, DP of 60, frequency-10 and required maximum inotropic support of Dopamine 20, Dobutamine 20, Adrenaline 0.5, and Milrinone 0.2 μg/kg/min. A chest X-ray on admission was suggestive of white out lungs; therefore, the baby was given surfactant and within 24 h was changed to conventional ventilation (SIMV mode 18/5/50/50%). The baby also had PAH and was given Sildenafil by injection. Meropenem and Vancomycin were also administered. Colistin injection was added on day three after admission due to worsening clinical condition with shock and DIC. In addition to DIC, the baby also had thrombocytopenia, coagulopathy manifesting as orogastric and ET bleeding and received multiple platelet, fresh frozen plasma and packed red blood cell transfusions. The ventilator setting was gradually tapered and the baby was extubated to NIMV mode on the twelfth day after admission, and changed to nasal CPAP by day fifteen after admission and off oxygen by day seventeen. Blood culture sent on admission grew *S. maltophilia* with sensitivity to Tigecycline which was added and Colistin continued. The baby received Vancomycin for seven days plus Tigecycline and Colistin for fourteen days. Tube feeding was started on day six of life and gradually increased to full feeding by day eleven after admission. The baby was subsequently breastfed.

Case 3

The baby required ionotropic support with Dopamine, Adrenaline and intravenous fluids and was started on SIMV mode (18/6/45/50%). A sepsis screen was sent and the child was started on Meropenem, Vancomycin and Colistin. As the baby was critically ill and did not show an improvement in symptoms, Ceftriaxone was started and Meropenem was discontinued on day three after admission, as soon as the tracheal aspirate report was received. CSF analysis was performed after the platelet count had improved, which was suggestive of meningitis. The child received fresh frozen plasma and platelet transfusions for DIC. Ionotropic support was gradually tapered and then stopped by day seven after admission and tube feeding was started. The baby's sensorium and spontaneous efforts improved and he was extubated on the eleventh day after admission and changed to NIMV mode (16/6/50/30%). He was subsequently weaned off to CPAP by day fourteen. He was gradually weaned off CPAP by day sixteen and oxygen by day eighteen. Intravenous antibiotics were administered for 21 d, and he received full tube feeding by day twelve after admission and direct oral feeding by day sixteen.

OUTCOME AND FOLLOW-UP

Case 1

The baby was discharged from hospital on day fifteen of life, was being breastfed and had normal neurological status. At follow-up, the baby was being breastfed and was neurologically normal.

Case 2

The baby was discharged after eighteen days of hospitalization. At follow-up, the baby was being breastfed and was healthy.

Case 3

The baby was discharged after almost twenty two days of hospitalization on full feeds. At follow-up, the baby was neurologically normal, on mixed feeds and repeat cranial ultrasound was normal.

DISCUSSION

S. maltophilia is currently an emerging multi-drug resistant, opportunistic pathogen in both hospital and community settings. Studies have shown various risk factors for infection or colonization by *S. maltophilia*, including prior use of broad-spectrum antimicrobial agents such as Carbapenem, Ampicillin, Gentamicin, Vancomycin, Metronidazole, Piperacillin, Cefotaxime, Ceftazidime, Ciprofloxacin, Tobramycin, and Cefepime, and other drugs such as corticosteroids, cytotoxic chemotherapy, immunosuppressive therapy, H2 blockers, and parenteral nutrition[11-16]. Prolonged hospital stay, invasive procedures including mechanical ventilation, intubation, urinary catheterization, central venous catheterization, lower gestational age and low birth weight, neutropenia, underlying diseases such as hepatobiliary, chronic pulmonary, and cardiovascular diseases, organ transplantation, dialysis, intravenous drug use, and human immunodeficiency virus infection, malignancy, and exposure to patients with *S. maltophilia* wound infection were significantly associated with *S. maltophilia* infections[17-21]. In our patients we found that intensive care unit (ICU) stay, administration of broad spectrum antibiotics, and invasive procedures would have contributed to infection with this organism. Although according to the literature, premature and low birth weight babies are more prone to developing this infection, all our cases were term and with good birth weights[21].

According to Jia *et al*[7], maximum isolation of *S. maltophilia* was from respiratory specimens, whereas Abdel-Aziz *et al*[6], reported maximum isolation from urine samples followed by swabs and blood. In our cases, *S. maltophilia* was isolated from blood in the first two cases and from tracheal aspirate in the third case. The identification and antimicrobial susceptibility testing was carried out using VITEK and the results were confirmed with manual MIC calculations.

S. maltophilia has several resistance mechanisms to various antibiotic classes such as beta-lactams due to two inducible beta-lactamases, a zinc-containing penicillinase (L1) and a cephalosporinase (L2), an aminoglycoside acetyl-transferase that confers resistance to aminoglycoside antibiotics, and temperature-dependent changes in the outer membrane lipopolysaccharide structure confers added resistance to aminoglycoside antibiotics and possesses efflux pumps[22,23]. Although according to previous reports the organism is resistant to the majority of commonly used drugs such as all Carbapenems and Levofloxacin, and is susceptible to Trimethoprim-Sulfamethoxazole, with variable susceptibility to Ceftazidime[6-9], in our cases except for one, which was sensitive to Ceftazidime and the others were sensitive to Ceftriaxone, all were resistant to Aminoglycosides, Carbapenems, and Cephalosporins. Of the three cases, one was resistant, one was sensitive and one had intermediate sensitivity to Colistin. The first and second cases were sensitive to Tigecycline and in the third case sensitivity was not tested. Two cases were sensitive to Levofloxacin and one was resistant. One case was sensitive to Trimethoprim-Sulfamethoxazole and two were resistant. We administered Colistin and Tigecycline to our patients. In the third case we administered Ceftriaxone, as the organism had intermediate sensitivity to Colistin and Tigecycline sensitivity was not performed. The same baby was monitored for serum bilirubin levels and for other adverse effects. As shown in the literature, Ceftriaxone can be used in neonates and is contraindicated in babies at risk of developing unconjugated hyperbilirubinemia and concurrent administration with calcium[24-26]. In our third case, although tracheal aspirate was positive for *S. maltophilia*, the baby was treated according to the antibiogram, as clinical features were consistent with the infection. However, most clinicians are reluctant to treat this pathogen, when isolated from tracheal aspirate and often treat it as colonization rather than a pathogen[27]. Antibiograms of the three patients are shown in Table 1.

Most infections caused by *S. maltophilia* are associated with severe morbidity and long-term, extensive ICU treatment. According to previous reports, the mortality rates vary between 14%-62%[28,29]. Our three babies were discharged on full feeds with a hospital stay of 14 to 21 d.

CONCLUSION

Various case studies on *S. maltophilia* infections in India, such as *S. maltophilia* endophthalmitis[29], tropical pyomyositis[30], unilateral conjunctival ulcer[31], nonhealing leg ulcer[32] and meningitis[33], have been reported in pediatric and adult patients and the isolation rate of *S. maltophilia* was found to be 2.5% (5 isolates) out of 193 *NFGNBs*

in various clinical samples[34]. However, neonatal sepsis due to *S. maltophilia* has been reported only by Viswanathan *et al*[1] and Soren *et al*[35]. Here we report three cases of neonatal sepsis due to *S. maltophilia* along with their antibiograms Although *S. maltophilia* infection has a grave outcome our three out-born babies were successfully treated and discharged.

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CASE REPORT

Cutaneous leishmaniasis in Louisiana - one-year follow-up: A case report

Ashaur Azhar, Hillary E Connell, Christopher Haas, Jelena Surla, Devin Reed, Sanjay Kamboj, Gordon L Love, Yussef Bennani

ORCID number: Ashaur Azhar 0000-0001-9629-6843; Hillary E Connell 0000-0002-6519-4745; Christopher Haas 0000-0002-8946-1190; Jelena Surla 0000-0001-7879-4996; Devin Reed 0000-0002-0177-2112; Sanjay Kamboj 0000-0002-6823-7050; Gordon L Love 0000-0001-5257-6747; Yussef Bennani 0000-0002-0539-2555.

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Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: The corresponding author declares that he has no conflict of interest related to this case report.

CARE Checklist (2016) statement: The corresponding author has read

Ashaur Azhar, Yussef Bennani, Department of Medicine, Section of Infectious Diseases, Louisiana State University Health Sciences Center, School of Medicine, New Orleans, LA 70112, United States

Hillary E Connell, Jelena Surla, Devin Reed, Sanjay Kamboj, Department of Medicine, Louisiana State University Health Sciences Center, School of Medicine, New Orleans, LA 70112, United States

Christopher Haas, Department of Dermatology, Louisiana State University Health Sciences Center, School of Medicine, New Orleans, LA 70112, United States

Gordon L Love, Jack Perry Strong Professor and Chair, Department of Pathology, Louisiana State University Health Sciences Center, School of Medicine, New Orleans, LA 70112, United States

Corresponding author: Ashaur Azhar, MD, Assistant Professor, Department of Medicine, Section of Infectious Diseases, Louisiana State University Health Sciences Center, School of Medicine, 1542 Tulane Avenue, Suite 331C, New Orleans, LA 70112, United States. aazha1@lsuhsc.edu

Abstract

BACKGROUND

Reports of leishmaniasis are scarce in North America. It is considered to be one of the neglected tropical diseases. It is seen in immigrants from endemic areas to United States. Treatments are not readily available in the United States. Untreated or inadequately treated cutaneous leishmaniasis not only causes localized disfigurement but can advance to more permanent and devastating mucosal disfigurement and perforation, if caused by a species that can also cause mucocutaneous leishmaniasis.

CASE SUMMARY

A 42-year-old human immunodeficiency virus negative male immigrant from Honduras presented to the emergency department of our facility in Louisiana with a 2-mo history of a left lower extremity ulcer. It started as a painless blister that progressed in size and developed into other smaller lesions tracking up the thigh and became tender and erythematous. Clinically looked nontoxic and healthy. He was afebrile. Blood tests, except inflammatory markers, were within normal limits. The cellulitis of the leg was treated with 6 d of vancomycin that

the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016) for a case report.

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also relieved the pain. Skin biopsy was obtained, and histopathology was suspicious for leishmania. Polymerase chain reaction/deoxyribonucleic acid sequencing done by centers for disease control and prevention confirmed the diagnosis as *Leishmania panamensis*. There was no involvement of naso-oropharyngeal mucosa, confirmed by otolaryngology. The patient was treated with miltefosine for 28 d. Clinic follow-up after approximately 11 mo revealed a healed skin ulcer.

CONCLUSION
Cutaneous leishmaniasis should be in the differential diagnosis of skin ulcers of travelers from endemic areas. Awareness regarding diagnosis and treatment of leishmaniasis needs to be enhanced.

Key Words: Cutaneous leishmaniasis; Neglected diseases; Leishmania (Viannia) panamensis; Miltefosine; Leishmania; Case report

Core Tip: This case highlights the importance of prompt and accurate diagnosis, and appropriate treatment of cutaneous leishmaniasis to prevent further complications and advancement to mucosal form. It should be considered in the differential diagnosis of skin lesions with appropriate epidemiologic context. Oral therapy with miltefosine is available for use as in this case. It is important to evaluate for human immune-deficiency virus disease since presentation and complications in immunosuppressed individuals can be more severe.

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INTRODUCTION

Leishmaniasis is one of the neglected tropical diseases as per World Health Organization (WHO)[1]. Leishmaniasis is a vector-borne zoonotic disease which is caused by intracellular flagellated protozoans of the genus *Leishmania*. These are transmitted to the humans or other animals by the bite of infected female phlebotomine sand flies during blood feeding[2,3]. The disease is widespread in the tropical and subtropical areas. Per WHO, it is estimated that between 700000 to 1.0 million people are newly infected every year with leishmaniasis[4].

The disease has three main forms[4-6]. Cutaneous leishmaniasis (CL) is the most common form and can be localized or diffuse. Though it causes various types of skin lesions[7-9], it typically manifests as ulcers. The ulcers are usually well-defined, with raised edges and a reddish base (referred to as volcano-like or pizza-like ulcers), leading to permanent scarring and serious disability. Visceral leishmaniasis (Kala-azar), the most serious form, is fatal in more than 95% of cases if left untreated and includes irregular bouts of fever, bone marrow involvement and hepato-splenomegaly. Some species of CL if not treated can lead to mucocutaneous leishmaniasis (Espundia), which can cause devastating destruction of the nasopharyngeal mucous membranes. We present a case of CL with subgenus *Viannia* and species *panamensis* [*L. (V.) panamensis*].

CASE PRESENTATION

Chief complaints

"Skin lesion on left lower leg for last 2 mo, now with small "lumps and bumps"

tracking up my thigh with discomfort."

History of present illness

A 42-year-old male who immigrated from Honduras to the United States approximately 2 mo before presenting to our facility's emergency department in Louisiana. He reported 2 mo ago he was climbing mountains and cutting wood with his friends in Honduras when he felt a bite on his left lower leg. A few weeks later, he developed a blister at the site. Over the next 2 mo period, the lesion started to necrose and enlarge. Approximately 5-10 d prior to this presentation he started to see "lumps and bumps" on his leg tracking up from the wound to his thigh, with mild discomfort in his thigh. Prior to this presentation, the lesions were non-tender.

He denied any trauma, dog or cat bite, swimming in fresh or salt water, any thorn prick or gardening, fishing, seafood use. He denied any history of immunocompromise.

Review of systems: Positives: Skin: wound and tender nodules on leg; Negatives: (1): Constitutional: No fevers/chills, no weight loss; (2) Cardiac: No palpitations, no chest pain, no dyspnea, no edema; (3) Pulmonary: No shortness of breath, no cough, no hemoptysis; (4) Gastrointestinal: No nausea, vomiting or diarrhea; and (5) Genitourinary: No urinary symptoms.

History of past illness

Patient reported no known past medical or surgical history.

Personal and family history

Nonsmoker, no alcohol or illicit drug use history. No history of diabetes, and no history of immunosuppression in either the patient or in family members.

Physical examination

On presentation to the emergency department, patient was afebrile with temperature of 98 °F, heart rate 86 beats/min, respiratory rate 16 per min, blood pressure 127/79 mmHg and oxygen saturation of 98% on room air. His body mass index was 25 kg/m^2. He appeared clinically non-toxic and healthy. Nasal and oral examination was benign with no lesions or perforation noted. Abdominal examination did not reveal any tenderness or hepato-splenomegaly. There was an approximately 3 cm × 3 cm left lower extremity wound on the anterior tibial area, with some erythema in the surrounding area. There were tracking tender nodules from the wound up to his thigh, with indurated skin with mild tenderness on the thigh and on the nodules (Figure 1A).

Laboratory examinations

Blood counts were within normal limits with white blood cell count 9.7 (4.5 × 10^3/μL-11 × 10^3/μL), Hemoglobin 13.7 (13.5-17.5 g/dL), platelet count 254 (130 × 10^3/μL-400 × 10^3/μL). Chemistry revealed normal sodium, potassium, chloride and glucose levels with creatinine 0.82 (0.7-1.4 mg/dL), normal transaminases and lactic acid level. Inflammatory markers were elevated with C reactive protein of 2.5 (normal less than 0.9 mg/dL) and erythrocyte sedimentation rate 45 (normal 0-15 mm/h). Later in the hospital course, human immunodeficiency virus (HIV) was ruled out by a 4th generation HIV antibody/antigen test.

Imaging examinations

Plain X-rays of the ankle and tibia-fibula were normal. Venous doppler ultrasound of the lower extremity ruled out thrombosis. Computer tomography scan of the extremity with intravenous (IV) contrast revealed lymphadenopathy at left popliteal and left groin area. Small fluid collections or phlegmons at the nodules and ulceration sites were present (Figure 2).

Diagnostic assessment and interventions

Intravenous vancomycin was started for the leg cellulitis. Our suspicion was high for leishmaniasis because of his history of recently living in an endemic area, having a known insect bite, and friends with similar histories in Honduras being diagnosed with CL. He was evaluated by dermatology, who obtained a skin punch biopsy per Centers for Disease Control and Prevention (CDC) recommendations. Tissue was sent to our hospital laboratory and to the state public health laboratory where it was shipped to CDC. The results from our laboratory revealed negative bacterial, fungal and acid-fast bacilli cultures and stains. Histopathology was compatible with

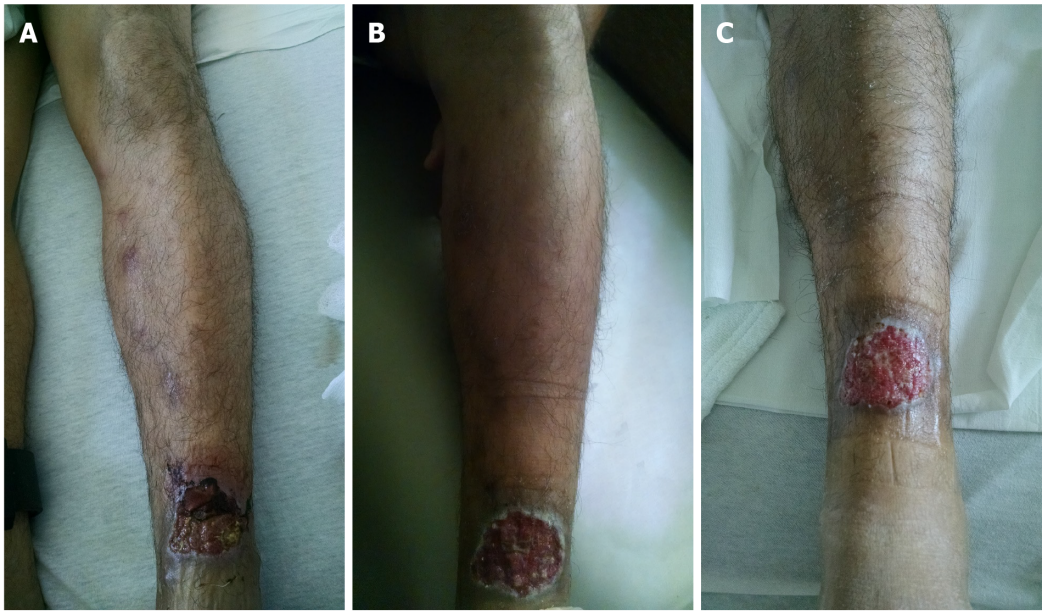


Figure 1 Physical examination. A: Skin ulcer with tracking nodules on admission; B and C: Skin ulcer after antibiotics for cellulitis.

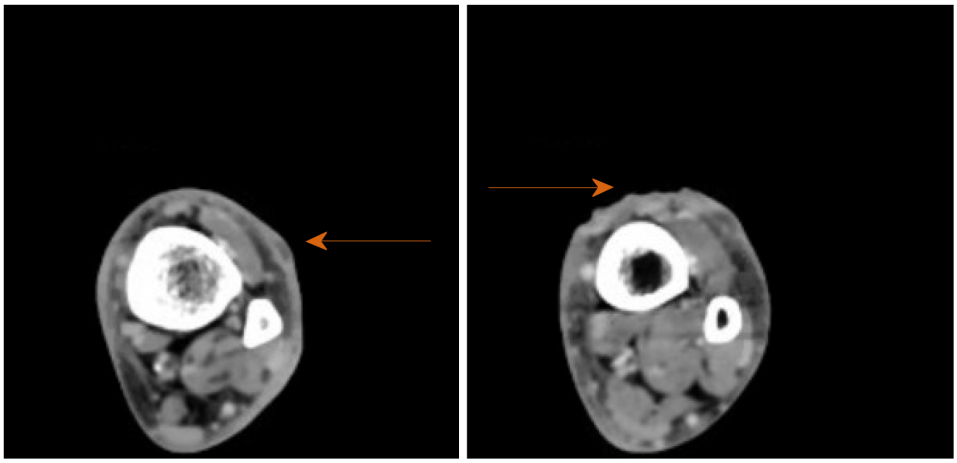


Figure 2 Computer tomography scan of left lower extremity, cross sectional view showing phlegmon and ulcerated skin (orange arrows).

leishmaniasis amastigotes (Figure 3).

Initial diagnosis

CL with sporotrichoid lymphangitis with cellulitis of the leg. After 6 d, IV vancomycin was stopped after resolution of the cellulitis and leg tenderness (Figure 1B and C). Final diagnosis was reported as *Leishmania panamensis* that was confirmed through polymerase chain reaction (PCR)/deoxyribonucleic acid (DNA) sequencing by CDC (Figure 4).

FINAL DIAGNOSIS

CL with *Leishmania (Viannia) panamensis.*

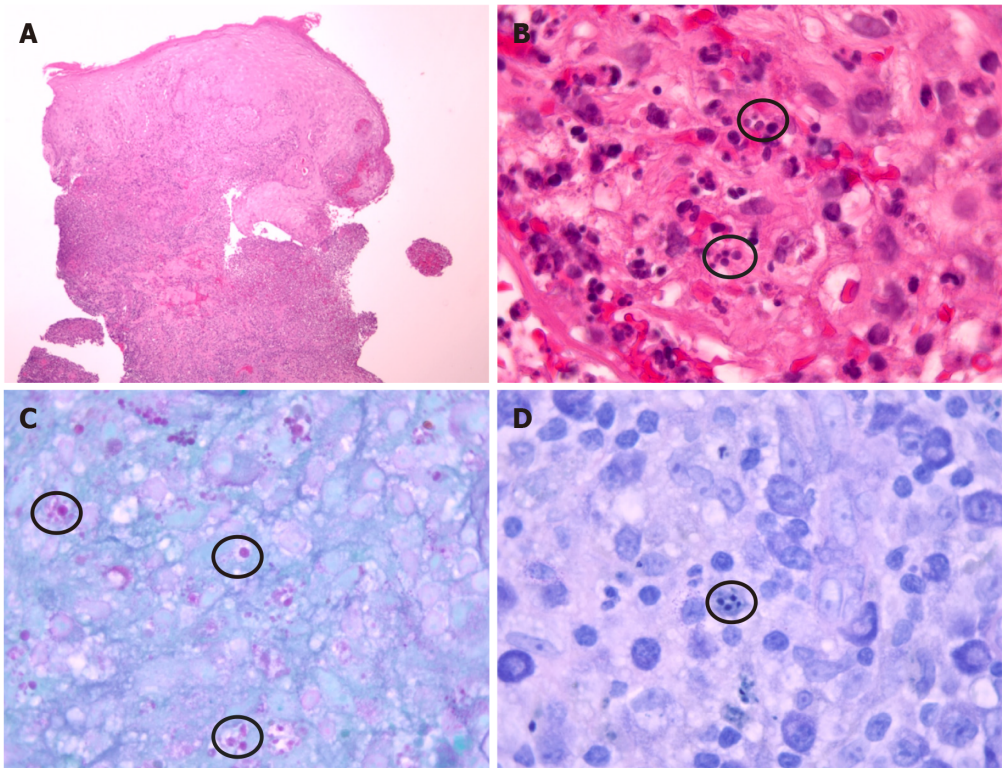
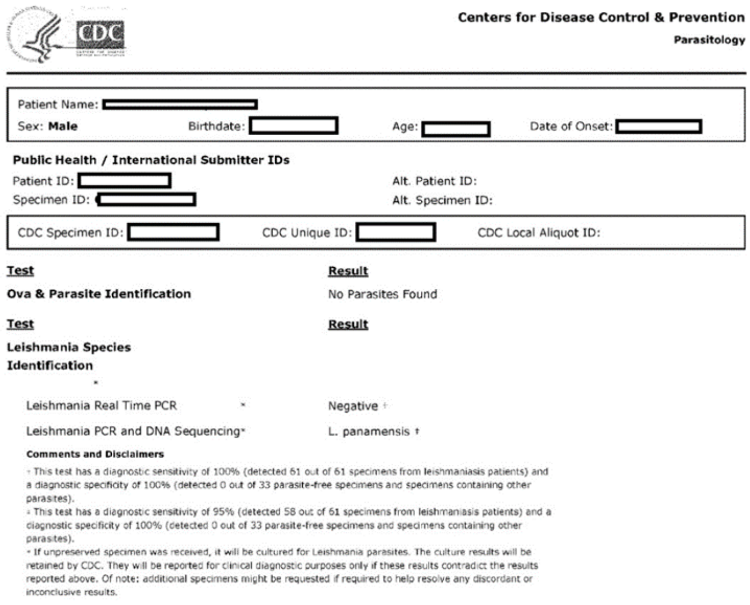


Figure 3 Histopathology was compatible with leishmaniasis amastigotes. A: Reactive squamous epithelium with mixed superficial and deep inflammatory infiltrate (hematoxylin-eosin staining, original magnification × 40); B: Organisms compatible with *Leishmania* amastigotes (hematoxylin-eosin staining, original magnification × 1000). Location within histiocytes is obscured by marked acute inflammatory infiltrate; C: Parasitized histiocytes with staining of *Leishmania* amastigotes (PAS, original magnification × 1000); and D: Parasitized histiocytes with staining of *Leishmania* amastigotes (Giemsa, original magnification × 1000).



Centers for Disease Control & Prevention
Parasitology

Patient Name: [redacted]
Sex: **Male** Birthdate: [redacted] Age: [redacted] Date of Onset: [redacted]

Public Health / International Submitter IDs
Patient ID: [redacted] Alt. Patient ID:
Specimen ID: [redacted] Alt. Specimen ID:

CDC Specimen ID: [redacted] CDC Unique ID: [redacted] CDC Local Aliquot ID:

Test	Result
Ova & Parasite Identification	No Parasites Found

Test	Result
Leishmania Species Identification	
Leishmania Real Time PCR *	Negative †
Leishmania PCR and DNA Sequencing*	L. panamensis †

Comments and Disclaimers

* This test has a diagnostic sensitivity of 100% (detected 61 out of 61 specimens from leishmaniasis patients) and a diagnostic specificity of 100% (detected 0 out of 33 parasite-free specimens and specimens containing other parasites).
† This test has a diagnostic sensitivity of 95% (detected 58 out of 61 specimens from leishmaniasis patients) and a diagnostic specificity of 100% (detected 0 out of 33 parasite-free specimens and specimens containing other parasites).
* If unpreserved specimen was received, it will be cultured for Leishmania parasites. The culture results will be retained by CDC. They will be reported for clinical diagnostic purposes only if these results contradict the results reported above. Of note: additional specimens might be requested if required to help resolve any discordant or inconclusive results.

Figure 4 Report from centers for disease control and prevention.

TREATMENT

As per CDC recommendations, otolaryngology consultants performed flexible fiberoptic laryngoscopy/nasopharyngoscopy and confirmed no mucosal involvement. The patient was treated with miltefosine 50 mg PO three times daily for 28 d.

OUTCOME AND FOLLOW-UP

Patient followed up with dermatology and infectious diseases clinic at several occasions, and then visited at approximately 11 mo with a healed ulcer (Figure 5).

DISCUSSION

About 95% of CL cases occur in the Americas, the Mediterranean basin, the Middle East and Central Asia. According to WHO, in 2018, over 85% of new CL cases occurred in 10 countries: Afghanistan, Algeria, Bolivia, Brazil, Colombia, Iran, Iraq, Pakistan, the Syrian Arab Republic and Tunisia. It is estimated that between 600000 to 1 million new cases of CL occur worldwide annually[4]. Reports of leishmaniasis are scarce in North America. In the United States, it is seen in travelers from endemic areas. CL has also been reported in American military personnel returning home from assignments in Iraq and Afghanistan[10]. Usually CL skin lesions are painless. But if painful, there is generally an indication to treat it also as a bacterial superinfection. In our patient, the lesions were painful initially, but the pain subsided after treating the cellulitis. CL typically presents with skin lesions after an incubation period of 2 wk to 6-8 mo. There has been one reported case of CL with *Leishmania panamensis* with incubation period as long as 18 mo, that was successfully treated with IV amphotericin. This patient was also from Honduras and had atypical multiple lesions[9]. A sporotrichoid-like pattern of skin lesions is not typical of CL but has been seen in various other case reports in addition to our patient[11-13]. The case report published recently by Mann *et al*[13], discusses about a couple that traveled from Costa Rica. The husband had sporotrichoid like pattern of skin lesions.

In immunocompromised patients such as those with HIV, the disease course can be worse. Chances of reactivation is possible with decreased immunity[14].

Diagnosis

Diagnosis starts with obtaining a good history taking, including travel history, and a detailed physical examination. It is confirmed with biopsy of a skin lesion, ideally the active part of the lesion at the edge. Typical microscopic findings are mixed inflammatory infiltrate with many histiocytes and granuloma formation containing amastigotes[15]. But atypical microscopic findings such as tuberculoid granulomatous processes has also been identified without organisms seen in some reports[16]. Sensitivity of histopathologic examination in diagnosing CL is low, perhaps only 14%–18%[17]. The use of multiple diagnostic modalities including PCR and DNA sequencing helps confirm the diagnosis as well as provides speciation, useful to its management[18,19], like in our case also.

Treatment

Extensive guidelines regarding diagnosis and treatment have been created by professional medical societies[20]. The pentavalent antimonials have been considered the mainstay treatment for CL in most parts of the world except in North America, where they are not readily available[20]. Our patient's friends who had similar presentations in Honduras reportedly did respond to pentavalent antimonials, per his report. Topical paromomycin and parental amphotericin have also been used. Resistance against amphotericin and antimonials have been reported[21,22].

Miltefosine is thus far the only oral drug reported that can be used for all three types of leishmaniasis including in cases with HIV[23,24]. Miltefosine belongs to the class of alkyl phosphocholine drugs. It has shown antileishmanial activity, linking its activity mainly to apoptosis and disturbance of lipid-dependent cell signaling pathways[23]. Patients on treatment should be monitored for elevations in transaminases and serum creatinine. It should not be given to pregnant patients[23,24]. The recommended duration of therapy is 28 d, but longer duration of therapy has also been given as mentioned by Mann *et al*[13] where they offered 56 d therapy.

Like other reported cases[11,13,25], our case was also successfully treated with miltefosine (Figure 5). He was following with the corresponding author in the outpatient setting for approximately 11 mo as of the time of this submission. Our patient had no adverse events during treatment with miltefosine.

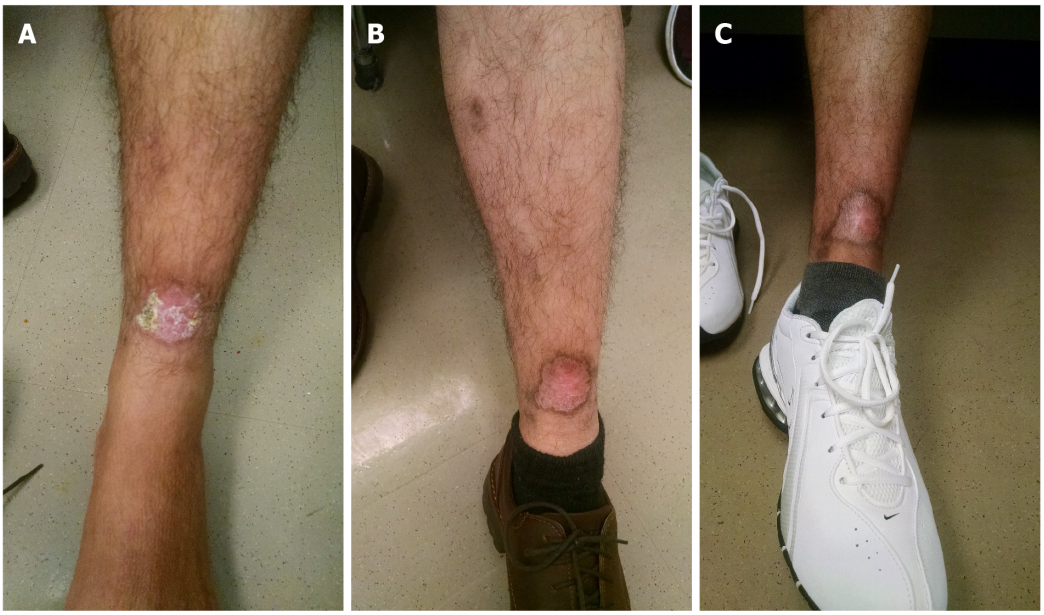


Figure 5 Patient followed up with dermatology and infectious diseases clinic at several occasions, and then visited at approximately 11 mo with a healed ulcer. A: Skin ulcer after 13 d of 28 d treatment with miltefosine; B: After 5 mo of treatment; and C: After 11 mo of treatment.

CONCLUSION

Though leishmaniasis is not common in North America, clinicians should be aware of it and include it in the differential diagnoses of skin lesions in patients who have traveled from endemic areas. Optimal therapy of CL is vital to prevent progression into mucosal form. As of today, there are no available preventive or therapeutic vaccines. The most effective way to prevent infection is avoiding sand fly bites by adopting controlled measures.

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CASE REPORT

Liver transplantation in patients with SARS-CoV-2: Two case reports

Camilla Bezerra Bastos Limeira, Camila Monteiro Veras, José Hicaro Hellano Gonçalves Lima Paiva, Marina Seixas Studart e Neves, Themístocles Mesquita Teles de Carvalho, Natália Stefani de Assunção Ferreira, Alessandra Maria Mont`Alverne Pierre, Ivelise Regina Canito Brasil

ORCID number: Camilla Bezerra Bastos Limeira 0000-0003-1394-3377; Camila Monteiro Veras 0000-0002-7536-8219; José Hicaro Hellano Gonçalves Lima Paiva 0000-0002-6232-003X; Marina Seixas Studart e Neves 0000-0002-3070-8486; Themístocles Mesquita Teles de Carvalho 0000-0002-1388-5763; Natália Stefani de Assunção Ferreira 0000-0002-5038-0879; Alessandra Maria Mont`Alverne Pierre 0000-0002-9071-0692; Ivelise Regina Canito Brasil 0000-0002-4886-7442.

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Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

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Camilla Bezerra Bastos Limeira, Camila Monteiro Veras, Marina Seixas Studart e Neves, Themístocles Mesquita Teles de Carvalho, Alessandra Maria Mont`Alverne Pierre, Ivelise Regina Canito Brasil, Transplantation Division, Hospital Geral de Fortaleza, FORTALEZA 60175742, CE, Brazil

José Hicaro Hellano Gonçalves Lima Paiva, Natália Stefani de Assunção Ferreira, UECE, Uece, FORTALEZA 60175742, Ceara, Brazil

Corresponding author: José Hicaro Hellano Gonçalves Lima Paiva, UECE, Uece, Valdetario mota 1121, FORTALEZA 60175742, Ceara, Brazil. hellanohicaro@gmail.com

Abstract

BACKGROUND

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19). This disease was declared a worldwide health problem with the characteristics of a pandemic. Most patients have mild symptoms and a good prognosis. Information on the evolution and prognosis of COVID-19 in solid organ recipients is scarce.

CASE SUMMARY

We describe two patients who underwent liver transplantation with a positive test result for detection of the viral sequence for COVID-19, using reverse-transcription polymerase chain reaction (RT-PCR), immediately before transplantation. The patients showed good evolution in the postoperative period, without signs of graft dysfunction. The immunosuppressive therapy was not modified. Both patients were discharged for subsequent outpatient follow-up.

CONCLUSION

In conclusion, it is expected that the experience at this center can be used as an example, aimed at the continuation of transplantations by other services and, thus, the morbidity and mortality of patients with liver disease on the transplantation waiting list can be reduced. Transplant centers must be able to readjust daily to the evolution of the COVID-19 pandemic.

Key Words: COVID-19; Liver transplantation; Coronavirus; Pneumonia; Immunosuppressed patients; Case report; Infection diseases

The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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Core Tip: Coronavirus disease 2019 (COVID-19), caused by the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its consequences have resulted in high rates of morbidity and mortality worldwide in the first half of this year. This infection shows worse outcomes in certain at-risk populations, including those with cirrhosis of any etiology. Most patients with decompensated cirrhosis have poor quality of life and a high chance of progressing to death if they have high prognostic scores, such as the Model for End-Stage Liver Disease score. The definitive treatment for these patients is liver transplantation. Data related to the evolution and outcome of these patients when infected with SARS-CoV-2, including those undergoing transplantation, are scarce and contributions to the literature on this topic can help the adequate management of these patients, supporting the development of additional research and even guidelines. Thus, the publication of this report on two cirrhotic patients with COVID-19 who underwent liver transplantation is justified.

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INTRODUCTION

In December 2019, the first cases of viral pneumonia of unknown origin were documented in Wuhan, the capital of China's Hubei province. The virus was identified as a new coronavirus, called "Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)". The infection was documented in hospital and community settings. Soon the virus spread throughout the Chinese territory and, subsequently, increasing numbers of cases were also observed in several continents[1]. Considering the severity of the situation, the World Health Organization (WHO) declared Coronavirus Disease 2019 (COVID-19) a public health emergency of international interest[2]. Liver transplantation programs were affected worldwide.

Most patients with COVID-19 have mild symptoms and a good prognosis. It is worth mentioning that asymptomatic cases have been described. However, patients with risk factors can develop severe SARS-CoV-2 disease, secondary to severe pneumonia, pulmonary edema, severe acute respiratory syndrome, acute kidney injury, coagulopathy or multiple-organ failure[3].

Based on data from other viruses, including SARS-CoV-2, immunosuppressed patients with COVID-19 were expected to have more severe clinical manifestations and a longer period of viral dispersal. However, the effects of immunosuppression on COVID-19 are not well established. Due to this fact, it remains controversial whether organ transplantation should be performed during the COVID-19 pandemic. Some recent guidelines suggested that transplantation can be performed as long as careful measures are taken[4].

A timely and accurate diagnosis, especially in cases with the potential to develop into the severe form of the disease, is extremely important to provide adequate clinical support to patients, and to limit the spread of the virus. Currently, detection of the viral sequence by reverse-transcription polymerase chain reaction (RT-PCR) is the test routinely used to confirm the diagnosis of SARS-CoV-2 infection[5].

This study aims to describe two patients with confirmed SARS-CoV-2 infection who successfully underwent liver transplantation.

CASE PRESENTATION

Chief complaints

Case 1: A 55-year-old male patient was admitted on March 9, 2020 to Hospital Geral de Fortaleza, state of Ceará, Brazil with a clinical picture of hepatic encephalopathy, abdominal pain, fever and upper gastrointestinal bleeding.

Case 2: A 40-year-old male patient, followed at the Liver Transplantation Service of Hospital Geral de Fortaleza was admitted on June 22, 2020 to undergo a liver transplantation with a Model for End-Stage Liver Disease-Sodium (MELD-Na) score of 24. The patient had no clinical complaints and was hemodynamically stable.

History of present illness

Case 1: The patient had a diagnosis of alcoholic-induced liver cirrhosis and a one-year withdrawal period.

Case 2: The patient was followed at the Liver Transplantation Service of Hospital Geral de Fortaleza due to liver cirrhosis caused by hepatitis B virus infection.

History of past illness

Case 1: The patient had no comorbidities, such as hypertension or diabetes. Moreover, he had no recent travel history.

Case 2: Previous complications in this patient included portal vein thrombosis. He had a history of peripheral vascular disease, with a healing venous ulcer in the left lower limb, with no signs of active infection. He had no other comorbidities and denied a travel history in recent months. He had a recent hospitalization history (20 d before) for intravenous antibiotic therapy due to erysipelas.

Personal and family history

Cases 1 and 2: No relevant family history.

Physical examination

Case 1: Physical examination revealed the presence of massive ascites. The other systems showed no changes. On admission, vital signs showed a respiratory rate of 22 breaths/min (brpm), heart rate of 97 beats/min (bpm), 96% oxygen saturation in ambient air and blood pressure of 140/80 mmHg.

Case 2: On clinical examination, only mild jaundice and an ulcer in the left lower limb without signs of infection were observed. The other systems showed no changes. On hospital admission, vital signs showed a respiratory rate of 18 brpm, heart rate of 89 bpm, oxygen saturation of 97% in ambient air and blood pressure of 110/70 mmHg.

Imaging examinations

Case 1: A computed tomography scan of the chest was performed, which showed lungs with reduced volume, left pleural effusion, atelectasis of the adjacent parenchyma and multiple diffuse ground-glass opacities (Figure 1A and B).

Case 2: A computed tomography scan of the chest showed evidence of discrete foci of ground glass attenuation affecting the bases of the lungs and discrete bilateral parenchymal bands (Figure 1C and D).

Further diagnostic work-up

Case 1: The patient's evolution required dialysis for acute kidney injury and his ascites were refractory to clinical measures, and required several relief paracenteses. Piperacillin/tazobactam therapy was started, due to bacterial peritonitis. An upper gastrointestinal endoscopy was performed, which did not show the presence of gastroesophageal varices, but demonstrated the presence of severe candidiasis and thus, antifungal therapy with fluconazole was started, which was later replaced by caspofungin. However, due to the lack of improvement in the patient's clinical status and laboratory tests, he was listed for liver transplantation according to the MELD-Na score of 35 and the Child-Pugh score of C. Despite the absence of respiratory symptoms, screening for SARS-CoV-2 infection was performed, with the collection of a nasopharyngeal swab for viral sequence detection by RT-PCR, but the result, which was positive, was only released after the transplant had been performed.

Liver transplantation was carried out on March 25, 2020, according to the standard surgical technique. During the procedure, the recipient developed cardiorespiratory arrest in asystole during the graft reperfusion period, which was effectively reversed with a cardiac massage cycle. The time of cold and hot ischemia was 6 h and 28 min and 32 min, respectively. The patient was extubated in the immediate postoperative period in the Intensive Care Unit and an O_2 saturation of 96% was maintained in ambient air, with an oxygenation index of 400.

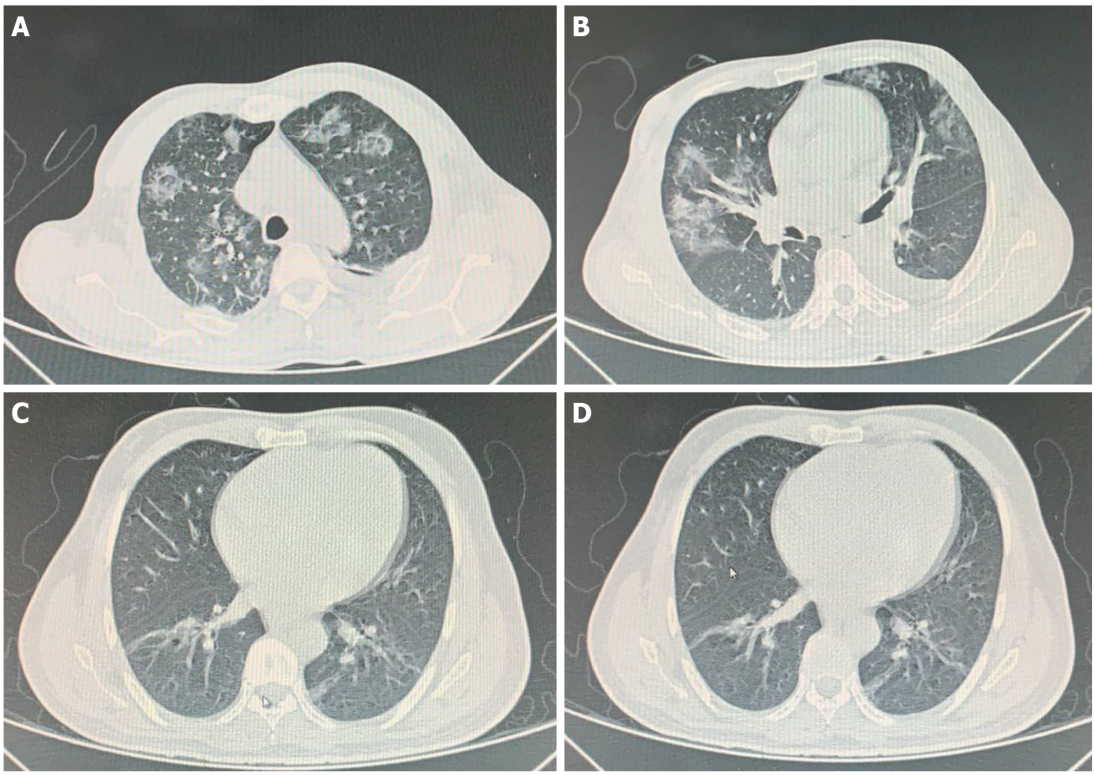

Figure 1 Chest computed tomography of transplanted patients with coronavirus disease 2019. A and B: Case 1, the lungs show reduced volume, left pleural effusion, atelectasis of the adjacent parenchyma and multiple diffuse ground-glass opacities; C and D: Case 2, discrete foci of ground glass attenuation affecting the bases of the lungs and discrete bilateral parenchymal bands.

The donor was a 56-year-old female patient with a previous history of diabetes mellitus. The patient developed a history of hypertensive peak and a decrease in the level of consciousness due to an intraparenchymal brain hematoma, with significant midline deviations. There was no screening for COVID-19, as the transplant occurred at the beginning of the pandemic and there was no defined protocol on the screening of donors at that time.

Case 2: According to the protocol of our service, screening for SARS-CoV-2 infection was performed using a nasopharyngeal swab (RT-PCR), as well as chest radiography. There were no alterations in the chest X-ray, and it was not possible to obtain the nasopharyngeal swab result before transplantation. Considering the patient's clinical condition of chronic liver failure at risk of worsening, the transplant team chose to proceed with the surgery.

The donor was a 42-year-old male patient who suffered a traumatic brain injury. He was receiving piperacillin-tazobactam due to a bacterial infection. He screened negative for COVID-19 following RT-PCR.

During the intraoperative period, the patient developed massive bleeding during the anastomoses, requiring vigorous volume replacement (3500 mL), 4 units of fresh frozen plasma and 2 units of packed red blood cells, in addition to blood recovery by cell-salvage. Moreover, an intraoperative thrombectomy was performed for portal vein thrombosis.

During the postoperative period, the patient was transferred to the Intensive Care Unit for patients with Coronavirus (ICU-COVID), and required invasive mechanical ventilation and vasopressors. Laboratory test results are shown in Table 1. The nasopharyngeal swab collected prior to surgery for viral sequence detection by RT-PCR was positive for SARS-CoV-2.

Table 1 Laboratory characteristics of the two transplanted patients with coronavirus disease 2019

	Case 1			Case 2		
	At hospital admission	Preoperative	At hospital discharge	At hospital admission	Preoperative	At hospital discharge
Fibrinogen	83	NA	NA	178	NA	NA
aPTT	1.97	1.6	1.2	1.4	0.96	0.88
Hemoglobin	8.7	6.0	11.1	11.8	8.9	6.4
Hematocrit	24.8	19.5	32.9	35.5	25.9	18
Leukocytes	22900	15100	9300	3100	16700	4300
Lymphocytes	711	615	2615	1092	754	492
Platelets	109000	100000	376000	42000	53000	20000
INR	2.72	2.78	1.02	1.84	1.28	1.32
Total bilirubin	7.44	23.25	0.74	2.87	2.07	1.46
Albumin	2.5	NA	NA	3.2	NA	NA
Urea	136	113	55	16	53	69
Creatinine	2.1	5.4	1.0	1.3	1.2	1.02
AST	105	NA	28	68	3005	1924
ALT	59	NA	39	35	1807	950
Sodium	125	127	NA	129	131	NA

Reference values: Urea (13-43 mg/dL); Creatinine (0.7-1.3 mg/dL); AST (< 32 mg/dL); ALT (< 31 mg/dL); TB (< 1 UI/L); PT (10-14 s); aPTT (22-28 s); Albumin (> 3.5 g/dL); Hemoglobin 11.3/15.2 g/dL); Leukocytes (3600-10000/mm^3); Platelets (150000-450000/mm^3); INR (1-1.3 s). AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; PT: Prothrombin time; aPTT: Partial thromboplastin time; INR: International normalized ratio. NA: Not available.

FINAL DIAGNOSIS

Cases 1 and 2

SARS-CoV-2 infection and alcoholic-induced liver cirrhosis.

TREATMENT

Case 1

Following the release of the RT-PCR test result with a detectable SARS-CoV-2 viral load, the patient was transferred to the ICU-COVID; he was initially asymptomatic and therapy was started with azithromycin 500 mg/d for 5 d, ivermectin 12 mg/d for 2 d and oseltamivir 150 mg/d for 5 d. Additionally, an immunosuppression protocol was prescribed, with methylprednisolone 250 mg/d with dose tapering on subsequent days, associated with tacrolimus 1 mg/kg/d with a goal serum level of 4-7 ng/mL and everolimus 2 mg/d.

Case 2

Prophylactic intravenous fluconazole for candidemia (risk due to several transfusions) and immunosuppression protocol with methylprednisolone 250 mg/d with dose tapering on subsequent days, associated with tacrolimus 1 mg/kg/d with a goal serum level of 4-7 ng/mL were initiated, plus everolimus 1 mg/d. Additionally, due to the history of hepatitis B, hyperimmune immunoglobulin and entecavir were prescribed. The patient developed a pulmonary infection, and piperacillin-tazobactam, azithromycin 500 mg/d for 5 d and ivermectin 12 mg/d for 2 d were started.

OUTCOME AND FOLLOW-UP

Case 1

On the third postoperative day, he had a fever peak of 38.5ºC associated with desaturation (91% oxygen saturation), and antibiotics were replaced by polymyxin B and meropenem, as the blood culture showed the growth of *Escherichia coli* sensitive to such drugs. Oxygen was supplied through a nasal catheter, with a flow rate of 3 L/min, with the patient remaining comfortable and with an oxygen saturation > 94%. Table 1 shows the laboratory test results. The patient continued to receive acetylsalicylic acid and sulfamethoxazole with prophylactic trimethoprim, according to the liver transplantation protocol of the service. Over the next few days, the patient showed an improvement curve and no new clinical complications. He was discharged to outpatient follow-up after 38 d of hospitalization.

Case 2

The patient's evolution showed clinical improvement and he was extubated on the second postoperative day, with an initial need for 5 L/min of oxygen through a nasal catheter to maintain adequate oxygen saturation and an oxygenation index of 420. Over the next few days, complete weaning from oxygen support was attained.

He showed clinical and laboratory improvement and was discharged from the ICU after 1 wk, and discharged from the hospital after 12 d. He was then referred to outpatient follow-up. During the follow-up period, a new nasopharyngeal swab was collected to screen for SARS-CoV-2 infection, 16 days after the first test and a detectable result has remained to date.

DISCUSSION

The liver is the second most commonly transplanted solid organ worldwide, second only to the kidney. The transplanted population is exposed to several emerging diseases and may even develop symptomatic and, sometimes, severe infections[6,7]. The SARS-CoV-2 pandemic presents a challenging scenario to the reality of transplantations, considering that due to immunosuppression, newly transplanted patients are subject to a high risk of developing complications from infections[8].

The most frequently reported symptoms of SARS-CoV-2 infection in the general population comprise fever, dry cough, myalgia and headache. A Swiss study described the results of a series of 21 patients submitted to solid-organ transplantations who contracted COVID-19, in whom the clinical presentation did not significantly differ from the symptoms described in the general population[9]. In the reported cases, the patients did not have flu-like symptoms during hospitalization.

However, case 1 had a fever peak and showed oxygen desaturation on the third postoperative day, which can be attributed to symptoms of infection by SARS-CoV-2 or by another bacterial infectious process. The evolution of case 2 showed a slower weaning from oxygen support in the postoperative period. A North American study reported a worse prognosis in solid organ recipients with COVID-19[10]. Preliminary data indicate that late transplant recipients have more severe disease than recent transplant recipients, suggesting that immunosuppression itself is not a criterion for severity, and a metabolic component, such as arterial hypertension, diabetes and obesity, which are typically present in late recipients is responsible for the worse prognosis in this population[11].

A study reported on four transplant recipients who were diagnosed with SARS-CoV-2 between 7 and 10 d after the transplant. Three had a good evolution and one died due to a cause unrelated to COVID-19[12]. In our center, only these two patients were transplanted with SARS CoV-2 infection detected by RT-PCR during surgery and both showed a good evolution. To date, there has been no description in the world literature of other recipients with SARS-CoV-2 infection detected by RT-PCR immediately before transplantation. Despite our small sample, our data confirmed the recent literature indicating that immunosuppression alone is not a factor of poor prognosis in the presence of COVID-19. As recommended by the transplant societies, our patients were screened for COVID-19 prior to the procedure, in order to predict possible adverse developments in the postoperative period and allow more adequate multidisciplinary patient care. However, the difficulty in obtaining the results and the fact that the patients did not have respiratory symptoms were essential in the decision by the medical team to proceed with the transplant, even without the COVID-19 test results. Another important fact was the patients' disease severity, as both patients had

an important risk of worsening liver disease, given their high MELD score.

There are reports in the literature of several pathogens that can be transmitted through grafting. In the case of heart and lung transplantation, the International Society of Heart and Lung Transplantation recommends considering the exclusion of suspected or confirmed donors with SARS-CoV-2 infection, as the microorganism is predominantly found in respiratory secretions[13]. With regard to liver transplantation and COVID-19 infection, recent recommendations suggest that the procedure can be performed during the pandemic[14]. However, transmission *via* the liver graft cannot be excluded, since the virus has been found in blood in up to 15% of cases. A study described the autopsy results of 27 patients and showed that SARS-CoV-2 can be detected in multiple organs, including the lungs, pharynx, heart, liver, brain and kidneys[15]. It is noteworthy that liver damage may be caused by direct liver injury due to COVID-19, medication-induced hepatotoxicity and immune-mediated inflammation.

In our center, we chose to continue to perform transplants during the pandemic, limiting the procedure to candidates with greater need for transplantation, as in the described cases. The use of personal protective equipment to reduce the transmission chain as much as possible is mandatory among health professionals, and any professional who is symptomatic or has positive results for COVID-19 is removed from the procedure.

The current proposal in our center is to screen all possible donors for SARS-CoV-2 infection using RT-PCR. If the donor is positive, they are immediately excluded.

With regard to the recipient, the current proposal of this transplantation center is that during the outbreak of certain diseases, as in the case of COVID-19, an initial screening is carried out by telephone, to determine flu-like symptoms and contact with suspected or confirmed cases of SARS-CoV-2 infection. It is also advised that the patient should remain in social isolation for at least 14 d before the transplant, to avoid possible infectious contamination.

A clinical history of flu-like symptoms is again performed upon hospital admission. Additionally, chest X-rays and nasopharyngeal swab screenings are performed to minimize the risk of transmission. Computed tomography of the chest is reserved for patients with significant alterations shown on chest X-rays. If the patient is suspected of having COVID-19, the transplant is postponed and should be performed in a timely manner. However, it is important to emphasize that the clinical condition is taken into account, in order to define whether the patient has the possibility of an adverse evolution if the transplant is postponed, especially in patients without respiratory complaints.

As relevant data are scarce, it is important to identify a population of recipients that can safely undergo solid organ transplant even with RT-PCR detected SARS-CoV-2 infection, in whom the risk of not undergoing the transplantation is higher than that of the infection.

To date, there is no proven therapy for the treatment of symptomatic coronavirus cases. Recent studies have shown clinical improvement after the use of corticosteroid therapy in cases of severe acute respiratory syndrome associated with COVID-19[16].

Hydroxychloroquine, lopinavir/ritonavir and remdesivir were not used in the present study and immunosuppressive therapy after liver transplantation was not altered, as the patients showed progressive clinical improvement and they were easily weaned from mechanical ventilation in the postoperative period.

CONCLUSION

Two cases of successful liver transplant are described in patients with a positive test for COVID-19 immediately after transplantation, with minimal symptoms and no graft dysfunction after the procedure. In this new post-COVID-19 era, the experience in this center can be used as an example, in order that other services can continue to perform transplants and, thus, reduce the morbidity and mortality of this population on the waiting list. Transplant centers must be able to readjust daily to evolution of the COVID-19 pandemic and care during the pandemic must be intensified, requiring a donor and recipient screening process to detect COVID-19. If the disease is detected, transplantation should be carefully considered. It is worth mentioning that the care and use of personal protective equipment by the multidisciplinary team is crucially important to prevent the viral propagation cycle.

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Editor-in-Chief of *World Journal of Clinical Infectious Diseases*, Wei Wang, MD, PhD, Associate Professor, Jiangsu Institute of Parasitic Diseases, Key Laboratory on Technology for Parasitic Disease Prevention and Control, National Health and Family Planning Commission, Jiangsu Provincial Key Laboratory on Molecular Biology of Parasites, Wuxi 214064, Jiangsu Province, China. wangweijipd@163.com

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LETTER TO THE EDITOR

COVID-19 mortality and gross domestic product loss: A wake-up call for government leaders

Atsushi Sakuraba, Toshiro Sato

ORCID number: Atsushi Sakuraba 0000-0003-2519-6129; Toshiro Sato 0000-0001-8353-8137.

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Atsushi Sakuraba, Department of Medicine, University of Chicago, Chicago, IL 60637, United States

Toshiro Sato, Department of Organoid Medicine, Keio University School of Medicine, Tokyo 108-8345, Japan

Corresponding author: Atsushi Sakuraba, MD, PhD, Associate Professor, Department of Medicine, University of Chicago, 5841 S Maryland Ave, Chicago, IL 60637, United States. asakurab@medicine.bsd.uchicago.edu

Abstract

Government leaders have struggled to reduce the infection and deaths due to coronavirus disease 2019 (COVID-19) as well as to keep the economy and businesses open. There is a large variation of mortality and damage to economy among countries. One possible cause leading to the large variation is the manner in which countries have delt with COVID-19. Some countries or regions such as China, New Zealand, and Taiwan, acted quickly and aggressively by implementing border closures, lockdown, school closures, mass testing, *etc.* On the other hand, many European countries, United States, and Brazil delayed their decisions to implement these restrictions and measures. No study has assessed the correlation between gross domestic product (GDP) and COVID-19 mortality. In the present study, there was a negative correlation between GDP and COVID-19 mortality suggesting that countries that failed to control the virus (larger COVID-19 mortality) would see a larger decline in GDP. Governmental leaders should act fast and aggressively when making decisions because data shows that countries who have run after two hares have caught neither. Furthermore, citizens of each country need to do their own part by following guidelines and practicing social distancing and mask wearing, which are considered the most effective, easiest, and cheapest measures that can be taken, so that repeated lockdowns can be avoided.

Key Words: Coronavirus; COVID-19; Mortality; Gross domestic product; Economy; Global

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Core Tip: There is a large variation of mortality and damage to economy due to coronavirus disease 2019 (COVID-19) among countries. In the present study, we demonstrated that there was a negative correlation between gross domestic product (GDP) and COVID-19 mortality suggesting that countries that failed to control the virus would see a larger decline in GDP. Some countries or regions (China, New Zealand, and Taiwan) have acted quickly and aggressively to prevent the spread of COVID-19, which resulted in relatively small damage to the economy. Governmental leaders should act fast and aggressively when making decisions because data shows that countries who have run after two hares have caught neither.

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TO THE EDITOR

Coronavirus disease 2019 (COVID-19) has caused varying degree of infections and deaths among countries worldwide. Governmental leaderships have taken various measures, including border closure, lockdowns, and school closures, to mitigate the spread of COVID-19 infection[1]. A majority of these government implemented measures have a large impact on the daily life of the people and the economy causing dilemma and controversies. China and New Zealand rapidly implemented extremely strict measures and successfully contained the infection whereas some countries took minimum or delayed measures and decided COVID-19 to run its course[1,2]. While healthcare system, structural inequality, population characteristics, *etc.* may also influence COVID-19 infection and mortality, governmental leaders take various factors into consideration when making decisions, so that they can maintain a balance between the casualty caused by COVID-19 and the economy[3]. One of the rationales to keep social activities intact is that restrictions would cause more economic crisis, societal damage, and ultimately loss of lives.

Strict restrictions on economic activity including lockdowns are effective in flattening the surge of infections, however, there is limited data regarding the relationship between the degree of COVID-19 tragedy and economic damage. In order to gain knowledge about these two dichotomous outcomes, we analyzed the association between COVID-19 mortality and gross domestic product (GDP) among countries in the Organisation for Economic Co-operation and Development (OECD) and partnering countries. Data of mortality was obtained from worldometers.info and that of GDP of the second quarter (Q2) 2020 were obtained from OECD.org. on October 2, 2020.

Among 46 countries, we found that there was a statistically significant negative association between COVID-19 mortality and GDP growth (Figure 1, R^2 = 0.18, P = 0.0034). The association suggested that with every 10 deaths/million increase, the GDP decreased by 0.53%. China, which took aggressive measures after experiencing the outbreak in Wuhan and kept the mortality low at 3/million population was the only country that had a positive GDP growth. Other countries had a negative GDP growth ranging from 0-5% in Russia, South Korea, and Finland, 5%-10% in Japan, United States, *etc.*, and over 10% in France, Spain, *etc.* There was a significant trend for increasing loss of GDP among countries that had mortality in the range of 0-50/million, 50-250/million, and ≥ 250/million (Jonckheere-Terpstra test for trend, P = 0.00033) confirming that countries with greater mortality had larger loss of GDP.

A limitation of this analysis is that we only included countries included or partnered with OECD. Each country has a different portfolio of personal consumption, business investment, and net exports, thus, it remains to be determined whether our results are generalizable to other countries. Furthermore, the COVID-19 pandemic is still ongoing, so the mortality and economic damage are dynamically changing, especially during the third wave of winter 2020 happening right now. Case fatality rate is often used as between country comparison, but we chose mortality as there is less variation in identifying cases of death between countries. It should also be noted that some countries have different criteria when reporting deaths due to COVID-19

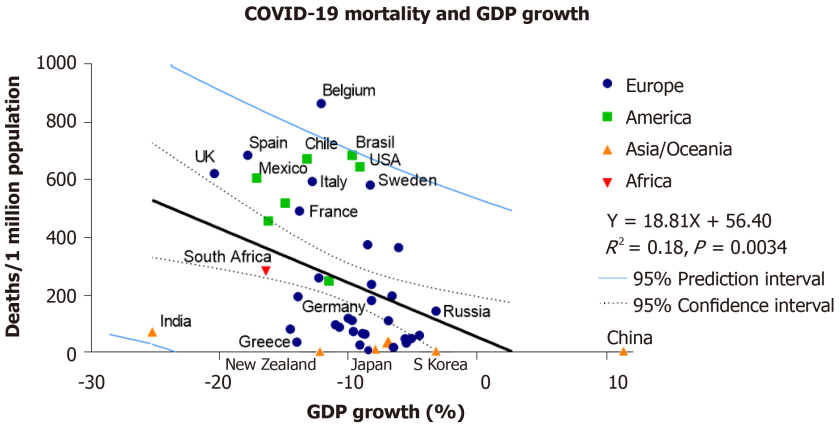

Figure 1 Association between coronavirus disease 2019 mortality and gross domestic product growth. Data of coronavirus disease 2019 (COVID-19) mortality was obtained from Worldometer and that of 2020 Q2 gross domestic product (GDP) was obtained from OECD.org. on October 2, 2020. Among 46 countries, there was a strong negative association between COVID-19 mortality and GDP growth (R^2 = 0.18, P = 0.0034). COVID-19: Coronavirus disease 2019; GDP: Gross domestic product.

and possibility of underreporting of cases/deaths have also been mentioned. Furthermore, we showed an association, but it does not mean that there is a causal relationship and other environmental and economic factors likely play a role[4].

The current pandemic has caused enormous damages to human lives and economy. Our data demonstrated an association between COVID-19 mortality and economic loss suggesting that keeping the mortality low by various measures may result in smaller economic loss. Governmental leaders should take this fact into consideration and must act fast and aggressively when making decisions because data shows that countries who have run after two hares have caught neither. Furthermore, citizens of each country need to do their own part by following guidelines and practicing social distancing and mask wearing, which are considered the most effective, easiest, and cheapest measures that can be taken[5], so that repeated lockdowns can be avoided.

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Peer Reviewer of *World Journal of Clinical Infectious Diseases*, Ming-Ming Yu, PhD, Doctor, Department of Nuclear Medicine, The Affiliated Hospital of Qingdao University, Qingdao 266100, Shandong Province, China. mingmingyu@bjmu.edu.cn

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SYSTEMATIC REVIEWS

Prevalence of anal human papillomavirus infection in patients with human immunodeficiency virus infection: A systematic review

Cinara Dourado Pereira Correia Santos, Caio Caires Brandão, Fernanda Santos Mota, Isis Souza Ferreira, Caline Novais Teixeira Oliveira, Cláudio Lima Souza, Fabrício Freire de Melo, Márcio Vasconcelos Oliveira

ORCID number: Cinara Dourado Pereira Correia Santos 0000-0002-4093-6423; Caio Caires Brandão 0000-0003-3145-4497; Fernanda Santos Mota 0000-0001-8392-8936; Isis Souza Ferreira 0000-0002-8634-9662; Caline Novais Teixeira Oliveira 0000-0003-3094-4363; Cláudio Lima Souza 0000-0002-8094-8357; Fabrício Freire de Melo 0000-0002-5680-2753; Márcio Vasconcelos Oliveira 0000-0002-8959-0478.

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Caio Caires Brandão, Medical School, Faculdade Santo Agostinho, Vitória da Conquista 45028-100, Bahia, Brazil

Corresponding author: Fabrício Freire de Melo, PhD, Postdoctoral Fellow, Professor, Instituto Multidisciplinar em Saúde, Universidade Federal da Bahia, Rua Hormindo Barros 58 Quadra 17 Lote 58, Vitória da Conquista 45029-094, Bahia, Brazil. freiremelo@yahoo.com.br

Abstract

BACKGROUND

Human papillomavirus (HPV) is one of the most common sexually transmitted viruses nowadays.

AIM

To analyze the prevalence of HPV infection in human immunodeficiency virus (HIV)-positive patients and the risk factors associated with this infection through a review of studies published in the period from January 2010 to April 2020.

METHODS

A total of 384 articles were initially identified in our searches, of which ten were selected according to previously defined eligibility criteria.

RESULTS

Anal intercourse, absence of condom use, multiple partners, other specific sexual and life habits, and HIV infection are among the risk factors associated with anal HPV infection.

CONCLUSION

In general, there is a higher prevalence of anal HPV infection among HIV-positive patients, mostly in individuals over 30 years old, those with multiple partners, those who had an early homosexual debut, and cigarette, alcohol, and drug users.

Key Words: Human immunodeficiency virus; Anal human papillomavirus; Risk factors; Systematic review

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Core Tip: Human papillomavirus (HPV) is among the most common sexually transmitted viruses today. This systematic review aimed to analyze the prevalence of HPV infection in patients infected with human immunodeficiency virus (HIV) as well as the risk factors associated. Number of partners, absence of condom use, anal intercourse, multiple partners, sexual and life habits, and HIV infection are among the risk factors associated with anal HPV. There is a higher prevalence of anal HPV in patients infected with HIV, those with multiple partners, alcohol and drug users, and those with early age of first sexual intercourse with same-sex individuals.

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INTRODUCTION

Sexually transmitted infections (STIs) are among the most prevalent diseases, and human immunodeficiency virus (HIV) infection affects millions of people worldwide. In 2019, 1.7 million people were infected by HIV, which illustrates the relevance of this infection[1,2]. Another common STI is caused by human papillomavirus (HPV), which has a close relationship with the emergence of cancer in the perianal region, especially in individuals with weakened immune system, such as those who are seropositive for HIV[3].

The HPV is a DNA virus that causes a variety of benign and malignant lesions on the skin and mucous membranes[4]. More than 150 HPV types have been described, among which the HPV 16 and 18 are the most frequent and pathogenic types as they infect the genital tract and are associated with a high risk of oncogenesis.

In immunocompetent individuals, HPV is usually eliminated within 18 mo after infection, without clinical manifestations, and can be transmitted during this period. In addition, unprotected sexual intercourses, having multiple of partners, early initiation of sexual activity, and lack of immunization greatly contribute to the viral dissemination[4].

The most frequent clinical presentation of HPV is the cutaneous wart, with an estimated incidence of 7%-10% in the European population and of 1% in the American population. In immunosuppressed patients, these numbers are 50- to 100-fold higher, reaching more than 90% after 15 years of transplantation[5].

Another important feature is the association between HPV infection and carcinomas, among which cervical carcinoma is widely studied. However, this relationship is also well established in the anal region, with similarities between the lesions and the characteristics of the epithelia observed in those anatomical sites. Furthermore, the progression of the malignant lesions has similitudes between both regions as well[6-8].

HIV-seropositive patients have a higher risk of contamination by HPV because both infections have similar predisposing factors related to sexual habits. In addition, the persistence of HPV infection and a greater variety of HPV serotypes are observed in the HIV seropositive population[9,10].

The coinfection with HIV and HPV favors HPV DNA mutations, making this virus more pathogenic, regardless of the HIV viral load. The infection associated with immunosuppression can cause lesions with a higher carcinogenic potential, which implies greater aggressiveness of cell lesions and a worse prognosis[11,12].

The progression of HPV infection is established as the immunological damage associated with HIV infection progression. Papillomavirus persistence is inversely related to CD4+ T lymphocyte count and directly proportional to HIV load. In immunosuppressed people, the HPV recurrence rate becomes high[13,14].

In the general population, HPV-associated squamous cell carcinoma in the anal region is rare. However, anal cancer is more prevalent in HIV seropositive populations, men who have sex with men, and women with a history of cancer in the genital region[6,8,15,16].

Several studies have been pointing out the relationship between HIV and HPV, indicating a higher risk of papillomavirus infection in individuals with immune suppression. In this sense, it is essential to compile results of studies evaluating the coinfection with these viruses and demonstrating associated risk factors that contribute to the occurrence of anal changes by HPV. The aim of this systematic review was to verify the prevalence of anal HPV in HIV-seropositive patients as well as to list risk factors associated with this event.

MATERIALS AND METHODS

This is a systematic review conducted in accordance with the PRISMA recommendation (main items for reporting systematic reviews and meta-analyses).

Eligibility criteria

We selected articles on the prevalence and risk factors associated with HPV infection in anal and perianal sites in HIV-seropositive patients from January 2010 to April 2020 that were published in English, Portuguese, and Spanish.

Types of studies

Original research articles on clinical, experimental, and retrospective studies were included, and review articles, *in vitro* fertilization research, case series, and case reports were excluded. Articles that were not open access were not considered in this review.

Types of participants

The population chosen for this review was HIV- and HPV-seropositive patients, and all studies that only included individuals infected with HIV or HPV alone were excluded. We also excluded all articles that involved individuals under the age of 18.

Types of intervention

The articles that comprise the present review deal with the investigation of risk factors associated with HIV-seropositive patients with HPV coinfection at perianal site.

Information sources

The search for articles was conducted from March to April 2020, in the Scientific Electronic Library Online (SCIELO), United States National Library of Medicine (PubMed), and Virtual Health Library databases. In a strategy for searching data in all the bases, the following descriptors were used: HIV infections, papilloma virus infections, and anal canal.

Three authors independently carried out the selection of articles: Brandão CC, Ferreira IS, and Mota FS, co-authors of this paper. Then, duplicate articles were excluded and articles whose abstract did not address risk factors for HPV coinfection in anal/perianal sites in HIV seropositive patients were eliminated as well. Finally, the articles were fully read, including only those that addressed the topic of interest. The interpretative ambiguities and/or doubts were solved by consensus among the authors.

After reading the articles, the main data of each study were extracted, such as author(s), year of publication, factors associated with patients with viral coinfection, and prevalence data of the populations, described in Table 1.

Risk of bias analysis

Among the studies that compose this review, the cross-sectional ones have a greater risk of bias due to confounding factors, especially the lack of control methods used as statistical modeling. In cohort studies, the greatest risk of bias is identified as loss to follow-up. However, it is important to indicate that these biases were not able to significantly change conclusions, which can be verified through the coincident findings in the studies, regardless of the method used and the sample involved.

Table 1 Comparative summary of the articles studied

Ref.	Location	*n*	Study design	Predominant age	Predominant number of lifetime partners	Prevalence of anal HPV infection in HIV+ patients	Prevalence of anal HPV infection in HIV- patients
Li *et al*[17], 2016	China	889	Transversal	≤ 39 yr old: 79.53%	6-30: 58.71%	82.69%	62.81%
Wirtz *et al* [18], 2015	Moscow, Russia	124	Transversal	≤ 35 yr old: 82.1%	α ≥ 5: 64.5%	50%	30.30%
Hu *et al*[21], 2013	Beijing, China	671	Transversal	Median: 28 yr old	-	82.10%	57.50%
Lin *et al*[19], 2018	Taiwan	279	Transversal	< 30 yr old: 71%	< 10: 81.0%	85.30%	73.30%
Welling *et al* [25], 2015	Amsterdam	778	Prospective cohort	Median: 38 yr old	> 100: 64.42%	69%	45%
Wiley *et al* [24], 2013	United States	1262	Multicenter cohort	≤ 59 yr old: 71%	Average: 270	91%	70%
Zhang *et al* [22], 2014	Shenzhen, China	408	Transversal	20-39 yr old: 88.9%	Median: 3	71.40%	33.80%
Ren *et al* [26], 2017	China	164	Transversal	≤ 34 yr old: 91.4%	γ ≥ 1: 92.9%	81%	48.20%
Nowak *et al* [20], 2016	Nigeria	154	Transversal	≤ 29 yr old: 81.1%	≤ 50: 75.32%	91.10%	40.60%
Somia *et al* [23], 2018	Southeast Asia	392	Prospective cohort	≥ 30 yr old: 58.2%	Median: 42.5	89.80%	65.30%

α: Last 12 mo; γ: Last 3 mo. HPV: Human papillomavirus; HIV: Human immunodeficiency virus.

RESULTS

After applying the uniterms, 384 articles were found (4 in SciELO, 159 in PubMed, and 221 in BVS). Following the elimination of duplicate articles and analysis taking into consideration the eligibility criteria, ten articles were selected to compose the present review. Figure 1 shows the steps of this selection process.

All articles were published in English from 2013 to 2018, evenly distributed over this period.

Concerning the geographical areas where the studies analyzed were performed, there was a prevalence of studies conducted in Asia (70%), most of which were conducted in China. None of the studies that comprise this review was carried out in the Brazilian population.

Most articles (70%) used the cross-sectional methodological approach. All studies were conducted with groups of men who have sex with men (MSM) aged 18 years or older. The instruments used by the researchers included self-administered questionnaires and/or interviews that covered sociodemographic information and sexual behavior, which were used as variables associated with anal HPV infection. Most articles also assessed the relationship between the infection and lifestyle habits.

As for the sociodemographic aspects, no standardization of analyses such as age range and education level was verified within the selected studies. In 40% of the studies, most participants were less than 29 years old. Regarding education, half of the analyzed articles revealed a higher prevalence of individuals with complete or ongoing higher education.

The isolated or concomitant use of alcohol, cigarettes, and illicit drugs was little explored in the articles.

Regarding the number of homosexual partners of the participants in the studies which make up this analysis, less than half indicated data about the number of lifetime partners and a minority stratified this data into shorter periods (3 mo, 6 mo, and 12 mo prior to the date of the study).

As for the age of first sexual intercourse with same-sex partners, half of the studies did not analyze this characteristic in their populations. Moreover, the other half evidenced divergent results, partly indicating age over 18 and partly indicating age under 18.

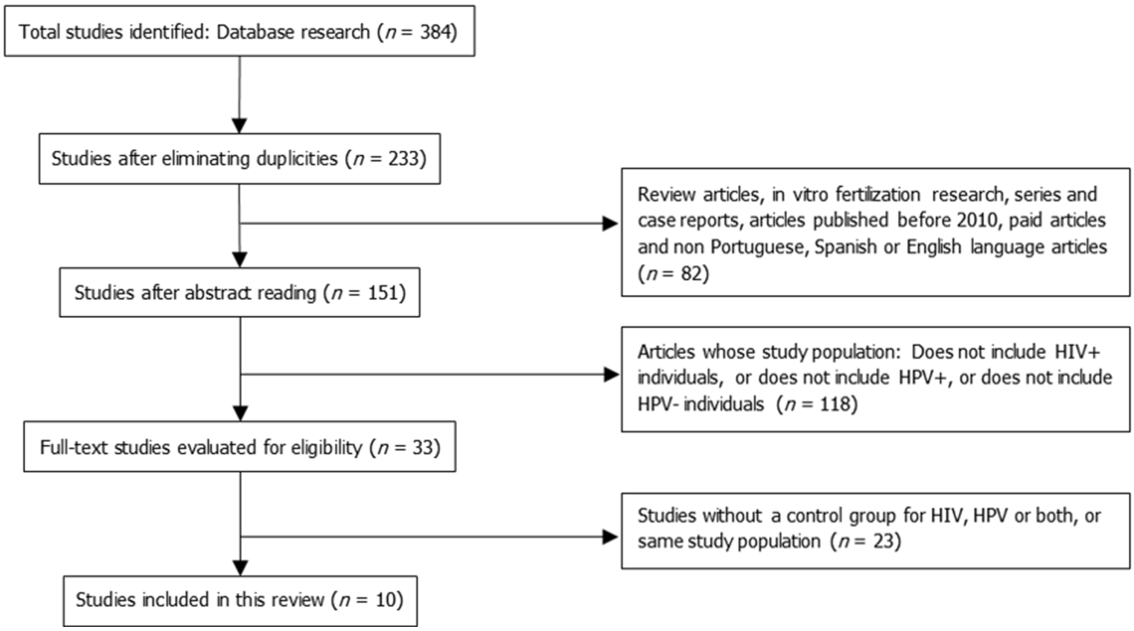

Figure 1 Flow chart of article selection. HPV: Human papillomavirus; HIV: Human immunodeficiency virus.

Overall, the studies were in agreement regarding the prevalence of anal HPV infection in HIV-seropositive patients, whereas the same levels of agreement were not found for anal HPV infection in HIV-seronegative patients (Table 1).

DISCUSSION

When analyzing the ten studies selected in this review, it was observed that none of them was conducted in Brazil. The methodological criteria listed for eligibility and the search mechanisms established here might have been responsible for this exclusion, especially concerning the non-inclusion of articles that were not open access.

Another important characteristic of this review was that most studies were cross-sectional. This methodological proposal is easier to execute, but it limits the evaluation of causality. The cause-and-effect relationship between the studied diseases is thus impaired, mainly because both diseases have similar epidemiological characteristics, and this kind of study does not offer a progressive perspective of the outcomes evaluated within the natural history of the disease.

In 40% of the studies[17-20], most patients were less than 29 years old. In the other studies, there was a wide variation in age classification, with two articles[21,22] reporting median ages of 28 and 29 years, respectively, and three articles[23-25] indicated a median age of greater than or equal to 30 years old.

Li *et al*[17], Wiley *et al*[24], and Ren *et al*[26] performed a more refined analytical approach in their studies, presenting more consistent results that indicate associations between age group and HPV infection. The research done by Wiley *et al*[24] demonstrated that patients aged between 40 and 69 years are more prone to infection by oncogenic high-risk HPV serotypes. The study by Ren *et al*[26], in its turn, showed that 78.6% of the MSM aged 35 years or older had anal HPV infection, a higher prevalence compared to all younger age groups. Li *et al*[17] showed that participants under the age of 29 had a 66.7% prevalence rate for HPV infection in the anal region.

The second point regarding socio-demographic criteria was education. The authors' reports diversified the approach to this assessment. The level of education of the population investigated by Li *et al*[17], Wirtz *et al*[18], Lin *et al*[19], Somia *et al*[23], and Ren *et al*[26] revealed a preponderance of individuals with completed or in training Higher Education. Conversely, Nowak *et al*[20] and Zhang *et al*[22] had the majority of individuals surveyed with lower educational levels.

The article by Lin *et al*[19] found a statistically significant association between high level of education and prevalence of anal HPV (P = 0.001). The studies by Li *et al*[17] and Somia *et al*[23] evaluated the educational level as a possible explanatory variable for the presence of high-risk oncogenic HPV but they found no statistically significant association. The other studies only described the participants' schooling. The lack of

standardization of the studies regarding the stratification of variables and the number of patients included hindered further inferential discussions.

Variables such as marital status, ethnicity, and skin color were only little explored in the studies listed in this review, which unfortunately does not allow us to make further inferences about them as possible risk factors associated with the occurrence of anal changes associated with HPV infection in HIV-positive individuals.

In the articles that make up this systematic review, little was explored about the relationship between smoking and use of illicit drugs and the presence of anal HPV infection. Furthermore, all the studies that assessed smoking found a higher frequency of tobacco use among HIV-positive individuals. Welling *et al*[25] demonstrated, through multivariate analysis, a relationship between HIV and HPV serological statuses and smoking. They have found that 23.5% of the HIV-seronegative and HPV-positive patients smoke (P = 0.467), whereas in seropositive patients for both viruses the percentage is 41.8% (P = 0.075). It demonstrates that smoking is a habit related to HPV and HIV infections, a finding reinforced in the study by Wiley *et al*[24], which reported that smoking habit is directly related to a higher prevalence of positive tests for low- and high-risk HPV (P = 0.04).

Regarding illicit drug use, Lin *et al*[19] and Hu *et al*[21] identified that individuals who use illicit drugs had a higher odds of HIV infection, HPV infection, or co-infection with both viruses.

The number of partners was a factor evaluated with regard to sexual habits. Three studies investigated the number of partners that respondents had throughout their lives. The study by Lin *et al*[19] used the parameters of less than 10 partners and 10 or more partners throughout life, and no statistically significant association was found regarding HPV prevalence. Nowak *et al*[20], on the other hand, found a significant relationship between having a greater number of sexual partners and the prevalence of high-risk HPV. The study showed that having a lifetime number of more than 50 partners is associated with a greater risk of infection (P = 0.02). Additionally, Li *et al*[17] demonstrated that individuals who had an above-30 lifetime number of partners had a higher risk of HPV infection (P = 0.02) than those who had up to 30 partners throughout their lives. Welling *et al*[25] found a statistically significant relationship between HIV seronegative participants who have reported over-500 lifetime number of partners and low-risk HPV infection (P < 0.001), with no significant association identified among participants without HIV infection.

The study by Wiley *et al*[24] observed a higher prevalence of HPV infection among men who had more than 30 partners throughout their lives (P < 0.05). Hu *et al*[21], Zhang *et al*[22], and Somia *et al*[23] indicated in their studies that the number of sexual partners that respondents ever had is an important factor for HIV and HPV infection but it should be noted that these studies found no statistically significant associations regarding this variable. All the other articles that comprise this review did not assess the relationship of lifetime number of partners with HPV infection; they did so by considering shorter periods of 6, 12, and 24 mo prior to application.

Another variable that has been evaluated is the age of initiation of sexual life among homosexual individuals. Li *et al*[17], Wirtz *et al*[18], Nowak *et al*[20], Somia *et al*[23], and Ren *et al*[26] assessed in their studies the age of sexual intercourse debut, but this parameter was not significantly associated with a higher prevalence of HPV infection in any of these studies.

Another factor evaluated was the practice of receptive and insertive anal sex. In the study by Lin *et al*[19], 82.1% of the subjects practiced receptive anal sex. Moreover, they have also found a higher prevalence of receptive anal sex among HPV-positive individuals than among HPV-negative people (91.3% *vs* 75.6%, P = 0.01). The study by Hu *et al*[21] revealed that 83.7% of the HIV-seropositive patients practiced receptive and insertive anal sex; in contrast, these sexual practices were reported by 58.2% of the HIV-seronegative patients (P < 0.01), and no statistically significant relationship was found between this variable and the prevalence of HPV in this study. Another important data observed by Li *et al*[17] was that 65.51% of individuals who always use condoms during anal intercourse had HPV infection. Somia *et al*[23] reported that HIV-seropositive individuals are more likely to use condoms, corresponding to 69.2% of the studied sample (P = 0.02), and no statistical significance was found in the association between this parameter and HPV prevalence.

The most important risk factor identified for HPV infection after analyzing the articles was HIV seropositivity. In all articles, HIV-seropositive patients had a higher prevalence of HPV infection than HIV-negative individuals. The study by Hu *et al*[21] described that immunosuppression due to HIV infection increases not only the risk of HPV infection, but also the persistence of infection and reactivation of latent infection status. This study also found that people at higher risk of acquiring HIV infection are

also at higher risk to be infected with HPV, since both infections are associated with high-risk sexual habits. The study by Ren *et al*[26] further demonstrated that HIV-seropositive MSM were 4.1 times more likely to be infected with any HPV serotype in the anal region compared to HIV seronegative MSM.

Two studies stood out for bringing very specific data on the topic. Lin *et al*[19] compared HIV-seropositive and HIV-seronegative individuals and found that HIV-positive individuals had infections with more than one HPV serotype. Likewise, Wiley *et al*[24] found that men who were not infected with HIV had a 1.8-fold higher odd of having infections with a single HPV serotype than HIV carriers.

In 20% of the articles analyzed, it was possible to observe that HIV-seropositive individuals had a higher risk for infection by high-risk HPV serotypes, especially serotypes 16 and 18. Wiley *et al*[24] found in their sample that 31% of the HIV patients were infected with HPV serotype 16 or 18, while, for HIV-negative patients, the percentage was 20%. The trial by Lin *et al*[19] attested that recent studies detected that HIV-seropositive men with HPV serotype 16 infection showed a higher affinity of the virus to the cells of the anal epithelium, which might be an excellent marker for predicting anal precancerous lesions. The results obtained by Wirtz *et al*[18] revealed that positivity for HPV 16 and 18 was associated with individual behaviors such as the number of male sexual partners, the greater number of stable partners with this same infection, and the use of lubricants incompatible with latex condom, which potentially facilitates exposure to HPV infection during anal intercourse.

All the studies listed here compared the prevalence of HPV infection in the anal region of HIV-seropositive and HIV-seronegative patients. The studies by Li *et al*[17], Wirtz *et al*[18], Hu *et al*[21], Somia *et al*[23], Wiley *et al*[24], and Welling *et al*[25] obtained similar results regarding the rates of HPV infection among HIV-positive and HIV-negative individuals, showing that this prevalence ranged from 18.6% to 24.6%, being higher for HIV seropositive people. In the same way, the studies by Nowak *et al*[20], Zhang *et al*[22], and Ren *et al*[26] also found a considerable difference between HIV-positive and HIV-negative individuals, but at higher levels, ranging from 32.8% to 37.6%. Only the study by Lin *et al*[19] found a smaller difference in anal HPV prevalence in HIV seropositive compared to seronegative individuals (12%). The studies showed statistical significance, except for the articles by Wirtz *et al*[18] and Welling *et al*[25], which did not indicate the significance test value for HPV infection.

After the analysis of the articles included in this review, it was possible to establish a concept map that traces the relationship between the presence of HPV infection and the risk factors associated with this infection (Figure 2).

The concept map shown here establishes the relationship between HIV and HPV infections, assessing several other risk factors in individuals with coinfection that may increase the prevalence of anal changes. Overall, this review has shown that individuals aged 30 years or older and with higher levels of education have been found to be more susceptible to HIV. The use of cigarettes, illicit drugs, having more sexual partners throughout life, starting sexual intercourses with same-sex partners at an earlier age, and performing receptive anal sex were also related to a greater propensity to HIV infection (represented by blue lines in Figure 2). As can be observed, the number of lines that focus on the HIV risk factor makes us infer that HIV seropositive patients have a higher prevalence of HPV infection, which have been represented by the red line in the Figure 2.

CONCLUSION

This review sought to address the HPV prevalence among HIV seropositive patients. After applying all methodological criteria, only ten articles were selected, and all of them addressed risk factors linked to a higher prevalence of HPV infection in individuals infected with HIV. We initially expected a greater number of articles, which may indicate the need for further studies on this theme.

As expected, after a thorough reading of the selected articles, this study reinforced the understanding that the most important factor for the presence of anal HPV infection is HIV seropositivity. The studies used here always compared this relationship between HIV-positive and HIV-negative individuals, but other factors that further increase the risk of HPV infection were also assessed, such as age, smoking, alcohol intake and use of illicit drugs, multiple partners, early age for homosexual debut, and number of homosexual partners.

The importance of studying HPV lies in the fact that it is an agent legitimately associated with the occurrence of cancer, including anal cancer. It becomes even more

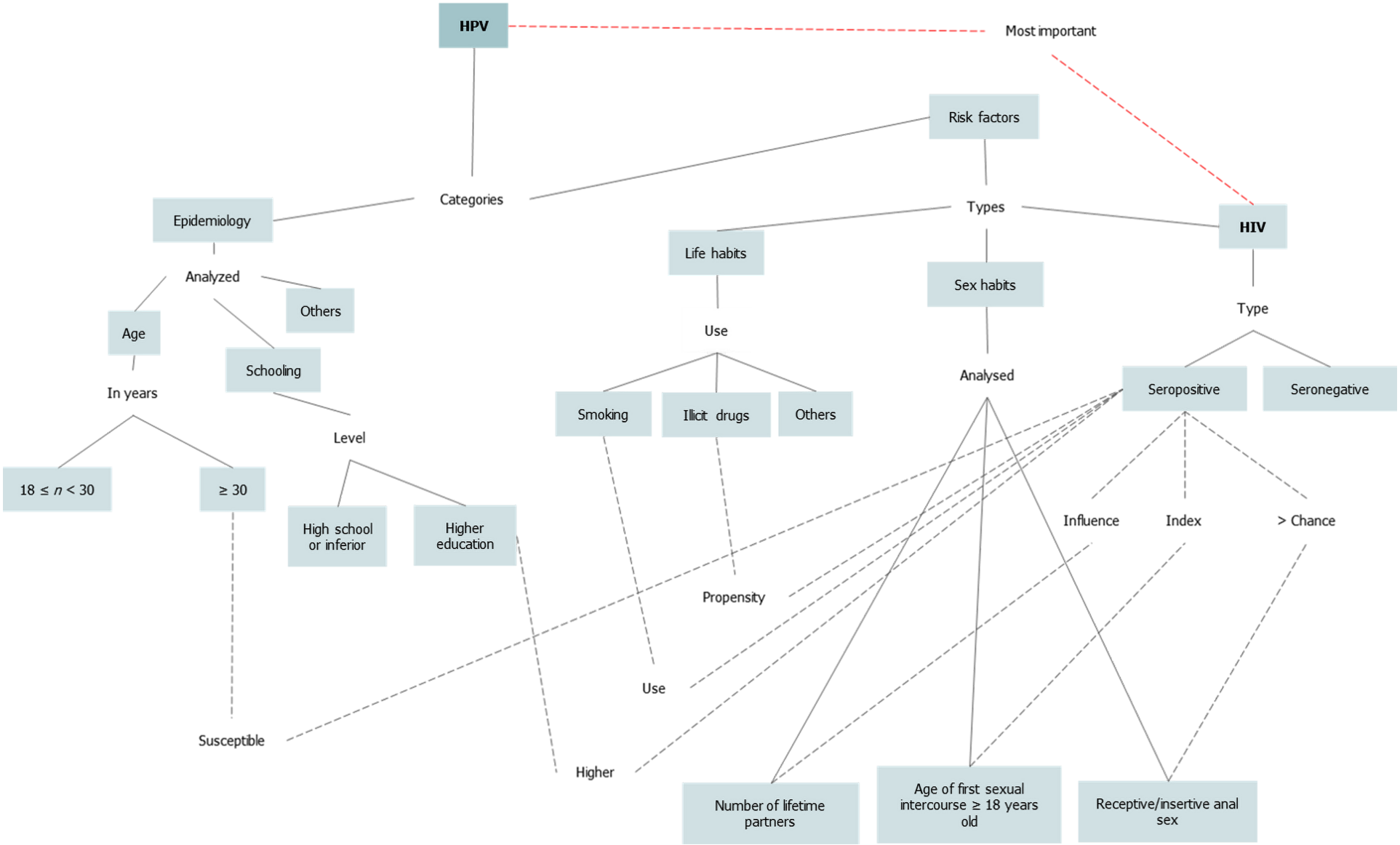

Figure 2 Conceptual map of the relations between human papillomavirus infection and the categories of analysis. HPV: Human papillomavirus; HIV: Human immunodeficiency virus.

important when there are individuals who are under a risk condition that greatly increases the chance of occurrence of this event, such as HIV-seropositive individuals. Thus, with regard to public health management, it is extremely important to recommend a close follow-up of these people, which can change the natural history of HPV disease. This review points out associated factors which in many cases can be modified, which has the potential to greatly contribute to reducing the incidence of high-grade lesions and anal cancer.

In addition, regarding overall patient management, it is possible to reduce the risk of infection by vaccination of groups that are more vulnerable to HPV-mediated high-grade lesions and cancer. The public health system in Brazil currently offers the quadrivalent vaccine for boys and girls aged 9 to 14 years, and this vaccination should be extended to groups of patients that are more susceptible to poorer HPV-related outcomes emphasized in this study.

The articles involved in this review lacked more refined statistical analysis and this decreased the possibility of making some inferences which were previously expected in the methodological planning process.

ARTICLE HIGHLIGHTS

Research background

Sexually transmitted infections are among the most prevalent diseases worldwide, which is considered a public health issue. In immunocompetent individuals, human papillomavirus (HPV) is usually eliminated within 18 mo after infection. However, several studies have been pointing out the relationship between the infection by HIV and HPV, indicating a higher risk of papillomavirus infection in individuals with immune suppression. HPV has also a close relationship with the emergence of cancer in the perianal region, especially in individuals with weakened immune system, such as those who are seropositive for HIV.

Research motivation

In the above-mentioned context, it is essential to compile results of studies evaluating the coinfection with these viruses and demonstrating associated risk factors that contribute to the occurrence of anal changes by HPV. Since HPV is an agent legitimately associated with the occurrence of cancer, in public health management, it is extremely important to recommend a close follow-up of these people, which can change the natural history of HPV disease.

Research objectives

This study aimed to explore the prevalence of anal HPV infection in HIV-seropositive patients as well as to list risk factors associated with this event.

Research methods

For this systematic review, PRISMA recommendation was followed. Articles on the prevalence and risk factors associated with HPV infection in anal and perianal sites in HIV-seropositive patients from January 2010 to April 2020 that were published in English, Portuguese, and Spanish were selected and analyzed.

Research results

Ten articles were selected, and all of them addressed risk factors linked to a higher prevalence of HPV infection in individuals infected with HIV. This study reinforced the understanding that the most important factor for the presence of anal HPV infection is HIV seropositivity.

Research conclusions

The analysis of the articles points to a higher prevalence of anal HPV infection in patients infected with HIV, those with multiple partners, alcohol and drug users, and those with early age of first sexual intercourse with same-sex individuals. Number of partners, absence of condom use, anal intercourse, multiple partners, sexual and life habits and HIV are among the risk factors associated with anal HPV infection.

Research perspectives

We initially expected a greater number of articles, which may indicate the need for further studies on this theme. This review points out associated factors which in many

cases can be modified, which has the potential to greatly contribute to reducing the incidence of high-grade lesions and anal cancer.

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META-ANALYSIS

Lymphocyte count predicts the severity of COVID-19: Evidence from a meta-analysis

Yi-Si Zhao, Ying-Xi Yu

ORCID number: Yi-Si Zhao 0000-0002-8154-854X; Ying-Xi Yu 0000-0002-4070-5959.

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Yi-Si Zhao, Ying-Xi Yu, Department of Critical Care Medicine, The First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, China

Corresponding author: Yi-Si Zhao, MM, Doctor, Department of Critical Care Medicine, The First Affiliated Hospital of Chongqing Medical University, No. 1 Youyi road, Yuzhong District, Chongqing 400016, China. 476663973@qq.com

Abstract

BACKGROUND

In December 2019, coronavirus disease 2019 (COVID-19) was reported firstly in Wuhan, China. COVID-19 is currently a global pandemic.

AIM

To assess the suitability of lymphocyte count as a biomarker of COVID-19 severity.

METHODS

Five literature databases (PubMed/MEDLINE, Web of Science, Google Scholar, Embase, and Scopus) were searched to identify eligible articles. A meta-analysis was performed to calculate the standard mean difference (SMD) and 95% confidence interval (CI) of lymphocyte counts in coronaviral pneumonia cases.

RESULTS

Eight studies, including 1057 patients, were integrated in the meta-analysis. Lymphocyte counts were associated with severe coronavirus (CoV) infection (SMD = 1.35, 95%CI: 1.97 to 0.37, $P < 0.001$, $I^2 = 92.6\%$). In the subgroup analysis stratified by prognosis, lymphocytes were associated with CoV infection mortality ($n = 2$, SMD = 0.42, 95%CI: 0.66 to 0.19, $P < 0.001$, $I^2 = 0.0\%$), severity ($n = 2$, SMD = 0.93, 95%CI: 1.20 to 0.67, $P < 0.001$, $I^2 = 0.0\%$), and diagnostic rate ($n = 4$, SMD = 2.32, 95%CI: 3.60 to 1.04, $P < 0.001$, $I^2 = 91.2\%$).

CONCLUSION

Lymphocyte count may represent a simple, rapid, and commonly available laboratory index with which to diagnosis infection and predict the severity of CoV infections, including COVID-19.

Key Words: COVID-19; Lymphocyte count; Coronavirus; Severe of disease; Meta-analysis

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Core tip: Lymphocyte count reflects immune function and inflammatory state in infectious disease. Severe acute respiratory syndrome coronavirus 2 spreads and invades through respiratory mucosa, triggers a series of immune responses and induces a cytokine storm, resulting in changes in immune components such as lymphocytes. Previous studies have shown that the decrease in lymphocyte count can be used as an indicator of severity for both severe acute respiratory syndrome and Middle East respiratory syndrome; both of which are coronavirus (CoV) infections. Therefore, this systematic review and meta-analysis evaluate the diagnostic and prognostic utility of the lymphocyte count in patients with viral pneumonia by CoV infections.

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INTRODUCTION

In December 2019, in Wuhan, China, a novel CoV was identified as the causative agent of a novel pneumonia. The disease and the virus were subsequently termed coronavirus disease 2019 (COVID-19) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), respectively, by the World Health Organization (WHO)[1,2]. To date, COVID-19 has infected over 465 000 people in 199 countries, with nearly 21 000 deaths [3]. These numbers continue to increase. As a CoV hypotype, SARS-CoV-2 is similar to the CoVs causing severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS)[4,5]. Both SARS and MERS spread rapidly worldwide, and have led to more than 10 000 human infections and 1000 deaths[4,6]. The largest epidemiological study of COVID-19 performed by the Chinese CDC showed that 13.8% of all COVID-19 cases were severe, and 4.7% were critical[7]. Critical patients, with a 49% case fatality rate, are at the most risk of death from COVID-19[7]. Therefore, it is important to develop a rapid, simple clinical method to identify severe COVID-19 cases.

Lymphocytes play a decisive role in the maintenance of immune homeostasis and the inflammatory response[8]. During the progression of an infectious disease, lymphocyte count reflects immune function and inflammatory state. SARS-CoV-2 invades *via* the respiratory mucosa, triggering a series of immune responses, including a cytokine storm, and affecting immune components, such as peripheral blood leukocytes and lymphocytes[9]. Consistent with this, studies have shown that lymphopenia, particularly the depletion of CD4 and CD8 lymphocytes, is a clinical characteristic of COVID-19 patients, especially those with severe infections[10-12]. Indeed, previous studies have shown that the decrease in lymphocyte count can be used to indicate the severity of SARS and MERS, both of which are CoV infections[13, 14]. However, due to the lack of analytical data, as might be provided by case–control or cohort studies, it is unclear whether lymphocyte count can also be used to reflect COVID-19 severity. Although Tan *et al*[15] had reported that lymphocyte count predicted the severity of COVID-19, this study had too few samples. However, relying on the association of CoV infection, we found some evidence in a small number of observational studies of COVID-19. Here, we performed a systematic review and meta-analysis to evaluate the diagnostic and prognostic utility of lymphocyte count in patients with viral pneumonia caused by CoV infections. Our aim was to explore the possibility that lymphocyte counts can predict COVID-19 severity and provide associated evidence.

MATERIALS AND METHODS

Search strategy and selection criteria

This protocol was registered with the PROSPERO international prospective register of systematic reviews (CRD42020177132, available from: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=177132) and followed the recommendations

established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[16]. We conducted a systematic review across five literature databases: PubMed/MEDLINE, Web of Science, Google Scholar, Embase, and Scopus. The search terms used were as follows: "lymphocyte count," and "pneumonia, viral" or "SARS" or "MERS" or "COVID-19". All of the searches were concluded by March 21, 2020, and two researchers independently evaluated the search results.

Eligibility criteria

We included published peer-reviewed articles describing case–control, cohort, or cross-sectional studies, where lymphocyte counts were measured in peripheral blood samples from humans of any age with CoV infections. Case reports, conference abstracts, and review articles were excluded.

COVID-19 infections were diagnosed using next-generation sequencing or real-time reverse transcription polymerase chain reactions (RT-PCRs)[17]. MERS-CoV was diagnosed according to the WHO criteria: a confirmed case was defined as a suspected case that was positive for MERS-CoV based on RT-PCR results[18]. SARS infections were confirmed based on a definite exposure history, as well as either a positive RT-PCR test during acute infection or detectable CoV-specific antibodies during convalescence[19]. We excluded studies conducted exclusively in patients with active cancer, chronic liver disease, HIV, or immunosuppression. When an article reported duplicate information from the same patient, the reports were combined to obtain complete data, but the case was only counted once.

Study selection

All of the titles and abstracts returned by the database search (Figure 1) were reviewed by first author (Zhao YS) independently to assess the need for a full-text review. Any disagreements were resolved through discussion between the same author and another author (Yu YX). Reasons for exclusion were recorded.

Assessment of risk of bias

Publication bias was assessed using a funnel plot, Begg's test and Egger's test.

Statistical analysis

According to a study by Hozo *et al*[20], we estimating the mean and standard deviation from the median and range, and the size of a sample as data extrapolation. When sample size was small (n < 25), we used a simple formula: x = (a + 2m + b)/4 to estimate the mean (x) using the values of the median (m), low and high end of the range (a and b, respectively). As soon as sample size exceeded 25, the median itself was the best estimator. When sample size was small (n < 15), we used the formula: S^2 = 1/12 × (((a - 2m + b)2)/4 + (b - a) 2) to estimate the standard deviation (S^2). When the sample size increased (15 < n < 70), Range/4 was the best estimator for S^2. For large samples (n > 70) Range/6 was the best estimator for S^2[20]. To indicate the severity of CoV infection, we designed a cohort that combined three different measures of prognosis with respect to the control group: diagnosed *vs* nondiagnosed, severe *vs* nonsevere, and death *vs* survival. The control group included nondiagnosed, nonsevere and survival groups. The case group was severe, including diagnosed, severe and death groups.

We used the random-effects model to calculate the standard mean difference (SMD) and 95% confidence interval (CI) for lymphocyte count in the CoV-infection patients and to draw a forest plot. Subgroup analysis was performed based on the study definition of severity. Heterogeneity between pairs of studies was quantified using the I^2 statistic. We investigated potential sources of heterogeneity, including prognosis and data source (original data *vs* extrapolated data), by performing subgroup analyses. One was prognosis subgroup that was divided into mortality, severity and diagnostic rate subgroups according to different prognosis investigated in included studies. One was data source subgroup that was divided into original data and extrapolated data subgroups. The criterion was whether the data extrapolated according to the study by Hozo *et al*[20]. All of the analyses were performed using Stata version 14 (Stata Corp., College Station, TX, USA).

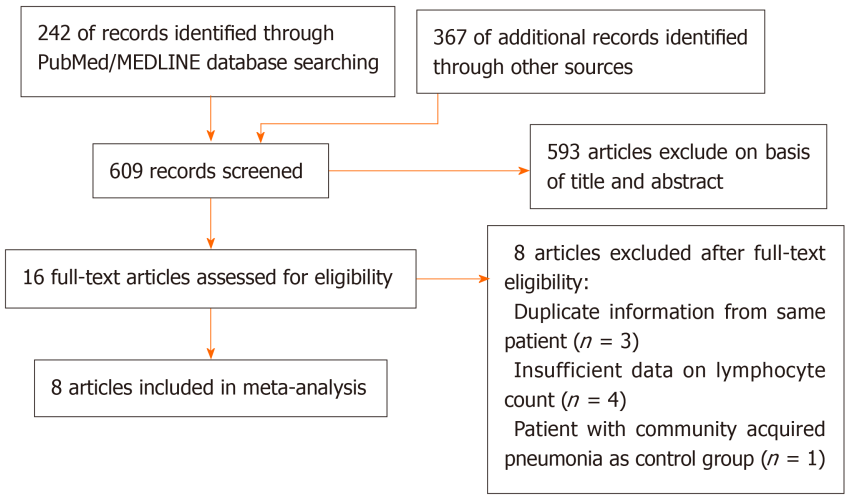

Figure 1 Article selection process.

RESULTS

Results of the electronic search

We identified 609 articles using database searches. After screening, 16 articles remained. After examination of the full-text articles, we excluded eight of these articles: three contained duplicate information from same patient; four articles had insufficient data on lymphocyte count; and one article chose a patient with community-acquired pneumonia as a control group. Therefore, eight studies were included in our meta-analysis[10,13,14,19,21-24].

Characteristics of the included studies

The characteristics of the eight included studies are summarized in Table 1. All of the studies included were prospective or retrospective case–control studies, cohort studies, or cross-sectional studies. The patient population in each study ranged from 30 to 346 (1057 patients in total). The earliest publications were from 2003[22,24], and the most recent article was published in 2020[10,21,23]. Most studies were based in China (n = 7), including Taiwan (n = 3)[13,19,24], Wuhan (n = 2)[10], Beijing (n = 1)[22], and Shanghai (n = 1)[23]. One study was based in Saudi Arabia[14]. The CoV diseases studied were COVID-19 (n = 3; 37.5%)[10,21,23], MERS (n = 1; 12.5%)[14], and SARS (n = 4; 50%)[13,19,22,24]. Four studies (50%) investigated prognosis with respect to diagnostic rate (diagnosed *vs* nondiagnosed)[19,22-24], two studies (25%) investigated prognosis with respect to severity (severe *vs* nonsevere)[10,21], and two studies (25%) investigated prognosis with respect to mortality (death *vs* survival)[13,14].

Characteristics of lymphocyte count

The means and standard deviations of lymphocyte counts from four studies[10,14,21,23] were extrapolated from sample size, median, and IQR (Table 1). In the forest plot, if the SMD (95%CI) was < 0, it showed that the mean and standard deviation of lymphocyte counts in the case group were less than those in the control group. That meant lymphocyte counts were less in severe CoV infection. Analysis showed that lymphocyte counts were associated with severe CoV infection (SMD = 1.35, 95%CI: 1.97 to 0.37, P < 0.001, I^2 = 92.6%) (Figure 2). There was heterogeneity among studies. Therefore, subgroup analysis, stratified by prognosis and data source, was performed. In the subgroup analysis stratified by prognosis, lymphocytes were associated with mortality due to CoV infection (n = 2, SMD = 0.42, 95%CI: 0.66 to 0.19, P < 0.001, I^2 = 0.0%), with severity of CoV infection (n = 2, SMD = 0.93, 95%CI: 1.20 to 0.67, P < 0.001, I^2 = 0.0%), and with the diagnostic rate of CoV infection (n = 4, SMD = 2.32, 95%CI: 3.60 to 1.04, P < 0.001, I^2 = 91.2%) (Figure 3). In the subgroup analysis stratified by data source, lymphocytes were associated with both the extrapolated data (n = 4, SMD = 0.92, 95%CI: 1.33 to 0.51, P < 0.001, I^2 = 64.0%) and the original data (n = 4, SMD = 1.97, 95%CI: 3.35 to 0.60, P < 0.001, I^2 = 96.5%) (see Supplementary Figure 1, which illustrates the forest plot of subgroup analysis stratified by data source), explaining the observed overall heterogeneity among studies. In addition, because few studies were included in our analysis, it was unclear whether the funnel plot was symmetrical

Table 1 Characteristics of the included studies

Ref.	City, country	Coronavirus disease	Outcome	*n* (case)	Lymphocyte count of case, mean ± SD (× 10^9/L)	*n* (control)	Lymphocyte count of control, mean ± SD (× 10^9/L)
Das *et al* [14], 2015	Saudi Arabia	MERS	Mortality	19	18.25 ± 11.75	36	24.00 ± 19.75
Chang *et al* [13], 2006	Taiwan, China	SARS	Mortality	73	0.81 ± 0.38	273	1.02 ± 0.48
Wang *et al* [10], 2020	Wuhan, China	COVID-19	Severity	36	0.80 ± 0.10	102	0.90 ± 0.10
Zhang *et al* [21], 2020	Wuhan, China	COVID-19	Severity	58	0.70 ± 0.13	82	0.80 ± 0.10
Cui *et al*[22], 2003	Beijing, China	SARS	Diagnostic rate	38	0.91 ± 0.44	200	3.00 ± 1.00
Chen *et al* [19], 2006	Taiwan, China	SARS	Diagnostic rate	15	0.60 ± 0.30	15	2.00 ± 0.20
Li *et al*[23], 2020	Shanghai, China	COVID-19	Diagnostic rate	10	1.22 ± 0.20	30	1.75 ± 0.33
Chen *et al* [24], 2004	Taiwan, China	SARS	Diagnostic rate	8	0.90 ± 0.30	62	1.50 ± 1.10

SARS: Severe acute respiratory syndrome.

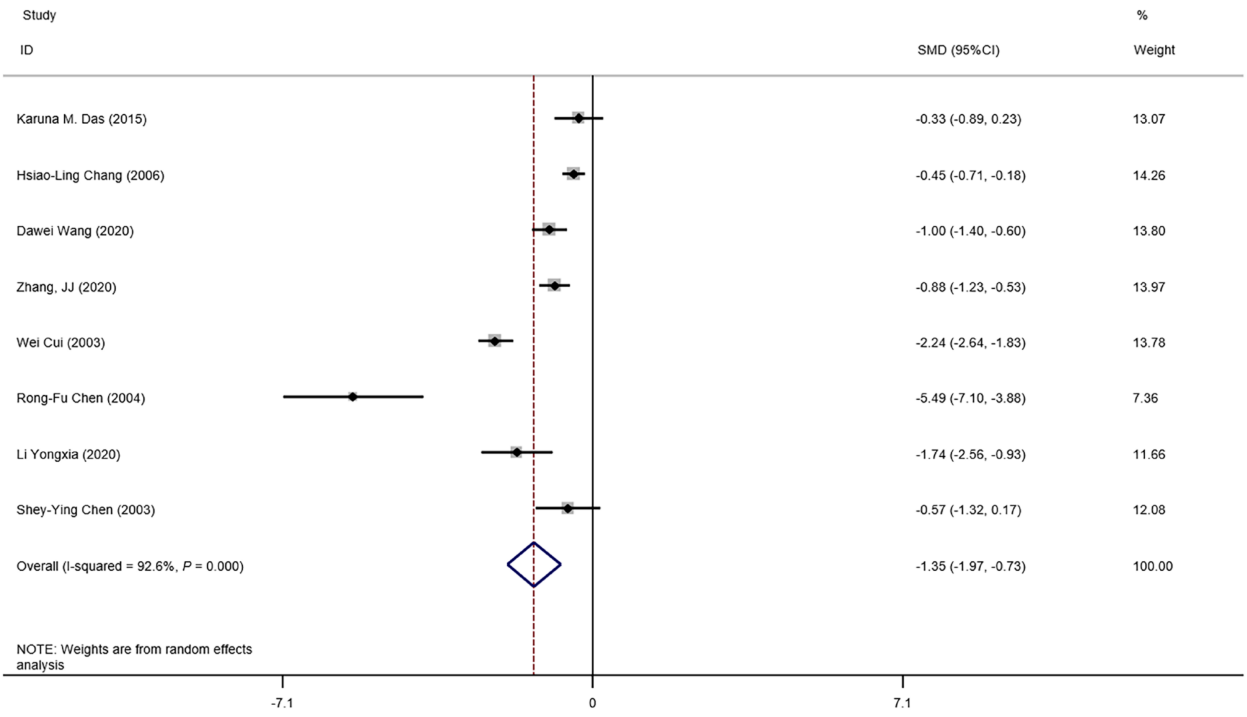

Figure 2 Forest plot: overall identification of lymphocyte count in patients with coronaviral pneumonia. P = 0.000 means P < 0.001. CI: Confidence interval.

(Figure 4), but Begg's test and Egger's test showed that publication bias had no significant effects on the results of the meta-analysis (P = 0.174).

DISCUSSION

COVID-19 is rapidly infectious and highly severe, with a high mortality rate[3]. Patients with COVID-19 exhibit a wide range of variability in disease severity. In clinical practice, we believe that low levels of lymphocytes are disadvantageous for

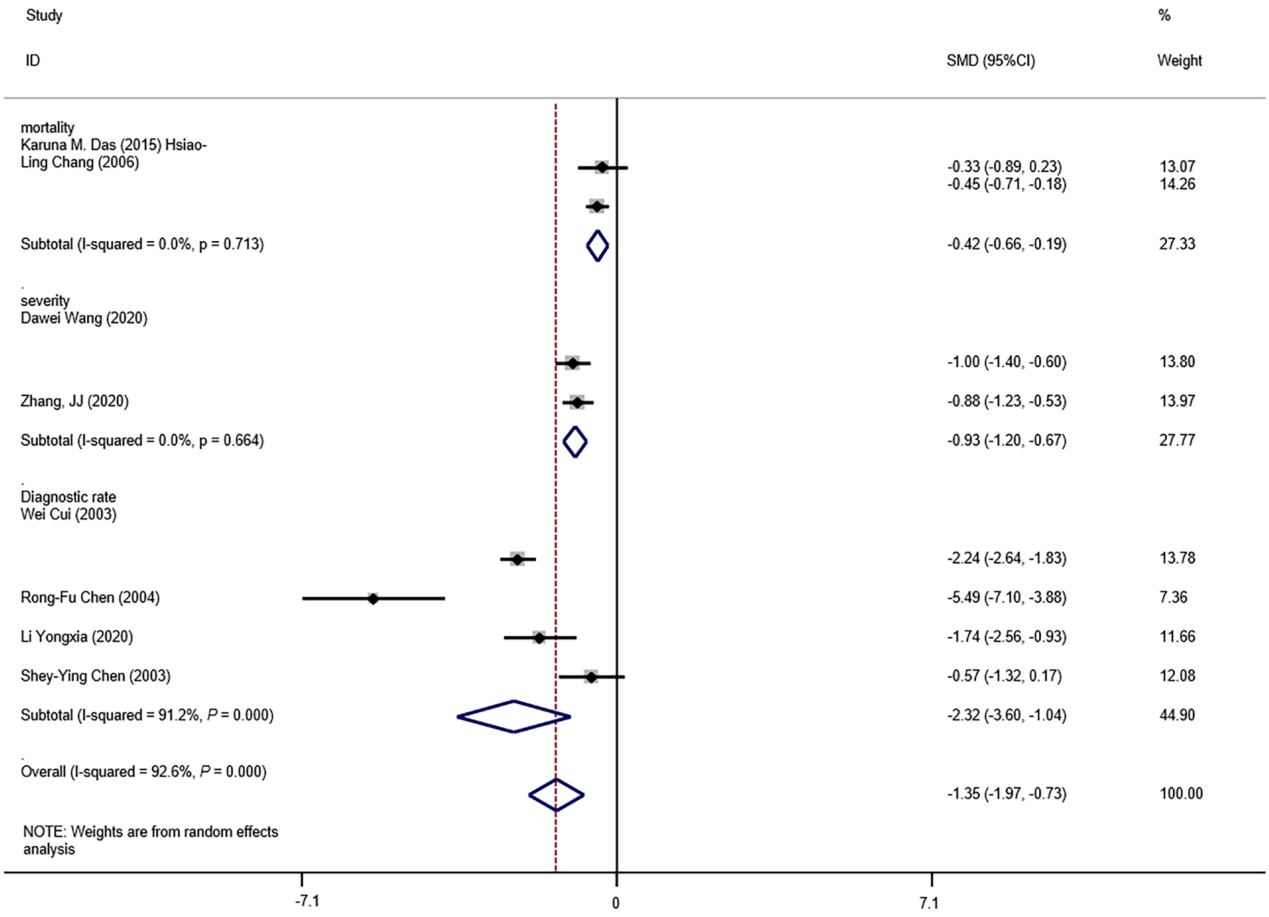

Figure 3 Forest plot: overall identification of lymphocyte count in patients with coronaviral pneumonia, subgroup analysis stratified by prognosis. *P* = 0.000 means *P* < 0.001. CI: Confidence interval.

COVID-19 patients. Because lymphocyte count reflects disease characteristics, it might potentially help in the evaluation of COVID-19 severity. Usefully, this measure is easily available in laboratory tests.

Lymphocytes are vital cells that maintain immune function and execute the immune response in the body[8]. In the best-case scenario, the cellular immune response rapidly clears CoV with little or no clinical signs of infection. Alternatively, the virus causes a state of immunosuppression, which debilitates and sometimes overwhelms the host's defenses[25]. Currently, no detailed study of the immunological response to SARS-CoV-2 is available. Thus, we must rely on previous studies of other CoVs, especially SARS-CoV and MERS-CoV[26]. Based on other CoVs, SARS-CoV-2 might induce a T-lymphocyte-mediated protective immune response[25]. However, lymphopenia is associated with many types of infections, including coronavirus[14,27]. Studies have shown that lymphopenia is related to cell apoptosis in SARS patients[19,28]. In addition, hospitalized patients infected with SARS-CoV-2 frequently manifest lymphopenia, suggesting that cellular immune responses may be suppressed[10,21]. However, lymphopenia in MERS but not SARS cases could be a result of direct infection of T cells and infection-induced apoptosis[29]. Although the lymphopenia in patients with SARS and those with MERS may have different mechanisms, they forecast similar outcome. Furthermore, lymphocyte count as a biomarker to predicting severity in other non-CoV diseases (such as measles, herpes and vaccinia) is effective [19]. Therefore, the hypothesis which predictive role of lymphopenia in COVID-19 is reasonable, and some recently study also provide some evidence to prove this hypothesis[15]. However, studies of the role of lymphocytes in COVID-19 are rare.

In this study, we designed a meta-analysis to explore the feasibility of using lymphocyte count to predict COVID-19 severity. All of the eight studies included in our meta-analysis involved SARS, MERS or COVID-19, and were prospective or retrospective case–control, cohort or cross-sectional studies (Table 1). Existing research results do not always rank the severity of COVID-19 infections using the same criteria. Even during the earliest part of the Chinese outbreak, the guidelines for COVID-19 diagnosis and treatment issued by the Chinese National Health Commission were

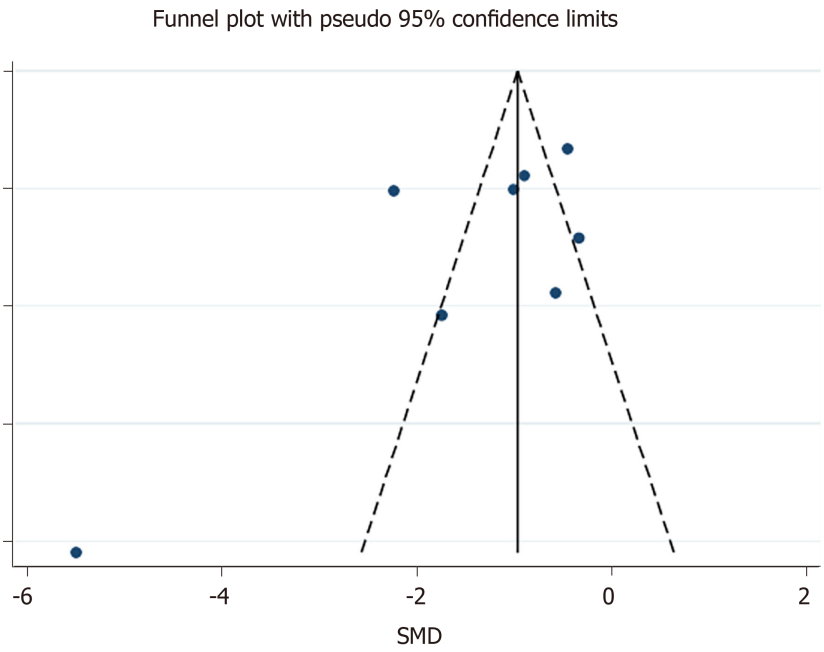

Figure 4 Funnel plot: publication bias of eight studies included.

revised seven times based on clinical experiences[30]. Therefore, we roughly evaluated disease severity using paired concepts: diagnosed *vs* nondiagnosed [19,22-24]; severe *vs* nonsevere[10], and death *vs* survival[13,14].

We found that lymphocyte count was associated with severe CoV infection (Figure 2). Lymphocytes were also associated with CoV mortality, severity and diagnostic rate (Figure 3). Thus, lymphocyte count may represent a simple, rapid, and commonly available diagnostic and severity-prediction tool for CoV infections, including COVID-19. Because we included studies of SARS-CoV-2 infections, our results indicate the value of lymphocyte count for the assessment of COVID-19 severity. A recent related study suggested that lymphocyte percentage might be a reliable indicator of moderate, severe or critical infections, independent of auxiliary indicators[15]. However, this study included few severe (n = 39) and critical (n = 28) cases[15]. In combination, our analysis and the most recent research results suggested that lymphocyte counts potentially reflect COVID-19 severity. Meanwhile, some research has shown that the viral load of SARS-CoV-2 is associated with the lymphocyte count: A study of interleukin (IL)-3 (a cytokine produced by T lymphocytes) discovered that patients with high viral load presented had lower plasma IL-3 levels than low viral load[31]. CD4:CD8 ratio and T regulatory cells significantly decrease in mice with high viral load[32]. Not only T cells, but also B cells and natural killer cells in patients with severe COVID-19 were significantly lower than those in patients with the mild form[33,34]. Lymphopenia in COVID-19 may have several underlying causes, including the destruction of lymphatic organs, the direct attack on lymphocytes by SARS-CoV-2[35], lymphocyte apoptosis due to the continual release of inflammatory cytokines, or, in severe cases, the inhibition of lymphocytes by hyperlactacidemia[36]. It is clear that hyperlacticacidemia- and cytokine-storm-related acute respiratory distress syndrome is the primary presentation of patients with critical COVID-19[30]. Thus, lymphocyte count is an important indicator of severe or critical COVID-19.

For the acute outbreak of COVID-19, the meta-analysis has limitations. We faced a shortage of data sources during the research. Even now, the data on COVID-19 are insufficient. The research results in the previous response to CoVs should be used for reference. The most mainstream of these were SARS and MERS. As other important CoV diseases, they have similarities to COVID-19. From the perspective of the important characteristics of respiratory infections, SARS and MERS could be included in the reference category. The prevention and treatment methods of COVID-19 all often refer to methods of SARS and MERS. A meta-analysis about prevention of person-to-person transmission of COVID-19 also included SARS and MERS coincidentally[37]. Studies have shown that lymphopenia is related to apoptosis in SARS[28]. Lymphopenia is the result of direct T cell infection and infection-induced apoptosis in MERS[29]. Although we think that this conclusion is insufficient, because there are

some treatments (for example: hormone use, antibody titer, *etc*.) that affect the lymphocyte count in the clinic. However, from the current situation of prevalence, spread and treatment, it is of reference value. In studies that were included in the meta-analysis, five referred to lymphocyte counts that were obtained on the day of hospital admission, and two studies did not report clearly the time that lymphocyte counts were obtained. In clinical research, because it is difficult to make a complete review of the course of disease admission, it is generally accepted to choose the day/time of hospital admission as the sampling point[10]. It has been shown that the degree of lymphopenia is steady during the first week[38], and lymphocyte counts progressively decrease and reach their lowest point on day 14 in most cases[38]. Therefore, our analysis did not divide these studies by time of lymphocyte count acquisition. One week of hospital admission could be recognized as a stable interval for lymphocyte counts. However, a recent study showed that lymphocyte count varied at different times of hospitalization[39]. Thus, further study of lymphocyte counts at varied times could increase the predicted efficiency in COVID-19.

CONCLUSION

Our meta-analysis provides information on three simple and common interventions to combat the immediate threat of COVID-19, while new evidence on pharmacological treatments, vaccines, hematology monitoring and other personal protective strategies is being generated[37]. It showed that lymphocyte count may represent a simple, rapid and commonly available laboratory index with which to diagnosis infection and predict the severity of CoV infections, including COVID-19. However, our study was limited by the lack of COVID-19 studies, especially those with homogeneous or uniform standards. Therefore, it was necessary to include SARS and MERS in our study; both of which can lead to coronaviral pneumonia. Thus, these diseases might represent a reference for COVID-19. During the current severe COVID-19 pandemic, we hope to provide a framework for the future predictions of COVID-19 severity. Indeed, if critical infections could be predicted and treated earlier, mortality would be lower. Lymphocyte count is a potential indicator of COVID-19 severity and deserves further examination. However, the high heterogeneity among studies suggests that additional research, including case–control and cohort studies, is required for detailed analyses of the relationship between lymphocyte count and COVID-19 severity.

ARTICLE HIGHLIGHTS

Research background

In December 2019, coronavirus disease 2019 (COVID-19) was reported first in Wuhan, China. COVID-19 is currently a global pandemic.

Research motivation

COVID-19 with high morbidity is a life-threatening disease globally. It is important to develop a rapid, simple clinical method to identify severe COVID-19 cases.

Research objectives

The aim of this study was to assess the suitability of lymphocyte count as a biomarker of COVID-19 severity.

Research methods

We searched five literature databases (PubMed/MEDLINE, Web of Science, Google Scholar, Embase, and Scopus) to identify eligible articles. A meta-analysis was performed to calculate the standard mean difference (SMD) and 95% confidence interval (CI) of lymphocyte counts in coronaviral pneumonia cases.

Research results

Our research integrated eight studies, including 1057 patients. Lymphocyte counts were associated with severe coronavirus (CoV) infection (SMD = 1.35, 95%CI: 1.97 to 0.37, $P < 0.001$, $I^2 = 92.6\%$). In the subgroup analysis stratified by prognosis, lymphocytes were associated with coronavirus infection mortality ($n = 2$, SMD = 0.42, 95%CI: 0.66 to 0.19, $P < 0.001$, $I^2 = 0.0\%$), severity ($n = 2$, SMD = 0.93, 95%CI: 1.20 to

0.67, $P < 0.001$, $I^2 = 0.0\%$), and diagnostic rate ($n = 4$, SMD = 2.32, 95%CI: 3.60 to 1.04, $P < 0.001$, $I^2 = 91.2\%$).

Research conclusions

Lymphocyte count may represent a simple, rapid and commonly available laboratory index with which to diagnosis infection and predict the severity of CoV infections, including COVID-19.

Research perspectives

As a CoV hypotype, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is similar to the CoVs causing severe acute respi-ratory syndrome and Middle East respiratory syndrome. Hence, we performed a systematic review and meta-analysis of the literature to evaluate the diagnostic and prognostic utility of lymphocyte count in patients with viral pneumonia caused by CoV infections. Our aim was to explore the possibility that lymphocyte counts predict COVID-19 severity and provide associated evidence.

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This article also commemorates the Chinese medical staff who gave their lives in the fight against COVID-19.

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LETTER TO THE EDITOR

Can a radioimmunoassay kit be developed for accurate detection of the S protein of severe acute respiratory syndrome coronavirus 2?

Ming-Ming Yu

ORCID number: Ming-Ming Yu 0000-0002-1156-005X.

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Ming-Ming Yu, Department of Nuclear Medicine, the Affiliated Hospital of Qingdao University, Qingdao 266100, Shandong Province, China

Corresponding author: Ming-Ming Yu, PhD, Doctor, Department of Nuclear Medicine, the Affiliated Hospital of Qingdao University, No. 59 Haier Road, Qingdao 266100, Shandong Province, China. mingmingyu@bjmu.edu.cn

Abstract

The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) at the end of 2019 spread worldwide within only a few months. The screening and timely isolation of infected individuals have been regarded as an effective means of epidemic prevention and control. Therefore, effective screening of infected individuals plays a vital role in epidemic prevention and control. At present, reverse transcription-polymerase chain reaction (RT–PCR) is the main method for the *in vitro* detection of SARS-CoV-2. However, RT–PCR requires certified laboratories, expensive equipment, and trained technicians. Therefore, it is necessary to develop simpler and more convenient methods. Some studies have shown that the PepKAA peptide has a high affinity for the S protein of SARS-CoV-2. The tyrosine in PepKAA is labeled with ^{125}I and used to design a radioimmunoassay kit for the detection of the S protein of SARS-CoV-2, which is of great significance for the early diagnosis of COVID-19.

Key Words: SARS-CoV-2; COVID-19; Spike protein; Detection; Radioimmunoassay kit

Core Tip: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is highly infectious, and early detection of SARS-CoV-2 is the key factor in preventing another epidemic. Radioimmunoassay (RIA) exhibits high sensitivity and specificity. The detection of the S protein on the surface of SARS-CoV-2 by RIA is expected to be applied for the early diagnosis of coronavirus disease 2019, which may have a considerable impact on the control of the epidemic.

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TO THE EDITOR

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is highly infectious, and people are generally susceptible to this pathogen. Coronavirus disease 2019 (COVID-19) has caused a global pandemic and has been categorized as a Class B infectious disease in China, and Class A management measures have been implemented[1]. The early laboratory detection of COVID-19 is a key factor for ensuring the early admission, treatment, and timely control of patients to prevent the development of another epidemic[2]. At present, reverse transcription-PCR (RT–PCR) is the main method for the *in vitro* detection of SARS-CoV-2[3]. However, PCR requires certified laboratories, expensive equipment, and trained technicians[4]. The use of a low-cost and simple radioimmunoassay to detect a protein on the surface of SARS-CoV-2 may be of clinical value.

The spike (S) protein is located on the surface of SARS-CoV-2. This protein has a receptor-binding domain (RBD) that can interact with the angiotensin I-converting enzyme 2 (ACE2) receptor in human cells[5]. Souza PFN[6,7] showed that eight antibacterial peptides (*Mo*-CBP$_3$-PepI, *Mo*-CBP$_3$-PepII, *Mo*-CBP$_3$-PepIII, *RcAlb*-PepI, *RcAlb*-PepII, *RcAlb*-PepIII, PepGAT, and PepKAA) can target the S protein of SARS-CoV-2. Of these peptides, *Mo*-CBP$_3$-PepII and PepKAA exhibit the highest affinity. The *Mo*-CBP$_3$-PepII sequence is as follows: Asn-Ile-Gln-Pro-Pro-Cys-Arg-Cys-Cys. The PepKAA sequence is as follows: Lys- Ala- Ala- Asn-Arg-Ile-Lys-Tyr-Phe-Gln. We can label *Mo*-CBP$_3$-PepII or PepKAA sequences using ^{125}I to detect SARS-CoV-2.

Hypothesis

To improve the diagnostic sensitivity of COVID-19, the detection of the S protein of SARS-CoV-2 *via* the RIA method was specifically designed as follows.

The PepKAA sequence is labeled with ^{125}I: This sequence is characterized by: (1) A high affinity for the S protein of SARS-CoV-2; and (2) the existence of a tyrosine within the sequence for easy ^{125}I labeling. This sequence can be easily synthesized *via* solid-phase polypeptide synthesis, requiring only ten amino acids (Lys-Ala-Ala-Asn-Arg-Ile-Lys-Tyr-Phe-Gln). Thus, synthesis can be achieved at a low cost. PepKAA can be labeled *via* the chloramine-T method, which is simple and constitutes a mature method.

Preparation of RIA kit: RIA kits were prepared using following the steps: (1) PepKAA, a peptide targeting the S protein of novel coronavirus, was synthesized by solid-phase peptide synthesis (SPPS); PepKAA was purified by reversed-phase high-performance liquid chromatography (RP-HPLC). After purification, the peptide was analyzed by mass spectrometry; (2) ^{125}I labeling of PepKAA based on the chloramine T method was performed. One hundred and fifty micrograms of PepKAA powder was dissolved in 20 μL DMSO and then added to PB buffer (pH = 7.4) to generate 200 μL of PepKAA solution. After adding 20 μL of chloramine-T solution (5 mg/mL) into a mixed solution of 200 μL PepKAA and 10 μL of Na^{125}I (1.04 mci), the solution was placed in a mixer to react for 50 s at room temperature. Then, 150 μL of sodium metabisulfite (5 mg/mL) was added to terminate the reaction, and ^{125}I-PepKAA was purified using an activated C18 column; (3) preparation of coronavirus-inactivated specimens at six concentrations, including 100 ng/mL, 30 ng/mL, 10 ng/mL, 3 ng/mL, 1 ng/mL, and 0.3 ng/mL; (4) preparation of PEG virus precipitation solution. A 50% PEG solution was first prepared, or solid PEG was directly added to the virus suspension at the required concentration; and (5) the finished solution was packaged, inspected, and stored.

Detection method: Sample collection utilized throat swabs or patient serum. All of the samples were inactivated *via* high temperature before detection, and ^{125}I-labeled PepKAA was added to the samples or standards, which were then incubated in a water bath for 30 min. A PEG virus precipitator was added, and then the mixture was allowed to stand. The supernatant was discarded. Then, a gamma counter was used to measure the radioactive count in each tube (including standard tubes and the

measuring tube). Finally, the virus concentration in the measuring tube was calculated according to the radioactive counts of the standard tubes with different concentrations.

Discussion

Since Yalow and Berson[8] pioneered the development of the first competitive RIA of human insulin in 1959, RIA technology has been applied to a wide variety of fields. RIA has advantages of high sensitivity and specificity[9].

This method exhibits a high specificity. PepKAA was labeled with iodine-125 in this study, and PepKAA can bind specifically to the S protein on the surface of SARS-CoV-2. This method is also highly sensitive. RIA can detect the substance at a level of pg/mL. Other tests cannot achieve this level of sensitivity.

The detection of S protein on the surface of SARS-CoV-2 by RIA is expected to be applied to the early diagnosis of COVID-19, which may have a considerable impact on controlling the epidemic.

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