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Review Article

An overview of high altitude and mountain sickness

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Abstract

Acute mountain sickness (AMS) refers to the impact of the environment on body health at high elevations. It is classified into three based on the onset condition, namely, AMS, high-altitude cerebral edema, and high-altitude pulmonary edema. This type of sickness is a signal that tells the human body to adapt to the environment at 2500 m or above elevation, wherein low air pressure and oxygen will impair bodily functions. The Lake Louise AMS scale was created to assess the condition in adults. It was first developed in 1991 and remains a useful scale to help diagnose the severity of AMS. It was updated in 2018, in which sleep disturbance was removed as an indicating symptom.

Keywords: Acute mountain sickness, high altitude sickness, high-altitude cerebral edema, high-altitude pulmonary edema, Lake Louise acute mountain sickness scale

Introduction

Altitude sickness (AS), a potentially life-threatening disease, is caused by rapid exposure to low concentrations of oxygen at high altitudes. The reduced atmospheric pressure, i.e., a decrease in the partial pressure of oxygen, causes symptoms like headaches, vomiting, tiredness, confusion, trouble sleeping, and dizziness if the individual does not quickly adapt to such low oxygen levels. The aforementioned symptoms may aggravate by improper rest, limited sleep, stress and anxiety, and illness. It is usually the result of a rapid climb without acclimatization, such as the technique of "climb-high, sleep-low," wherein the climber repeats the process of staying a few days at a base camp and climbing slowly toward a higher camp before returning to the base camp, as a practice run and adjustment to high altitude. Studies have shown that these symptoms start to manifest above 2000 m or almost appear above 2500 m. Common complaints may include headaches, dizziness, nausea and vomiting, sleep disturbance, and loss of appetite. However, in the 2018 self-assessment questionnaire for acute AS by the Lake Louise Consensus Group, sleep disturbance was removed because studies have proven the cause to be low blood oxygen levels instead of being caused by the environment.[1] Moreover, the Lake Louise Acute Mountain Sickness (AMS) scale, first developed in 1991, was created to assess the condition among adults.[1] It is a useful scale to diagnose and grade the severity of AMS. The symptoms measured in the initial test included headaches, gastrointestinal upset, fatigue/weakness, and dizziness/light-headedness. Recent studies have shown that sleep disturbance is more likely caused by altitude hypoxia.

Clinical Features of Mountain Sickness

1. AMS occurs when an individual rapidly climbs at an altitude, resulting in headaches and a minimum of one of the following symptoms: gastrointestinal discomfort (loss of appetite, nausea, and vomiting), fatigue, lethargy, dizziness, and insomnia.[2]
2. High-altitude cerebral edema (HACE) will develop on a rapid climb in altitude that in addition to the

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common symptoms of AMS, the patient may have unsynchronized gait and instability of posture.
3. High-altitude pulmonary edema (HAPE) may even include a minimum of two of the following cardiopulmonary symptoms: wheezing, coughing, and chest tightness and pain, all of which being signs of decreased cardiorespiratory capacity, for these will also present as shortness of breath, tachycardia, and systemic cyanosis. The cardiopulmonary symptoms, such as rales or wheezing, can be heard through a stethoscope.[2-4]

Defining the Level of Severity

The definition revised by the Lake Louise Consensus Group in 2018 is classified into three major categories. (1) AMS is diagnosed by a minimum of four symptoms that develop in 6 h after arriving at an altitude higher than 2500 m, and headaches are the primary complaint. The score can be calculated as follows, for which the diagnosis is confirmed by a score of minimum three points [Table 1].

1. Headache: No headache (0), slight headache (1), moderate headache (2), and severe headache (3).[5]
2. Gastrointestinal symptoms: Good appetite (0), nausea or loss of appetite (1), moderate nausea or vomiting (2), and severe nausea or vomiting (3).
3. Fatigue and/or weakness: No fatigue/asthenia (0), mild fatigue/asthenia (1), moderate fatigue/asthenia (2), and severe fatigue/asthenia (3).
4. Dizziness: no dizziness (0), slight dizziness (1), moderate dizziness (2), and severe dizziness (3).[6]

Mild AMS will score a total of 3–5 points. Moderate AMS will score a total of 6–9 points, whereas severe AMS will score a total of 10–12 points. Regardless of the severity, all cases must have the symptom of headache at a total score of 3 to be diagnosed. The scoring of AMS should not begin until 6 h after ascent to avoid interference by transient body response to the tedious climb and acute hypoxia (due to vagal reflex). Frequently, patients with AMS usually experience headaches, followed by vomiting, as an indication of an aggravated condition. Symptoms may persist 6–12 h after reaching a high altitude higher than 2000 m. Mild symptoms can be spontaneously relieved in 2 days; however, HACE may develop in severe cases.[7-9]

High-altitude cerebral edema[10]

This category is defined as having or not having symptoms of AMS, accompanied by unsteady gait or altered consciousness due to the onset of cerebral edema at high altitude (3000–4000 m), which is rare with an incidence of 0.5%–1%. An unsteady gait can be checked using the tandem gait test and is a determining criterion of HACE. If left untreated or remained at a high altitude, the condition will progress to coma or uncal herniation, which are both fatal.

High-altitude pulmonary edema[5]

It involves rapid ascent and a minimum of two of the following symptoms, i.e., dyspnea at rest, cough, weakness or decreased activities, and chest tightness or swelling, and a minimum another two of the following conditions, i.e., rales or wheezing in one lung, systemic cyanosis, tachypnea, or tachycardia. This category of disease occurs above 2500 m and is the most common cause of death for patients with AS. Moreover, it has a mortality rate of 50% if left untreated and can occur in 1–4 days after onset. Hypobaric hypoxia aggravates hypoxic pulmonary vasoconstriction, leading to pulmonary hypertension. Its early symptoms include decreased physical activities, dry cough, fatigue, chest tightness, rapid heart rate, and rapid breathing, whereas late symptoms include dyspnea at rest, suffocation at night, coughing with pink foamy sputum, cyanosis (due to drop in blood oxygen levels), and rales. The most urgent treatment for late symptoms is oxygen therapy or to reach a lower altitude; otherwise, the condition may quickly develop and lead to death.[5,10,11]

Risk factors

The risk factors include rapid ascent (a climb of >400–600 m/day at an altitude of 2000 m and above), previous history of sickness, young age, genetic predisposition, strenuous exercise before acclimatization to altitude, and individual oxygen consumption.[2] The classification of altitude is as follows: high altitude of 8000–12,000 feet (2438–3650 m) above sea level, very high altitude

Table 1: The score can be calculated below, for which the diagnosis is confirmed by a score of at least three points or more[5]

Headache	No headache (0)	Slight headache (1)	Moderate headache (2)	Severe headache that cannot be relieved (3)
Gastrointestinal symptom	Good appetite (0)	Nausea or loss of appetite (1)	Moderate nausea or vomiting (2)	Severe nausea or vomiting that cannot be relieved (3)
Fatigue and/or weakness	No fatigue/ asthenia (0)	Mild fatigue/asthenia (1)	Moderate fatigue/ asthenia (2)	Severe fatigue/asthenia that cannot be relieved (3)
Dizziness	No dizziness (0)	Slight dizziness (1)	Moderate dizziness (2)	Severe dizziness that cannot be relieved (3)

of 12,000–18,000 feet (3650–5486 m), and very high altitude of over 18,000 feet (>5486 m), implying that higher the altitude and faster the ascent, greater the risk of developing AMS.

Headache

Headache, which is the most common complication associated with AS, can manifest as high-altitude headache (HAH) or occur together with AMS. The International Classification of Headache Disorders, Third Edition (ICHD-3), specifically differentiates headache into HAH or a nervous system disorder or humoral response caused by hypoxia. The primary mechanism involves increased microvascular pressure and cerebral vasodilation due to hypoxic conditions, which will induce edema. Symptoms include headache, accompanied by sleep disturbance, fatigue, dizziness, nausea, anorexia, and unsteady gait. However, a variation in individual response to hypoxia can be observed. Cerebral edema is the most severe outcome of AMS and occurs above 2500 m. The brain MRI indicates the presence of edema in the subcortical white matter and corpus callosum. HAH is treated with anti-inflammatory NSAIDs and analgesic drugs. Although steroid treatment can reduce cytokine release and inflammation, the overall effect of steroids on cerebral edema needs further investigation.[5,12,13]

Prevention and clinical management of AS

The recommended medication for the prevention of AMS and HACE are Diamox and Dexamethasone. Preventive medications for HAPE include nifedipine (a calcium channel blocker that can dilatate the vessels of the brain) and sildenafil (Viagra and Cialis).[14-16] Diamox, which is an acetazolamide-type diuretic for edema, can be administered twice a day at a dosage of 125 mg or 24 h before the climb and again in 48 h or on the second night after reaching the highest altitude of the climb. When it is used for the treatment of AMS, it is administered every 8–12 h (or 2–3 times a day) at a dosage of 250 mg. Moreover, it is used to treat insomnia at high altitudes, which is taken 1 h before bedtime at a dose of 125 mg. Its effects include numbness and hypokalemia.[17]

Dexamethasone, which is considered the second-line medication, requires the patient to observe any signs of symptoms for 18 h after stopping the drug, but it is not effective against HAPE. However, for acute AS, it is administered at a dose of 4 mg every 6 h. To treat HACE, the medication starts at an initial dosage of 8 mg and then 4 mg every 6 h. Its side effects include rebound symptoms, mood change, and hyperglycemia.[18-20]

Nifedipine is ineffective in preventing AMS and HACE. However, in its slow-release form, it is used to prevent HAPE at a dose of 20–30 mg every 12 h. Furthermore, another treatment for HAPE includes an initial dose of 10 mg in short-acting form, followed by its slow-release form every 12 h. The side effects are rapid heart rate and decreased blood pressure. Salmeterol (beta-agonist), a bronchodilator, can be used to prevent and treat HAPE. It must be used once every 12 h before the climb.[21] Sildenafil (Viagra) must not be used with nitrate drugs. For the prevention and treatment of HAPE, it is administered at a dose of 20–80 mg once a day. Although it has less hypotensive effects than nifedipine, it can still be associated with other issues, such as headache, flushing, and dizziness. AS can be treated by medication, but retreating to a lower altitude is still the safest way. Currently, drugs for prevention are not 100% safe; thus, acclimatization is crucial before climbing. As preventive drugs, such as Diamox (acetazolamide), must be prescribed by a physician, a climber should consult a high-altitude medicine expert beforehand. For patients with severe AS, a portable pressurized bag (Gamow bag) can be used, which utilizes a foot pump to inflate a portable bag to simulate a pressurized atmosphere for easier breathing during ascent. The effect is equivalent to lowering the altitude to 1500–1800 m.[5,17,21]

Conclusion

You can get AS if you traverse to a high altitude too quickly. Breathing becomes difficult because you are not able to take in as much oxygen. Moreover, AS can become a medical emergency if ignored. It is crucial for climbers to be familiar with and vigilant of the early symptoms of AS. They are advised to take preventive drugs before the climb to avoid AS. If the sickness occurs, they are to follow four rules, i.e., to lower altitude, increase atmospheric pressure, give oxygen, and rest. Furthermore, giving medication may help alleviate the symptoms and increase the chances of survival.

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Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Conflicts of interest

There are no conflicts of interest.

References

1. Roach RC, Hackett PH, Oelz O, Bärtsch P, Luks AM, MacInnis MJ, *et al*. The 2018 Lake Louise acute mountain sickness score. High Alt Med Biol 2018;19:4-6.
2. Bärtsch P, Saltin B. General introduction to altitude adaptation and mountain sickness. Scand J Med Sci Sports 2008;18: 1-10.
3. Basnyat B, Murdoch DR. High-altitude illness. Lancet 2003;361:1967-74.
4. Naeije R, Vanderpool R. Pulmonary hypertension and chronic mountain sickness. High Alt Med Biol 2013;14:117-25.
5. Imray C, Wright A, Subudhi A, Roach R. Acute mountain sickness: Pathophysiology, prevention, and treatment. Prog Cardiovasc Dis 2010;52:467-84.
6. Hackett PH, Roach RC. High altitude cerebral edema. High Alt Med Biol 2004;5:136-46.
7. Joyce KE, Lucas SJE, Imray CHE, Balanos GM, Wright AD. Advances in the available non-biological pharmacotherapy prevention and treatment of acute mountain sickness and high altitude cerebral and pulmonary oedema. Expert Opin Pharmacother 2018;19:1891-902.
8. Hsu TY, Weng YM, Chiu YH, Li WC, Chen PY, Wang SH, *et al*. Rate of ascent and acute mountain sickness at high altitude. Clin J Sport Med 2015;25:95-104.
9. Luks AM, McIntosh SE, Grissom CK, Auerbach PS, Rodway GW, Schoene RB, *et al*. Wilderness Medical Society practice guidelines for the prevention and treatment of acute altitude illness: 2014 update. Wilderness Environ Med 2014;25:S4-14.
10. Prince TS, Thurman J, Huebner K. Acute mountain sickness. In Stat Pearls [Internet]. Stat Pearls Publishing; 2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK430716/. [Last accessed on 09-Sep-2022].
11. Carod-Artal FJ. High-altitude headache and acute mountain sickness. Neurología (English Edition) 2014;29:533-40.
12. Zafren K. Prevention of high altitude illness. Travel Med Infect Dis 2014;12:29-39.
13. Fiore DC, Hall SL, Shoja P. Altitude illness: Risk factors, prevention, presentation, and treatment. Am Fam Physician 2010;82:1103-10.
14. Bartsch P, Bailey DM, Berger MM, Knauth M, Baumgartner RW. Acute mountain sickness: Controversies and advances. High Alt Med Biol 2004;5:110-24.
15. Grace D. Primary care attitudes towards the prescription of acetazolamide for altitude illness. Authorea Preprints 2022:1-11. Available from: https://d197for5662m48.cloudfront.net/documents/publicationstatus/84061/preprint_pdf/4f73a1f3f4a5475f0fd4fc9389e887f2.pdf. [Last accessed on 20 Sep 2022].
16. Wang SH, Chen YC, Kao WF, Lin Y-J, Chen J-C, Chiu T-F, *et al*. Epidemiology of acute mountain sickness on Jade Mountain, Taiwan: An annual prospective observational study. High Alt Med Biol 2010;11:43-9.
17. Davis C, Hackett P. Advances in the prevention and treatment of high altitude illness. Emerg Med Clin 2017;35:241-60.
18. Bärtsch P, Swenson ER. Acute high-altitude illnesses. NEJM 2013;368:2294-302.
19. Hackett PH, Roach RC. High-altitude illness. NEJM 2001;345:107-14.
20. Gallagher SA, Hackett PH. High-altitude illness. Emerg Med Clin 2004;22:329-55.
21. Barry PW, Pollard AJ. Altitude illness. BMJ 2003;326:915-9.

Review Article

Chronic pain syndrome—Fibromyalgia

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Abstract

Fibromyalgia is a systemic disease with multiple muscle and fascia tender points, combined with chronic inflammation or neuropathies. Apart from feeling many tender points all over the body, patients also have many atypical symptoms, such as anxiety and migraine. Pain can be caused by even light activities. Additionally, the incidence rate of women aged 20–50 years is much higher than that of men, and the main clinical symptoms are chronic and extensive pain and tenderness. Patients with fibromyalgia have many common clinical comorbidities, such as depression, anxiety, sleep disorders, chronic fatigue, chronic headaches, temporomandibular joint disorders, general numbness and tingling, irritable bowel syndrome, difficulty concentrating, and so on. The symptoms reduce the patient's quality of life. Patients with fibromyalgia often have symptoms other than muscle pain. Thus, it is clinically referred to as fibromyalgia syndrome. Moreover, fibromyalgia is similar to the symptoms of many autoimmune diseases, such as rheumatoid arthritis, lupus erythematosus, polymyositis, and so on. Physicians should exclude these diseases to ensure accurate diagnosis.

Keywords: Chronic widespread pain, fibromyalgia, fibromyalgia syndrome (FMS), myofascial pain syndrome, temporomandibular disorders (TMJ disorders, TMD)

Introduction

Fibromyalgia syndrome (FMS) is a systemic chronic musculoskeletal syndrome that is characterized by prolonged and generalized pain, fatigue, sleep disturbance, and physical dysfunction. According to the US statistics, chronic pain affects more than 75 million people, accounts for 20% of outpatient visits, and causes direct and indirect losses of more than 100 billion US dollars yearly. Fibromyalgia is one of the common diagnoses; if patients are not correctly diagnosed and treated in time, they seek medical treatment in various hospitals, consuming a lot of time and medical resources, and the symptoms cannot be effectively improved.[1,2] It is arguably the second most common rheumatic disease, after degenerative arthritis.[3] The patients may complain about widespread and persistent muscle pain and other common clinical symptoms, such as fatigue, insomnia, morning stiffness, cognitive impairment, depression, and anxiety; they may also exhibit various degrees of comorbidities, such as irritable bowel syndrome and chronic fatigue syndrome.[1,4] As diagnosed by using different standards in various countries, the incidence rate of FMS is approximately 2%–8%. Patients with fibromyalgia are more sensitive to pain and hot or cold stimuli,[5] and they may experience other symptoms, such as headache, joint pain, menstrual cycle pain, frequent muscle cramps, irritable bowel syndrome, urodynia, depression, anxiety, mood swing, and cognitive dysfunction.[6] Although fibromyalgia is a disease of which both etiology and treatment are still unclear and given the prevalence rate of the disease being estimated to be approximately 5% in the United States, it seems that the use of general analgesics alone is not as effective.[7] The treatment of FMS requires a combination of biopsychosocial interventions. It is generally believed that FMS is related to the oversensitization of the central

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nervous system (CNS),[2,8] even though FMS is often associated with chronic fatigue and severe depression.[9]

Epidemiology of Fibromyalgia

The overall prevalence of fibromyalgia is approximately 2%–4%, but women are seven to nine times more likely to develop symptom onset than men (note: countries may vary greatly in terms of the incidence rate).[10] Fibromyalgia was defined by the American College of Rheumatology (ACR) in 1990 with a requirement of the occurrences of multiple tender points (at the junction of muscles and tendons) and the criteria for other widespread and chronic symptoms. The disease must be differentiated from rheumatic polymyalgia, ankylosing spondylitis, chronic fatigue syndrome, hypothyroidism, and various systemic myositis.[10] The ACR established the diagnostic guideline in 1990 and then published the revised edition in 2010. Compared with the 1990 edition, the diagnostic criterion of multiple tender points was removed in 2010[11]; instead, it focused on the patient's self-assessed and reported physical symptoms and cognitive impairment. Fibromyalgia occurs in all populations worldwide, with an average morbidity rate of 2%–4%.[12] However, the prevalence rate of the actual clinical diagnosis of fibromyalgia is much lower. Clinical medicine has now proposed a mechanism of fibromyalgia, in which biological and psychosocial factors interact to influence susceptibility, as well as several predisposing and exacerbating factors by chronic diseases.[13] The diagnosis of the disease requires a history of typical cluster of symptoms and laboratory tests to confirm and interpret the manifestations. The current evidence-based guideline emphasizes the value of multimodal treatment, including nonpharmacological, and drug-specific treatments for individual symptom, targeting pain, fatigue, sleep problem, and mood swing.[14] Treatment should first start with health education and focus on nonpharmacological therapy unless the patient was nonresponsive to treatment or has sleep and mood disturbances. Fibromyalgia is classified as one category of chronic primary pain, which should be generalized, and chronic in association with fatigue, cognitive impairment, and sleep disorder.[15] FMS is a chronic disease characterized by widespread and persistent musculoskeletal pain and other common symptoms such as fatigue, insomnia, morning stiffness, cognitive impairment, depression, and anxiety. Fibromyalgia is also associated with comorbidities, such as irritable bowel syndrome and chronic fatigue syndrome.[16] Although negative life event, stress, and environmental or physical/emotional trauma may be its predisposing factors, the etiology of FMS remains unknown. Patients with obsessive–compulsive personality or posttraumatic stress disorder tend to have a high morbidity rate, which is often associated with more severe clinical symptoms.[17] There is also evidence of a high level of negative emotion, trait of neuroticism, and a sense of perfectionism accompanied by stress, anger, and mood swing in patients with fibromyalgia.[18] A strong alertness to avoid harm and a high sense of self-transcendence, as well as low self-direction and low level of cooperation with others, have been reported as the temperament and personality traits of these patients. Additionally, they tend to have negative self-image and body perception, apart from low self-esteem and self-efficacy.[18,19] FMS will reduce a person's functioning level in the physical, mental, and social domains, and it negatively affects cognitive performance, interpersonal relationships, and daily activities. In some cases, patients with fibromyalgia even exhibit suicidal intent, as they view the disease as stigmatized and incurable. This negative perception further hinders patient to adapt to the disease. Psychotherapy may be beneficial to treatment with a combination of drugs to improve the clinical symptoms and reduce the impact on health and quality of life.[20] FMS is among the most common syndromes in the general population, with a global prevalence rate of approximately 2%–4%. The complex symptoms of FMS include not only chronic widespread pain, fatigue, and sleep disturbance but also autonomic nervous system disorders, cognitive dysfunction, and anxiety, which are all related to hypersensitivity to external stimuli, physical symptoms, and psychiatric disorders.[1,21] Due to the subjectivity of symptoms and lack of biomarkers, the diagnosis is often based on clinical experience, despite the diagnostic criteria being constantly updated; thus, early diagnosis and prevention of fibromyalgia remain unattainable at this moment.[22] Fibromyalgia occurs mostly in adult women between 30 and 50 years old, but it can also occur in children, adolescents, or elderly. The majority of patients are women, with a male:female ratio of approximately 1:7–9. The prevalence rate is approximately 2%–5%, and globally, the rate is estimated to be at 0.7%–13.4%. In Taiwan, the prevalence rate of the disease is approximately 5.84%.[23] FMS patients account for approximately 2%–4% of the total population. Fibromyalgia is common in women aged between 20 and 50 years, but the prevalence rate in elderly people aged more than 80 years can be as high as 8%, and the prevalence rate increases with age in women after the age of 50 years; in the United States, this is approximately 6%.[24] FMS is diagnosed according to the clinical criteria, and laboratory and imaging evidence are often not determinants of the diagnosis.[24,25]

Causes of Fibromyalgia

The cause of fibromyalgia is still unknown, and the mechanism behind this chronic pain is still unclear, despite many scholars investigating the muscles, peripheral nervous system, and even the CNS to find specific

changes that could explain this condition. It is currently speculated that fibromyalgia is caused by the following mechanisms: changes in the brain caused by repeated nerve stimulation; the receptors responsible for pain in the brain become sensitive; the chemical substances that transmit pain are imbalanced; or the brain misinterprets the conduction information, reducing pain perception. The threshold of sensation, or amplification of the pain sensation, makes it easy for the patient to feel pain.[26] Many studies have pointed out that this is a problem of the CNS because neurotransmitters are related to pain, with serotonin, dopamine, and catecholamine being the most important ones.[20,27] The dysfunction of these pain-regulating nerves may play an important role. Some studies have also pointed out the role of psychological trauma and stress in the disease, but there is no definite conclusion on the causality of the two. It is currently known that there is no specific pathological change in the muscle tissues in relation to the pain in response to compressive stimulation on the muscles, skin, bones, and other tissues, but the threshold value for generalized pain is lower among patients than among normal healthy people, which is a main feature of chronic extensive pain in fibromyalgia. Therefore, it is generally believed that, in addition to the peripheral nervous system being stimulated, the sensitivity of the CNS has changed making patients more susceptible to pain.[18,28] The severity and progression or improvement of FMS can be assessed by several composite tests. The pathogenesis of FMS is not fully understood, but a hypothesis has pointed to the possible causes such as genetics, personal susceptibility, stressful life event, peripheral inflammatory response, cognitive–emotion interaction, and disturbance of pain perception due to neuromorphic changes (which is referred to as peripheral nerve or nociplastic pain).[29]

The sensation of pain is also classified as follows: (1) peripheral pain, often seen in osteoarthritis; (2) central pain, as seen in diabetes; (3) nociplastic pain; and (4) neuropathic pain.[29,30] Although factors such as negative or stressful event, as well as physical and emotional trauma, may predispose patient to the disease, the true etiology of FMS remains unknown. These patients frequently see negatively the disease as being stigmatized and incurable, as the pain has severely hindered their ability to adapt to the disease. Thus, psychological intervention may enhance the medication by improving some of these psychological symptoms, thereby reducing the negative impact of FMS on the patients' quality of life. Treatment should be multimodal and supportive in the following four major aspects: provide health education, encourage physical exercise, administer medication, and perform psychotherapy; these methods must be customized to fit personal preference to establish a symptom-based therapy with a common goal for the patient[31] [Table 1].

Table 1: Cause(signs) of fibromyalgia

Organ	Symptoms/Signs
Brain	Tiredness, inattention, sleep disorder, fatigue, depression, headache.
Oral (mandibular joint)	Difficulties swallowing, toothache, sensitivity to cold.
Muscle and joint	Joint pain in arm and legs, morning stiffness, cramps, chronic pain.
Lung and heart	Arrhythmia, shortness of breath, increased risk of infection.
Gastrointestinal	Irritable bowel, irritable stomach.
Fascia	Swelling in feet, hands, or face.
Bone or tendon	Neck, back, and chest pain.
Others	Trigger points, burning, prickling, and tingling sensation.

Fibromyalgia is a complex clinical syndrome characterized by a chronic extensive pain, which is often being confused with the myofascial pain of posterior muscle groups. Although the two are similar in nature, it is still imperative to differentiate fibromyalgia from myofascial pain, especially distinguishing pain from a secondary symptom of another disease, or primary muscle or joint problems. Despite the lack of specific finding in the experiments,[32] the disease is still said to be related to the imbalance of neurotransmitters in the CNS, which include serotonin, dopamine, and so on, or it may be related to psychological trauma and life stress. The disease is common in women aged between 20 and 50 years, but it can occur in any age group, especially in those with familial history of the disease. Its main symptoms are chronic extensive systemic pain and tender points, apart from fatigue, insomnia, headache, gastrointestinal disturbances, depression, anxiety, and so on.[33] Fibromyalgia is not an exclusive disease with specific clear-cut manifestations, since patients are likely to have other problems, such as degenerative arthritis, rheumatoid arthritis, lupus erythematosus, and so on.[34] In addition to the detailed medical history, physician may perform the tender-point examination by hands to see if the patient is indeed particularly sensitive to pain, because some of the signs are very similar to the features of other diseases, such as hypothyroidism, polymyalgia rheumatica, polymyositis, rheumatoid arthritis, or systemic lupus erythematosus. Thus, doctors may also check blood exams such as blood routine, or imaging studies, or even muscle biopsy to rule out the possibility of other diseases.[34,35]

Diagnosis of Fibromyalgia

FMS needs to be differentiated from other diseases that may present with widespread pain such as inflammatory or degenerative arthritis, thyroid disease, vitamin D deficiency, lupus erythematosus, polymyositis, liver diseases, kidney diseases, leukemia, malignancy, high

Table 2: The 18 tender points for fibromyalgia include following (if 11 of 18 tender points tested positive for sensitivity, this would help them make a diagnosis of fibromyalgia)

1. Lower neck in front	2. Edge of upper breast	3. Arm near the elbow	4. Back of the shoulders
5. Hip bone	6. Knee	7. Upper outer buttock	8. Back of the neck
9. Base of the skull in the back of the head			

Table 3: Widespread pain index: Please check the boxes below for each area in which you have had pain or tenderness during the past 7 days (1 point per check box; score range: 1–19)

Location	Points	Points
Shoulder girdle, left lower leg left	0	1
Shoulder girdle, right lower leg right	0	1
Upper arm, left jaw left	0	1
Upper arm, right jaw right	0	1
Lower arm, left chest	0	1
Lower arm, right abdomen	0	1
Hip (buttock) left neck	0	1
Hip (buttock) right upper back	0	1
Upper leg left lower back	0	1
Upper leg right none of these areas	0	1

or low levels of calcium and potassium in the blood, infection, and so on. Although the disease cannot be diagnosed by specific tests, any abnormal routine blood or imaging results as a possible indication of other diseases may still not rule out FMS. However, with a correct diagnosis based on proper assessment, patient can refrain from seeking several medical opinions elsewhere.[17,36] According to the definition by the ACR in 1990, the pain should be bilateral on both sides of the body, often in the upper and lower waist regions, and can last for more than 3 months. Fibromyalgia can be diagnosed if the chronic extensive pain were present along with more than 11 tender points in 18 specific parts of the body[1,4,37] [Table 2].

Many physicians are still skeptical about whether fibromyalgia is a disease. When a physician suspects a case of fibromyalgia, the patient will be assessed according to a scale developed by the ACR, which specifies the need of identifying at least 11 tender points out of the 18 specific parts of the body by fingers (with pressure of approximately 4 kg/cm^2).[24,38] The organization also released a new scale in 2016 to improve the diagnostic accuracy, and according to the latest diagnostic criteria for fibromyalgia published by ACR, there are two main indicators, which are as follows: widespread pain index (WPI, requiring a score of 19 points) [Table 3] and symptom severity scale (SS) [Table 4].

The new standard no longer emphasizes tender points but focuses on patient's subjective score about pain, which is reflected by the SS. When a patient obtains WPI of greater than or equal to 7 and SS of greater than or equal to 5 or WPI in the range of 3–6 points and SS of greater than or equal to 9, the patient is diagnosed with fibromyalgia, with symptoms having been persisted for more than 3 months and are differentiated from other medical conditions.[2,12,39]

FMS is clinically troublesome, especially in a patient experiencing chronic pain all over the body, which may also be accompanied by other symptoms, such as sleep disorder, paresthesia, headache, irritable bowel syndrome, and depression. Fibromyalgia is clearly characterized by chronic widespread pain, fatigue, sleep disturbances, and functional symptoms, but its etiology, diagnostic criteria, and classification criteria are still vague and sometimes controversial, as do the strategies to treat this condition. Fibromyalgia is the third most common musculoskeletal disorder and its prevalence increases with age. However, despite a progress in providing more accurate diagnostic criteria, many physicians are unsure of whether it is a real disease or a syndrome.[40] Many factors have contributed to the unique development of fibromyalgia, including genetic predisposition, personal experience, emotional–cognitive factors, mind–body relationship, and biopsychological capacity to cope with stress. Given its multiple characteristics in terms of pathogenesis, the treatment often takes a multimodal approach and must be customized to fit an individual's needs, especially with the current trend of further subdividing FMS into subgroups based on the variation in clinical features.[41]

Management of Fibromyalgia

While an evidence-based approach to fibromyalgia management is always desirable, physician may instead take an empirical approach and must build a trustful relationship with the patient to realize the purpose of such treatment. The treatment of fibromyalgia can either be drug or nondrug approach. Generally, the treatments for fibromyalgia include both medication and self-care strategies. The emphasis is on minimizing the symptoms and improving a patient's general health. No one treatment works for all symptoms, but trying a variety of treatment strategies can have a cumulative effect. Drug treatment includes muscle relaxants, pain relievers, antidepressants, antiepileptic drugs, and drugs that increase serotonin activity.[42] Food and drug administration has also approved pregabalin (Lyrica) for the treatment of FMS in adults, which is also one of the drugs currently approved by the National Health

Table 4: Symptom severity scale: score range: 1–12 (for each symptom listed below, use the following scale to indicate the severity of the symptom during the past 7 days)

Symptom	No problem	Slight or mild problem	Moderate problem	Severe problem
Fatigue	0	1	2	3
Trougle thinking or remembering	0	1	2	3
Waking up tired	0	1	2	3
During the past 6 months have you had any of the following symptoms?				
	No		Yes	
Pain or cramps in lower abdomen	0		1	
Depression	0		1	
Headache	0		1	

Table 5: Management of fibromyalgia

Medications	Nonmedications
Pain relievers	Physical therapy
Acetaminophen	Occupational therapy
Ibuprofen	Counseling
Naproxen	
Antidepressants/muscle relaxant	
Duloxetine (Cymbalta)	
Milnacipran (Savella)	
Amitriptyline	
Cyclobenzaprine	
Antiseizure drugs	
Gabapentin (Neurontin)	
Pregabalin (Lyrica)	

Insurance Bureau in Taiwan. Pregabalin is a calcium channel blocker and acts on the CNS to inhibit the release of neurotransmitters, such as glutamate, norepinephrine, substance P, and so on, to achieve an analgesic effect.[43] The commonly used drugs include antiepileptic drugs, antidepressants, muscle relaxants, analgesics, hypnotics, and antipsychotics, but only pregabalin and duloxetine have been approved by the Ministry of Health and Welfare in Taiwan for the treatment of fibromyalgia.[44] Both drugs with a similar action behavior as gabapentin have been shown to be effective in treating FMS in a large study.[45] In June 2008, the U.S. Food and Drug Administration also approved duloxetine for the treatment of FMS in adults, but it is not indicated in Taiwan. In 2008, the European League Against Rheumatism refocused on the treatment of fibromyalgia in adults, and based on the research evidence, it classified the treatment into four intensity levels (ABCD). Level A is considered as the drugs of highest strength, which includes tramadol, antidepressants (amitriptyline, fluoxetine, duloxetine, and milnacipran), pramipexole, and pregabalin, among others[46] [Table 5].

Conclusion

Fibromyalgia is a common musculoskeletal disorder whose prevalence increases with age. While its diagnostic rate has improved with the development of more accurate diagnostic criteria, many physicians still fail to acknowledge the disease. The complexity of pathogenesis means that treatment must take a multimodal customized approach.[47,48] Since fibromyalgia exhibits different clinical features and evidence-based fibromyalgia management is always available, the physician, contrarily, may take an empirical approach and establish a trustful doctor–patient relationship to work together in the treatment.

Data availability statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Conflicts of interest

There are no conflicts of interest.

References

1 Sarzi-Puttini P, Giorgi V, Marotto D, Atzeni F. Fibromyalgia: An update on clinical characteristics, aetiopathogenesis and treatment. Nat Rev Rheumatol 2020;16:645-60.
2 Clauw DJ. Fibromyalgia: A clinical review. JAMA 2014;311:1547-55.
3 Wolfe F, Walitt B. Culture, science and the changing nature of fibromyalgia. Nat Rev Rheumatol 2013;9:751-5.
4 Macfarlane GJ, Kronisch C, Dean LE, Atzeni F, Häuser W, Fluß E, *et al*. EULAR revised recommendations for the management of fibromyalgia. Ann Rheum Dis 2017;76:318-28.
5 Yunus MB. Fibromyalgia and overlapping disorders: The unifying concept of central sensitivity syndromes. Semin Arthritis Rheum 2007;36:339-56.
6 Galvez-Sánchez CM, Duschek S, Del Paso GAR. Psychological impact of fibromyalgia: Current perspectives. Psychol Res Behav Manag 2019;12:117.
7 Wolfe F, Walitt B, Perrot S, Rasker JJ, Häuser W. Fibromyalgia diagnosis and biased assessment: Sex, prevalence and bias. PLoS One 2018;13:e0203755.
8 Häuser W, Ablin J, Fitzcharles MA, Littlejohn G, Luciano JV, Usui C, *et al*. Fibromyalgia. Nat Rev Dis Primers 2015;1:1-16.
9 Fietta P, Fietta P, Manganelli P. Fibromyalgia and psychiatric disorders. Acta Biomed 2007;78:88-95.
10 El Miedany Y, Gadallah N, Mohasseb D, Gaballah NM, El Zohiery AK, Hassan M, *et al*. Consensus evidence-based

clinical practice recommendations for the management of fibromyalgia. Egypt Rheumatol Rehabil 2022;49:1-11.
11 Creed F. A review of the incidence and risk factors for fibromyalgia and chronic widespread pain in population-based studies. Pain 2020;161:1169-76.
12 Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Häuser W, Katz RS, *et al*. Fibromyalgia criteria and severity scales for clinical and epidemiological studies: A modification of the ACR preliminary diagnostic criteria for fibromyalgia. J Rheumatol 2011;38:1113-22.
13 Bair MJ, Krebs EE. Fibromyalgia. Ann Intern Med 2020;172:ITC33-48.
14 Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Häuser W, Katz RL, *et al*. 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. Arthritis Rheum 2016;6:319-29.
15 Kleykamp BA, Ferguson MC, McNicol E, Bixho I, Arnold LM, Edwards RR, *et al*. The prevalence of psychiatric and chronic pain comorbidities in fibromyalgia: An ACTTION systematic review. Semin Arthritis Rheum 2021;51:166-74.
16 Häuser W, Sarzi-Puttini, P Fitzcharles MA. Fibromyalgia syndrome: Under-, over- and misdiagnosis. Clin Exp Rheumatol 2019;37:90-7.
17 Chakrabarty S, Zoorob R. Fibromyalgia. Am Fam Physician 2007;76:247-54.
18 Bradley LA. Pathophysiology of fibromyalgia. Am J Med 2009; 122:S22-30.
19 Clauw DJ. Fibromyalgia: An overview. Am J Med 2009;122:S3-13.
20 Häuser W, Urrútia G, Tort S, Uçeyler N, Walitt B. Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia syndrome. Cochrane Database Syst Rev 2013:CD010292.
21 Jones GT, Atzeni F, Beasley M, Flüß E, Sarzi-Puttini P, Macfarlane GJ. The prevalence of fibromyalgia in the general population: A comparison of the American College of Rheumatology 1990, 2010, and modified 2010 classification criteria. Arthritis Rheumatol 2015;67:568-75.
22 Casale R, Sarzi-Puttini P, Botto R, Alciati A, Batticciotto A, Marotto D, *et al*. Fibromyalgia and the concept of resilience. Clin Exp Rheumatol 2019;37:105-13.
23 Su CH, Chen JH,L Lan J, Wang YC, Tseng CH, Hsu CY, *et al*. Increased risk of coronary heart disease in patients with primary fibromyalgia and those with concomitant comorbidity—A Taiwanese population-based cohort study. PLoS One 2015;10:e0137137.
24 Arnold LM, Bennett RM, Crofford LJ, Dean LE, Clauw DJ, Goldenberg DL, *et al*. AAPT diagnostic criteria for fibromyalgia. J Pain 2019;20:611-28.
25 Arnold LM, Clauw DJ, Dunegan LJ, Turk DC. A framework for fibromyalgia management for primary care providers. Mayo Clin Proc 2012;87:488-96.
26 Ablin J, Neumann L, Buskila D. Pathogenesis of fibromyalgia—A review. Joint Bone Spine 2008;75:273-9.
27 Boehnke KF, Gagnier JJ, Matallana L, Williams DA. Cannabidiol use for fibromyalgia: Prevalence of use and perceptions of effectiveness in a large online survey. J Pain 2021;22:556-66.
28 Siracusa R, Paola RD, Cuzzocrea S, Impellizzeri D. Fibromyalgia: Pathogenesis, mechanisms, diagnosis and treatment options update. Int J Mol Sci 2021;22:1-31.
29 Koroschetz J, Rehm SE, Gockel U, Brosz M, Freynhagen R, Tölle TR, *et al*. Fibromyalgia and neuropathic pain-differences and similarities. A comparison of 3057 patients with diabetic painful neuropathy and fibromyalgia. BMC Neurol 2011;11:1-8.
30 Clauw DJ, Arnold LM, McCarberg BH. The science of fibromyalgia. Mayo Clin Proc 2014;86:907-11.
31 Goldenberg DL, Burckhardt C, Crofford L. Management of fibromyalgia syndrome. JAMA 2004;292:2388-95.
32 Häuser W, Eich W, Herrmann M, Nutzinger DO, Schiltenwolf M, Henningsen P. Fibromyalgia syndrome: Classification, diagnosis, and treatment. Dtsch Arztebl Int 2009;106:383-91.
33 Wolfe F, Häuser W, Walitt BT, Katz RS, Rasker JJ, Russell AS. Fibromyalgia and physical trauma: The concepts we invent. J Rheumatol 2014;41:1737-45.
34 Atzeni F, Talotta R, Masala IF, Giacomelli C, Conversano C, Nucera V, *et al*. One year in review 2019: Fibromyalgia. Clin Exp Rheumatol 2019;37:S3–10.
35 Guymer E, Littlejohn G. Fibromyalgia. Aust Fam Physician 2013;42:690-4.
36 Perrot S. Fibromyalgia: A misconnection in a multiconnected world? Eur J Pain 2019;23:866-73.
37 Queiroz LP. Worldwide epidemiology of fibromyalgia. Curr Pain Headache Rep 2013;17:1-6.
38 Cohen SP, Vase L, Hooten WM. Chronic pain: An update on burden, best practices, and new advances. Lancet 2021;397: 2082-97.
39 Mascarenhas RO, Souza MB, Oliveira MX, Lacerda AC, Mendonça VA, Henschke N, *et al*. Association of therapies with reduced pain and improved quality of life in patients with fibromyalgia: A systematic review and meta-analysis. JAMA Intern Med 2021;181:104-12.
40 Rahman A, Underwood M, Carnes D. Fibromyalgia. BMJ 2014;348:1-12.
41 Meeus M, Goubert D, De Backer F, Struyf F, Hermans L, Coppieters I, *et al*. Heart rate variability in patients with fibromyalgia and patients with chronic fatigue syndrome: A systematic review. Semin Arthritis Rheum 2013;43:279-87.
42 Sarzi-Puttini P, Giorgi V, Marotto D, Atzeni F. Fibromyalgia: An update on clinical characteristics, aetiopathogenesis and treatment. Nat Rev Rheumatol 2020;16:645-60.
43 Queiroz LP. Worldwide epidemiology of fibromyalgia. Curr Pain Headache Rep 2013;17:356.
44 Macfarlane GJ, Kronisch C, Dean LE, Atzeni F, Häuser W, Fluß E, *et al*. EULAR revised recommendations for the management of fibromyalgia. Ann Rheum Dis 2017;76:318-28.
45 Spaeth, M. Epidemiology, costs, and the economic burden of fibromyalgia. Arthritis Res Ther 2009;11:2-3.
46 Lachaine J, Beauchemin C, Landry PA. Clinical and economic characteristics of patients with fibromyalgia syndrome. Clin J Pain 2010;26:284-90.
47 Lacasse A, Bourgault P, Choinière M. Fibromyalgia-related costs and loss of productivity: A substantial societal burden. BMC Musculoskelet Disord 2016;7:168.
48 Glass JM. Review of cognitive dysfunction in fibromyalgia: A convergence on working memory and attentional control impairments. Rheum Dis Clin 2009;35:299-311.

Evaluation of the impact of high-volume online hemodiafiltration on glycemic status, hydration status, and body fat content in diabetic patients

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Abstract

Background: The increasing patients with diabetes undergoing hemodialysis (HD) have concerned about the issue of glucose delivery with substitution fluid. We evaluate the effects of online high-volume hemodiafiltration (OL-HDF) versus high flux HD (HF-HD) on the influence of glycemic status and body fat content in patients with type 2 diabetes mellitus (T2DM) receiving HD. **Objectives:** The influence glucose in substitution fluid on glycemic status and body fat content in patients with type 2 diabetes mellitus.**Methods:** This study evaluated 117 patients receiving HD for more than 3 months (17 patients with T2DM receiving high-volume OL-HDF and the other 100 patients receiving HF-HD). Initially, we performed a cross-sectional study and later examined two modalities of high-volume OL-HDF in a 9-month cross-over study. Overall glycemic control was estimated from the fasting blood glucose (FBG) and the hemoglobin A1c (HbA1c) levels. Body composition and nutritional status were assessed by bioimpedance spectroscopy. **Results:** FBG and HbA1c were not significantly different in both groups of patients after having followed for 12 weeks. No significant differences were found in overhydration status and body fat content between the two therapy modalities. The blood hemoglobin (Hb) level increased in the high-volume OL-HDF group compared with the HF-HD group. Additionally, no differences were observed in glycemic status, body mass index, or body fat mass between both high-volume pre- and post-dilutional OL-HDF. **Conclusion:** High-volume OL-HDF did not have an adverse impact on glycemic status, body mass index, and body fat content in patients with diabetes undergoing HD in our short-term study. A large-scale and long-term follow-up study is required to confirm these results.

Keywords: HF-HD, high flux hemodialysis, high-volume online hemodiafiltration, OL-HDF

Introduction

The introduction of high-volume online high-volume hemodiafiltration (OL-HDF) technique marks a great step toward mimicking the blood purification of the native kidney. This technique offered a more effective uremic substance removal over a wider range of molecular sizes than other dialysis modalities, which had been associated with potential clinical advantages and survival benefits.[1-3] The amount of convective transport seems to determine the accomplishment benefits. Accordingly, efforts are currently made to deliver a convective volume of >20 L per dialysis session. A larger convection volume that leads to a larger amount of glucose delivery to patients has raised concern.

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Type 2 diabetes mellitus (T2DM) is the most common cause of end-stage renal disease (ESRD) in the most developed and emerging countries and may account for approximately 40%–50% of patients undergoing dialysis. The optimal glycemic target in this population is uncertain, although recent epidemiologic data suggest that hemoglobin A1c (HbA1c) levels, ranging between 6.5% and 8%,[4,5] are associated with increased survival among patients with diabetes undergoing dialysis. The substitution fluid in high-volume OL-HDF, the infuscate, has the same composition as the dialysis fluid. The glucose content of the substitution fluid would be excessive for more convection volume, causing an extra load of glucose to the patient during the treatment.[6] This could limit the volume of substitution in patients with intolerance to carbohydrates or poor glycemic control in T2DM.[7,8] However, whether glucose infused with convective technique impaired metabolic control or worsened cardiovascular risk in these patients remained unknown. The Membrane Permeability Outcome (MPO) study demonstrated that patients with diabetes showed a survival benefit with high flux hemodialysis (HF-HD), which can be considered a form of "low-dose" high-volume OL-HDF.[9] Additionally, most studies of high-volume OL-HDF revealed that survival improvement and cardiovascular mortality reduction are independent of the subgroups of evaluated patients.[7,10]

Moreover, we are aware that almost all dialysis baths contain glucose of 1 g/L (5.55 mmol/L) to prevent asymptomatic hypoglycemia and are particularly important in patients with diabetes and elderly.[11] The substitution fluid is delivered directly into the patient's bloodstream in the post-dilution mode, which is the most common infusion method, bypassing the filtering membrane, just like an intravenous administration. During each treatment, 20–30 L of substitution fluid is delivered,[12] along with 20–30 g of glucose. Conversely, a huge amount of substitution fluid is delivered during the pre-dilution mode. This extra source of energy may improve the caloric balance of the procedure, but it can negatively affect glycemic metabolism.[13]

This study primarily aimed to compare the influence of the volume of substitution on the metabolic profile and body composition in patients with T2DM receiving high-volume OL-HDF with HF-HD. Secondarily, we prospectively assess if the different mode of high-volume OL-HDF can affect their glycemic status.

Patients and Methods

Study design

This study was registered with the Clinical Trials Registry (ClinicalTrials.gov Identifier: NCT03288285). This study complied with the Declaration of Helsinki and was approved by the Institutional Review Board of Tungs' Taichung MetroHarbor Hospital (IRB TTMH106042). All participants gave their written informed consent.

Prevalent patients with diabetes undergoing HD on a three-times-per-week schedule from Tungs' Taichung MetroHarbor Hospital Dialysis program were recruited into the study after obtaining informed consent.

The present study comprised two sub-studies. The first sub-study was a cross-sectional study comparing the studied parameters between those who received HF-HD and OL-HDF. The second sub-study is a prospective, open-label randomized controlled study in which six patients receiving OL-HDF were randomized in a 1:1 ratio to two treatment arms and stabilized on each treatment modality for 9 months. The random allocation sequence was generated using a random number generator. The arms differed only in the sequence in which the modalities were administered (a crossover study following an A-B or B-A design as shown in Figure 1). The treatment settings of HDF were three times a week; duration of

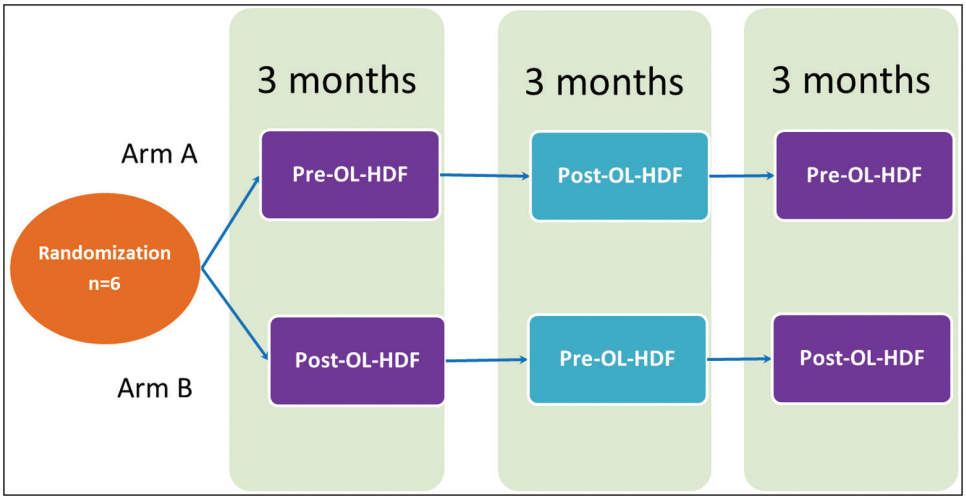

Figure 1: Design of the study: Prospective randomized controlled trial with two arms

4 h; dialyzer with Fresenius Medical Care FX CorDiax 1000 (Fresenius Medical Care, Bad Homburg, Germany; membrane: Helixone; surface area: 2.3 m^2; ultrafiltration coefficient: 68 mL/h/mmHg); blood flow rate of approximately 300 mL/min; dialysate flow rate of 800 mL/min. The convection volume was set at 20–23 L/session. The treatment settings of pre-dilution HDF were similar, but the convection volume was set at 48–55 L/session. Patients in the HF-HD groups received dialysis with the high-flux FX-100 dialyzer (Fresenius Medical Care; membrane: Helixone; surface area: 2.2 m^2; ultrafiltration coefficient: 74 mL/h/mmHg). All treatments were performed with the 4008 HD system (Fresenius Medical Care) and ultrapure dialysis fluid containing <0.1 colony-forming units/mL and <0.03 endotoxin units/mL. Routine laboratory tests (basic metabolic panel, calcium, phosphate, albumin, and complete blood count) were performed using an automated analyzer. Serum albumin was measured with the bromocresol green method. High-sensitivity C-reactive protein (CRP) was measured with a particle-enhanced immunoturbidimetric assay on a Roche-Hitachi analyzer (Roche Diagnostics GmbH, Mannheim, Germany), with a lower quantification limit of 0.1 mg/L.

Bioelectric impedance spectroscopy

Whole-body bioelectric impedance spectroscopy (BIS) measurement using a body composition monitor (BCM: Fresenius Medical Care) was performed on each of the participants enrolled in the study by a specific member of the staff who had completed a training course in the BCM technique. The BCM measures the impedance spectroscopy at 50 different frequencies between 5 kHz and 1 MHz. Measurements were taken on the day before dialysis with the patient calm, supine, and relaxed in the dialysis bed for 10 min. Four electrodes were placed on the patient's hand and foot on the side contralateral to their arteriovenous fistula. This study measured the body mass index (BMI) with dry body weight, which is the body weight after HD.

Data analysis

Data were tested for normality of distribution with the Kolmogorov-Smirnov statistic. Normally distributed data are summarized as mean ± standard deviation (SD), while non-normally distributed data are presented as median with interquartile range (IQR).The difference between the two groups was evaluated with a *t*-test or analyzed with the Mann–Whitney *U* test in the case of lack of normality. Categorical variables are presented as percentages. Pearson's chi-square test or Spearman test was used to determine the differences in categorical variables. A *P*-value of <0.05 was considered statistically significant. All statistical analyzes were performed using Statistical Package for the Social Sciences (SPSS) version 23 software (Chicago, Illinois).

Results

Table 1 showed the baseline clinical, anthropometric, laboratory, and BIS data of 117 patients, including 17 patients undergoing high-volume OL-HDF and 100 undergoing HF-HD. Age at baseline was 61.6 ± 9.2 years, and 56.4% were males.

The median vintage of the studied patients was 50 months (range: 11–303; IQR: 57.5 months). Approximately 35.8% received insulin, 23.3% received antidiabetic drugs, and 40.3% received a combination of insulin and antidiabetic drug therapy.

The mean substitution volume was 22 ± 1.6 L/session when in post-dilution mode and 50 ± 10.6 L/session in pre-dilutional mode.

Table 1 showed the change in laboratory parameters and body composition in patients undergoing HF-HD and high-volume OL-HDF. Fasting blood glucose (FBG) and HbA1c values revealed no

Table 1: Demographic and clinical characteristics of study patients

Parameters	HF (n = 100)	HDF (n = 17)	P
Age, year	62.24 ± 9.22	57.93 ± 8.41	0.067
Gender, Male (%)	52 (52)	12 (41)	0.149
Vintage, months	44.5 (23–75)	98 (51.4–134)	0.005*
Hypertension, %	43.0	52.9	0.308
Albumin, g/dL	3.96 ± 0.33	3.89 ± 0.29	0.379
Glucose, mg/dL	144.0 (110.5–189.5)	123.3 (94–186)	0.395
Hb, g/dL	10.97 ± 1.38	11.86 ± 1.31	0.017*
Chol, mg/dL	155.3 ± 34.5	154.1 ± 24.4	0.889
TG, mg/dL	158.5 (94.0–205.5)	155.0 (86–196.5)	0.561
nPCR, g/kg/day	1.20 ± 0.30	1.30 ± 0.25	0.150
HbA1c, %	7.17 ± 2.24	7.42 ± 1.41	0.545
hsCRP, mg/L	0.50 (0.20–1.20)	0.3 (0.10–0.55)	0.875
TCO_2, mEq/L	20.55 ± 2.11	20.82 ± 1.75	0.573
BMI, kg/m^2	25.48 ± 4.73	25.0 ± 3.48	0.621
Fat, kg	22.75 ± 10.08	21.76 ± 8.16	0.660
FTI, kg/m^2	12.05 ± 5.15	10.6 ± 3.41	0.146
Rel fat, kg	33.90 ± 10.5	30.73 ± 6.35	0.098
ATM, kg	30.94 ± 13.7	29.61 ± 11.09	0.661
OH, L	1.25 (0.43–2.15)	1.6 (0.15–2.45)	0.347
TBW, L	31.81 ± 7.21	35.12 ± 6.27	0.061
E/*I* ratio	0.94 ± 0.14	0.90 ± 0.11	0.192
OHA, %	46	47	0.570
Insulin, %	36	41.1	0.439

Hb = hemoglobin, Chol = total cholesterol, TG = triglyceride; nPCR = normalized protein catabolic rate, hsCRP = high sensitive C-reactive protein, HBA1c = glycated hemoglobin, TCO_2 = total carbon dioxide content, OH = overhydration, rel OH = relative overhydration, BMI = body mass index, V_{urea} = distribution volume of urea, TBW = total body water, *E*/*I* = ratio of extracellular water/intracellular water, FTI = fat tissue index, rel fat = relative fat content, ATM = adipose tissue mass, OHA = oral hypoglycemic agents

Quantitative data are expressed as mean ± SD or median (IQR)

*P < 0.05 was considered statistically significant

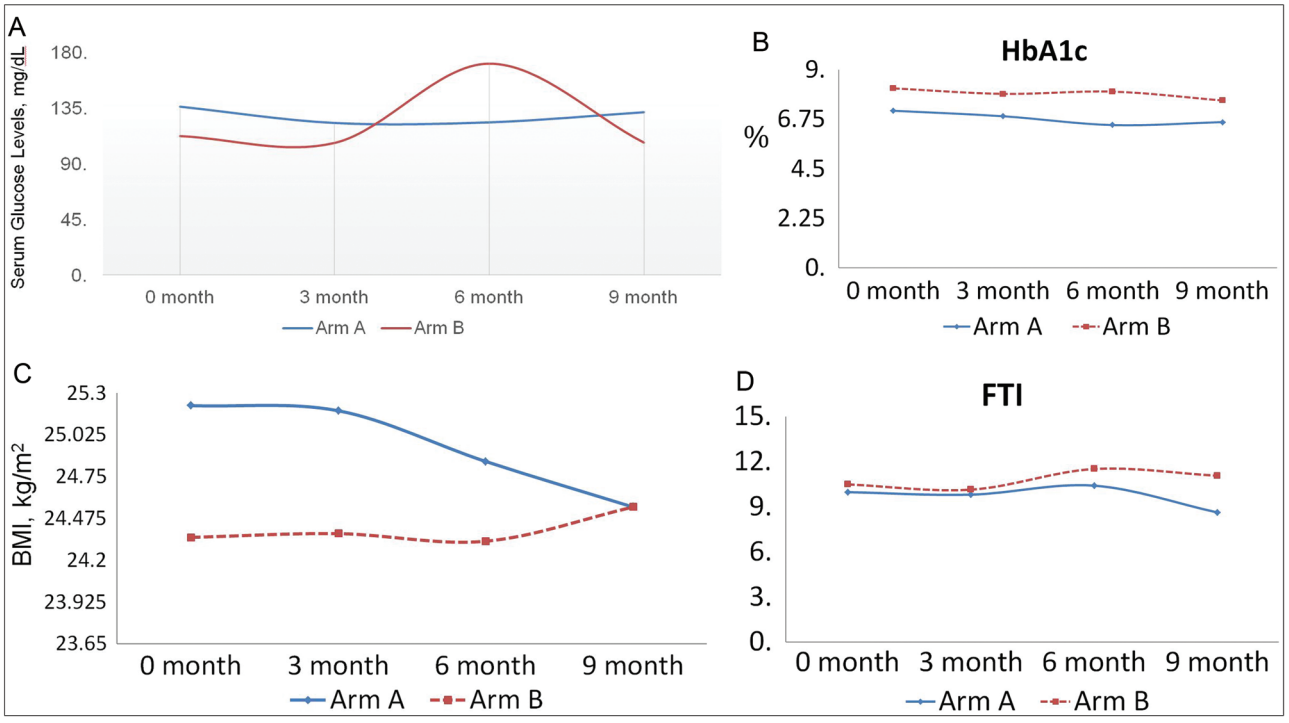

Figure 2: A. Effect of pre- and post-OLHDF on serum fasting blood glucose over time. B. Effect of pre- and post-OLHDF on serum HBA1c over time. C. Effect of pre- and post-OLHDF on BMI over time. D. Effect of pre- and post-OLHDF on FTI over time. Abbreviations: OLHDF, online hemodiafiltration; BMI, body mass index; FTI, fat tissue index.

difference between the groups. Patients in the high-volume OL-HDF group had longer dialysis vintage and significantly higher HbA1c levels but lower CRP values when compared with patients with diabetes on HF-HD.

Six of the patients on high-volume OL-HDF underwent a cross-over study to evaluate the pre- and post-dilution high-volume OL-HDF on glycemic control.

No difference was found in FBG and HbA1c values between pre- and post-dilution mode of convective therapy, as shown in Figure 2A–D. Additionally, no differences were found in BMI or BIS parameters in particular fat tissue index (FTI) and percentage of body fat content. No differences were found in lipid profiles, such as triglyceride and high-density lipoprotein (HDL) cholesterol levels, in patients with T2DM receiving these two modes of high-volume OL-HDF.

Discussion

This study revealed two important findings. First, high-volume OL-HDF does not cause worsening glycemic control in patients with T2DM undergoing dialysis compared with HF-HD. Second, no difference was found in the glycemic status of either modes, pre and post- of high-volume OL-HDF in our cross-over study.

More glucose is infused during the high-volume treatment, but they still displayed similar metabolic profiles and body fat content when compared to HF-HD. These findings may suggest that high-volume OL-HDF does significantly improve glucose metabolism in this short-term study.

The most common cause of ESRD in Asian countries, such as Taiwan, is diabetes, similar to the rest of the world. Nephrologists and dialysis facilities are confronted with a new and more difficult set of challenges to effectively care for patients with T2DM because of the sharp rise of diabetes.

Chronic diabetes complications may result not only from hyperglycemia [14,15] but also from glucose variability and hypoglycemia.[16,17] Hyperglycemia was reported to be strongly associated with sudden cardiac death in patients with T2DM undergoing HD, which may account for increased cardiovascular events and mortality.[17,18] Meanwhile, hypoglycemia is fatal, especially in the presence of cardiovascular diseases.[19] Multi-morbidity is likely to become an increasing challenge as health systems serve an ageing population with diabetes.

Routine monitoring and ensuring adequate glycemic control have become important components of the overall management of patients with diabetes undergoing HD.

In recent decades, dialysis baths contain low amounts of glucose to reduce hypoglycemic complications during the treatment and to avoid any glycemic disarrays.[11,20,21] All efforts have been pointed toward achieving the goal of sterile and pyrogen-free fluids, almost disregarding

the chemical composition, since the first attempts at making online substitution fluid.[22,23] Only recently, the issue of glucose in online substitution fluid during high-volume OL-HDF has not yet been fully investigated.[24]

Over the past decades, the results of most of the clinical trials suggested that higher convection volumes were generally associated with greater survival benefits with high-volume OL-HDF.[25] Conversely, a larger amount of glucose will be delivered during each treatment and may impose a substantial glucose burden on our patients, with high infusion volumes (>20 L per session). The extra energy supply may be beneficial for some malnourished and elderly patients, but harmful for those with diabetes or overweight patients. So far, the survival benefit of patients undergoing high-volume OL-HDF appeared to be independent of diabetic status from most of the recent trials. Additionally, the MPO study,[9] as well as a post hoc analysis in patients with diabetes,[26] revealed that HF-HD improved long-term survival in patients with hypoalbuminemia, as previously mentioned.

Currently, various modes of high-volume OL-HDF, differing by the site of replacement-fluid infusion, are used. Post-dilution high-volume OL-HDF is a reference method for convective therapies in European countries. In the past, the glucose load, being delivered intravenously, is believed to impact metabolism.

This conjecture suggested that the amount of glucose entered the circulation intravenously and might not adequately induce physiological reactions, such as insulin secretion stimulated by gastric and/or duodenal hormones (e.g., GLP-1), as compared to oral ingestion. Glucose remains at higher concentration for longer and is only belatedly removed by diffusion, as a consequence of blunted insulin secretion. However, one recent observational study[27] demonstrated that high-volume OL-HDF did not cause a deterioration of the metabolic profile of a cohort of 29 patients with incident diabetes. This prospective observational study revealed that patients with a mean substitution volume of >26.9 L/session had a higher reduction in triglycerides and CRP, and an increase in HDL cholesterol levels compared with lower substitution volume (23.9 ± 1.9 L/session).

A significant correlation was found between the volume of substitution and the decrease in HbA1c during the follow-up period, and an interestingly larger amount of replacement fluids was associated with a greater reduction in HbA1c.

However, no correlation was observed between the volume of substitution and the variations in weight, BMI, or BIS parameters. Our study revealed similar findings when patients with diabetes were compared between high-volume OL-HDF and HF-HD as well as when a comparison was performed between both pre- and post-dilution modes. Theoretically, the infused glucose load with high-volume OL-HDF could increase the glucose plasmatic concentration leading to an increasing diffusive removal toward the bath due to its low molecular weight. Moreover, a loss of glucose was found by convection with ultrafiltration (with a filtration coefficient close to 1 in high permeability membranes) [27] of the fluid gained between dialysis and the substitutional fluid replaced. Thus, only patients with glycemia of >100 mg/dL will have a negative glucose balance, and, therefore, only patients with glycemia of <100 mg/dL will have a positive glucose balance both by diffusion and by convection. Overall, glucose infusion in high-volume OL-HDF may have a small effect on glycemic metabolism and body fat content. The changes in glycemic status may be associated with a lower systemic inflammation observed with high-volume OL-HDF as shown by our study result (lowered CRP levels when compared to HF-HD) and also by previous studies.[28,29]

Pre-dilution high-volume OL-HDF is performed largely in the Asia Pacific region (Japan and Korea). In Japan, >95% of all patients undergoing high-volume OL-HDF are treated with pre-dilution HDF. The main reason for the use of the pre-dilution mode for patients undergoing high-volume OL-HDF results from the low blood flow rate (average: 200–220 mL/min) in Japanese patients.[30] Substituting an adequate volume during the limited (average: 4 h) treatment time is difficult with this average blood flow rate. Pre-dilution HDF removes more low-molecular-weight proteins, inflammatory proteins, and protein-bound toxins and is associated with more biocompatibility compared with post-dilution high-volume OL-HDF.[31]

Our patients with diabetes did not have worse glycemic control as reflected by FBG, HbA1c, and triglyceride levels despite a greater glucose infusion in patients with high replacement volume in pre-dilution mode. More importantly, this high volume did not cause negative effects on the body fat content (as measured by FTI and relative fat mass) of patients with diabetes on pre-dilution high-volume OL-HDF.

The main limitation of this work is its small sample size for both observation and cross-over studies. Data from more patients will be desirable to fully validate the favorable effects of convective transport in both modes of high-volume OL-HDF in particular the pre-dilution mode. Other limitations include inadequate information about dose changes of oral hypoglycemic agents or insulin and the dietary status of patients undergoing HD.

Conclusions

In conclusion, our study suggested that high-volume OL-HDF does not significantly alter the glycemic status or the body fat content of patients with diabetes when compared to HF-HD. Moreover, no difference

was found in glycated hemoglobin levels between the pre- and post-dilution mode of high-volume OL-HDF though more substitutional fluid containing glucose is infused during the pre-dilution mode. Hence, currently, limiting high-volume OL-HDF in patients with diabetes based on the glucose content commonly used in the substitution fluid is not reasonable.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Nil.

Conflicts of interest

Prof. Paik-Seong Lim, a section editor at *Tungs' Medical Journal*, had no role in the peer review process of or decision to publish this article. The other authors declared no conflicts of interest in writing this paper.

References

1. Maduell F. Hemodiafiltration. Hemodial Int 2005;9:47-55.
2. Canaud B, Vienken J, Ash S, Ward RA, Kidney Health Initiative HDF Workgroup. Hemodiafiltration to address unmet medical needs ESKD patients. Clin J Am Soc Nephrol 2018;13:1435-43.
3. Blankestijn PJ, Grooteman MP, Nube MJ, Bots ML. Clinical evidence on haemodiafiltration. Nephrol Dial Transplant 2018;33:iii53-8.
4. National Kidney Foundation. KDOQI clinical practice guideline for diabetes and CKD: 2012 update. Am J Kidney Dis 2012;60:850-86.
5. Hoshino J, Larkina M, Karaboyas A, Bieber BA, Ubara Y, Takaichi K, *et al*. Unique hemoglobin A1c level distribution and its relationship with mortality in diabetic hemodialysis patients. Kidney Int 2017;92:497-503.
6. Marano M, Cirillo G. The forgotten issue of glucose delivery to diabetes patients in on-line hemodiafiltration. Ther Apher Dial 2016;20:205.
7. Peters SA, Bots ML, Canaud B, Davenport A, Grooteman MP, Kircelli F, *et al*. Haemodiafiltration and mortality in end-stage kidney disease patients: A pooled individual participant data analysis from four randomized controlled trials. Nephrol Dial Transplant 2016;31:978-84.
8. Marano M, Capasso M, Cicchella T. On-line hemodiafiltration: All that glitters is not gold. Blood Purif 2016;41:315-6.
9. Locatelli F, Martin-Malo A, Hannedouche T, Loureiro A, Papadimitriou M, Wizemann V, *et al*. Effect of membrane permeability on survival of hemodialysis patients. J Am Soc Nephrol 2009;20:645-54.
10. Basile C, Davenport A, Blankestijn PJ. Why choose high volume online post-dilution hemodiafiltration? J Nephrol 2017;30:181-6.
11. Burmeister JE, Scapini A, da Rosa Miltersteiner D, da Costa MG, Campos BM. Glucose-added dialysis fluid prevents asymptomatic hypoglycaemia in regular haemodialysis. Nephrol Dial Transplant 2007;22:1184-9.
12. Canaud B, Barbieri C, Marcelli D, Bellocchio F, Bowry S, Mari F, *et al*. Optimal convection volume for improving patient outcomes in an international incident dialysis cohort treated with on-line hemodiafiltration. Kidney Int 2015;88:1108-16.
13. Marano M. On the advantage of glucose delivery by on-line hemodiafiltration. Ther Apher Dial 2018;22:560
14. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837-53.
15. Nathan DM, Genuth S, Lachin J, Cleary P, Crofford O, Davis M, *et al*. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977-86.
16. Monnier L, Mas E, Ginet C, Michel F, Villon L, Cristol JP, *et al*. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. JAMA 2006;295:1681-7.
17. Wentholt IM, Kulik W, Michels RP, Hoekstra JB, DeVries JH. Glucose fluctuations and activation of oxidative stress in patients with type 1 diabetes. Diabetologia 2008;51:183-90.
18. Drechsler C, Krane V, Ritz E, März W, Wanner C. Glycemic control and cardiovascular events in diabetic hemodialysis patients. Circulation. 2009;120:2421-8.
19. Alsahli M, Gerich JE. Hypoglycemia in patients with diabetes and renal disease. J Clin Med 2015;4:948-64.
20. Jackson MA, Holland MR, Nicholas J, Lodwick R, Forster D, Macdonald IA. Hemodialysis-induced hypoglycemia in diabetic patients. Clin Nephrol 2000;54:30-4.
21. Abe M, Kalantar-Zadeh K. Haemodialysis-induced hypoglycaemia and glycaemic disarrays. Nat Rev Nephrol 2015;11:302-13.
22. Henderson LW, Sanfelippo ML, Beans E. "Online" preparation of sterile pyrogen-free electrolyte solution. Trans Am Soc Artif Intern Organs 1978;24:465-7.
23. Ledebo I. On-line preparation of solutions for dialysis: Practical aspects versus safety and regulations. J Am Soc Nephrol 2002;13:S78-83.
24. Macías N, Vega A, Abad S, Santos A, Cedeño S, Linares T, *et al*. Is high-volume online hemodiafiltration associated with malnutrition? Ther Apher Dial 2017;21:361-9.
25. Davenport A, Peters SA, Bots ML, Canaud B, Grooteman MP, Asci G, *et al*. Higher convection volume exchange with online hemodiafiltration is associated with survival advantage for dialysis patients: The effect of adjustment for body size. Kidney Int 2016;89:193-9.
26. Vera KV, Krieter DH, Olschewski M, März W, Mann JF, Ritz E, *et al*. Dialyzer membrane characteristics and outcome of patients with type 2 diabetes on maintenance hemodialysis. Am J Kidney Dis 2007;49:267-75.
27. Macías N, Abad S, Vega A, Cedeño S, Santos A, Verdalles U, *et al*. High convective volumes are associated with improvement in metabolic profile in diabetic patients on online haemodiafiltration. Nefrologia 2019;39:168-76.
28. Carracedo J, Merino A, Nogueras S, Carretero D, Berdud I, Ramı´rez R, *et al*. On-line hemodiafiltration reduces the proinflammatory CD14+CD16+ monocyte-derived dendritic cells: A prospective, crossover study. J Am Soc Nephrol 2006;17:2315-21.
29. Rama I, Llaudó I, Fontova P, Cerezo G, Soto C, Javierre C, *et al*. Online haemodiafiltration improves inflammatory state in dialysis patients: A longitudinal study. PLoS One 2016;11:e0164969.
30. Akizawa T, Koiwa F. Clinical expectation of online hemodiafiltration: A Japanese perspective. Blood Purif 2015;40:12-6.
31. Tsuchida K, Minakuchi J. Clinical benefits of predilution on-line hemodiafiltration. Blood Purif 2013;35:18-22.

Original Article

COVID-19 early assessment outcomes on Internet data: A review study

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Abstract

Background: Severe acute respiratory syndrome coronavirus (SARS-CoV)-2, which is a novel coronavirus from the same family as SARS-CoV and Middle East respiratory syndrome coronavirus, has overrun worldwide leading the World Health Organization to declare a pandemic. **Objectives:** This study aimed to clarify high-risk factors for coronavirus disease 2019 (COVID-19) with multivariate analysis and establish a predictive model of disease progression to help clinicians better choose a therapeutic strategy. Clinical implications of COVID-19 will push society past this pandemic with the latest in technology and research and further studies into the pathogenesis evaluation. **Methods:** A comprehensive search of the PubMed, MEDLINE, Uptodate, Natural MEDLINE, Embase, and Web of Science electronic databases was made, using the following search terms: "COVID-19," "COVID-19 SCORE," "COVID-19 diagnosis," "COVID-19 management," "coronavirus," and "SARS-CoV-2." We included scientific publications from December 1, 2019, to April 31, 2021, which focused on clinical characteristics and treatments for SARS-CoV-2 that were eligible for inclusion. We screened all reference lists of relevant studies to identify any missing publications. **Results:** A total of 40 articles were reviewed. We revealed that the present review emphasizes that the higher risk of comorbidity, age, lymphocyte, and lactate dehydrogenase (CALL) score has a good predictive value for mortality in COVID-19 than the CURB-65 score. The 2021–2022 SARS-CoV-2 Omicron variant is a global concern due to its rapid spread to displace the main Delta and Omicron variants. This scoring system has been designed to categorize based on the systemic disease involvement and, thus, would serve as a reliable indicator for prognostic assessment in patients. **Conclusion:** This review highlights the higher predictive value of the CALL score for higher risk COVID-19 mortality than the CURB-65 score. The 2021–2022 SARS-CoV-2 Omicron variant is of global concern as its rapid spread has replaced the main Delta and Alpha variants. Scoring systems are designed to categorize disease and, thus, serve as reliable indicators of patient prognosis. Therefore, establishing corresponding standard assessment forms and admission criteria and preparing medical resources for critically ill patients is necessary as much as possible.

Keywords: Coronavirus, COVID-19 diagnosis, COVID-19 management, COVID-19 score, COVID-19, SARS-CoV-2

Introduction

A novel coronavirus named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) caused a cluster of pneumonia cases in Wuhan, China, in December 2019 and quickly spreads worldwide within a few months and become a global health emergency.[1-4] This pushed the limits of healthcare systems in many countries.[4,5] SARS-CoV-2 is a worldwide pandemic after the 2003 SARS pandemic,[5] followed by the 2012 Middle East respiratory syndrome.[4] The World Health Organization

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(WHO) named the pandemic coronavirus disease 2019 (COVID-19) in February 2020.

Angiotensin-converting enzyme 2 was identified as a receptor for the entry of SARS coronavirus into host cells.[4] The SARS-CoV-2 infection leads one-third of adults with COVID-19 to have upper respiratory symptoms ranging from mild illness to severe acute lung injury/acute respiratory distress syndrome (ARDS) and multiple organ failure and high mortality, especially in patients with cardiovascular disease, diabetes, or advanced age.[4,5] Approximately 10% of patients were hospitalized for severe/critical COVID-19.[6] Additionally, some coronaviruses may cause diarrhea in infants and children, and central nervous system disease has not been demonstrated.[7-10] The Centers for Disease Control and Prevention clinical guidelines recommended cities as areas for sustained outbreaks at the community level.[11-13] Since its first appearance, more than 280 million people were confirmed to be infected by the new coronavirus and more than 5 million deaths to date.[14] Suspected populations are isolated in terms of epidemiology for the rapid diagnosis and control of COVID-19, and clinical data can be used as a guide for clinical decision-making to the understanding of SARS-CoV-2 virus infection and to provide basic system construction.[7,8]

Currently, a few studies have systematically analyzed the clinical evaluation of COVID-19. This study analyzed 31 different articles from web-available data and selected the latest and most consistent information because data remained unavailable. Therefore, this study aimed to report COVID-19–related literature to aid clinical early diagnosis for timely medical treatment. The goal is to create an open-access comprehensive resource containing patient symptoms and clinical data that can better help clinicians understand risk stratification, allocate available medical resources, and ensure appropriate clinical management of high-risk patients to improve survival,[7,8] as well as facilitate international efforts to fight against COVID-19.

Materials and Methods

Search strategy

A comprehensive search was made of PubMed, MEDLINE, Uptodate, and Natural online databases using the primary search terms: "COVID-19," "COVID-19 SCORE," "COVID-19 diagnosis," "COVID-19 management," "coronavirus," and "SARS-CoV-2."

Inclusion criteria

Studies were written in English. Data collected from December 1, 2019, to March 15, 2022, related to COVID-19 literature and analyzed, were eligible for inclusion. Thirty-one retrospective articles were expected to be analyzed, and this study aimed to systematically analyze COVID-19 assessments based on COVID-19 case definitions and clinical classifications. Suspected cases were defined as follows: any epidemiological history of the following plus any two of the clinical manifestations, or three clinical manifestations without an obvious epidemiological history. A critical review of the existing literature examining COVID-19 prognosis was included.

Epidemiological history

1. History of contact with a case of COVID-19 infection within 14 days before onset (positive RNA test).
2. Contact history of a patient with fever or respiratory symptoms following contact with a case of COVID-19 infection within 14 days before the onset of illness.

Clinical manifestations

1. Fever and/or respiratory symptoms and/or changes in taste.
2. Chest computed tomography imaging evidence revealed the characteristics of COVID-19 pneumonia, including the appearance of multiple small plaque-like "ground glass opacity (GGO)," early qualitative changes and peripheral lung abnormalities, and progression to localized in severe cases of sexual or diffuse bilateral GGO.
3. Laboratory findings at the onset of disease: normal or decreased white blood cell count or lymphopenia.

Exclusion criteria

Case reports, ongoing studies, or studies with abnormal demographics were excluded from this review.

Data extraction and analysis

The title and abstract of the study were checked for appropriateness by two authors (Yu and Hu) and were rigorously checked by a third independent reviewer (Fan); conflicting views are discussed until a consensus is reached. Selected papers are further subdivided into:

1. Studies reporting the current state of research on COVID-19
2. Studies reporting current clinical symptoms and disease course in COVID-19
3. Studies reporting current supportive care in COVID-19

Relevant data collected as COVID-19 assessments were then classified and analyzed.

Results

A total of 31 studies were initially identified. Six were excluded because they included case reports (n = 2) and no informative studies (n = 4) for distinction. Finally, 31

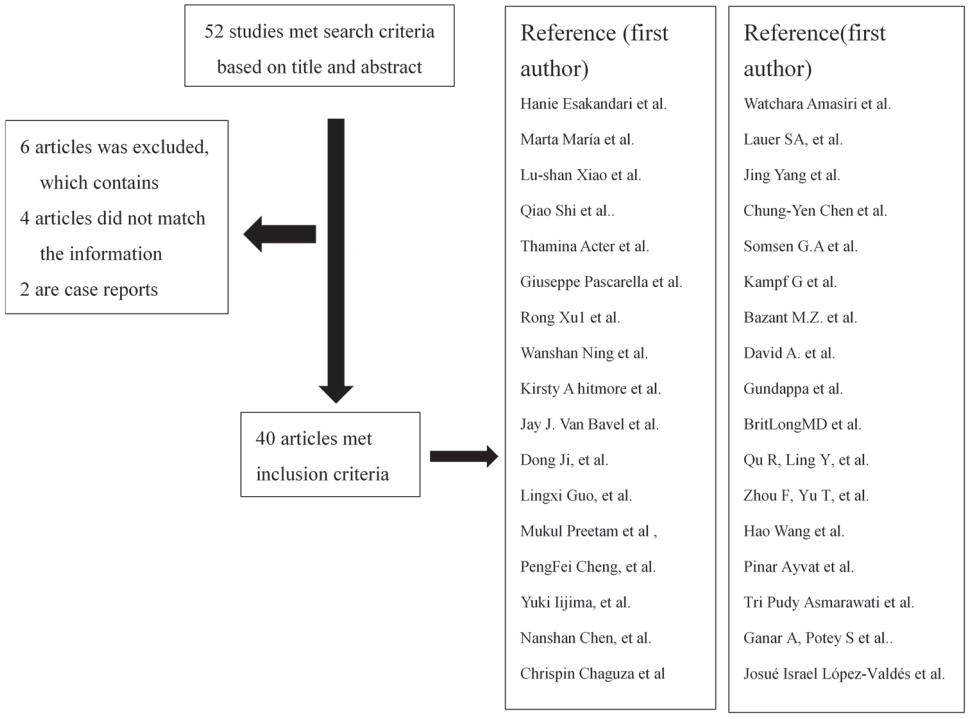

Figure 1: Flowchart for included studies

Table 1: Studies reporting COVID-19 assessment

Authors	Patients (*n*)	Age	M:F	Tool	Main results
García Clemente *et al.*[2]	249	65.6 + 16.1	143:106	CALL (13 point)	4–6 points were low risk 7–9 points were intermediate risk 10–13 points were high risk
Ji *et al.*[15]	208	44.0 ± 16.3	117:91	CALL (13 point)	4–6 points were low risk 7–9 points were intermediate risk 10–13 points were high risk
Guo *et al.*[16]	528	63.56 ± 19.08	323:205	MuLBSTA (12 point)	0–11 points were low risk ≥12 points were high risk
Xu *et al.*[7]	117	60	55:62	MuLBSTA (12 point)	0–11 points were low risk ≥12 points were high risk
Preetam *et al.*[17]	122	44.16	69:53	MuLBSTA (12 point)	<12 points dying within 14 days is 10.46 times. ≥12 points dying with 14 days is 22.29 times.
Cheng *et al.*[18]	53	61	36:17	APACHE II (12 point)	<9.5 points need high flow of O2 9.5–10.5 points need noninvasive ventilator support ≥12.5 points need invasive ventilator support
Iijima *et al.*[19]	72	57.3 ± 19.4	50:22	MuLBSTA (12 point)	7.5 ± 4.4 points was nondeterioration 13.5 ± 3.2 points was deterioration

articles were analyzed, including clinical assessments of COVID-19 [Figure 1].

COVID-19 studies reporting

A total of 15 studies introduced COVID-19, 10 studies reported the assessment of COVID-19, and 15 were retrospective case reports. The summary of the studies is presented in Table 1, and the clinical symptom assessment is presented in Table 2. All four studies indicated that the MuLBSTA score is valuable and easy to calculate for risk stratification, and can effectively screen high-risk patients at admission. A higher score on admission indicates a higher risk of infection, increased intensive care unit resources, and 14-day mortality for patients with COVID-19.[16-18] The study emphasized the MuLBSTA score as a potentially useful tool for predicting COVID-19 behavior by Iijima *et al.*[19] This scoring system can be used as one of the criteria for identifying high-risk patients who have deteriorated to a life-threatening state. A MuLBSTA score of 7.5 ± 4.4 indicates no deterioration, and a

Table 2: Symptoms observed in various cohorts of patient

Symptom	Garcia Clemente *et al*.[2]	Xu *et al*.[10]	Ji *et al*.[15]	Guo *et al*.[16]	Kodama *et al*.[20]	Feng *et al*.[21]
Patients (*n*)	249	98	208	528	207	126
Fever/°C	86%	59.2%	81.7%	60.8%	30%	73.0%
Cough	69%	17.3%	49.5%	76.9%	38%	52.4%
Sore throat	—	5.1%	7.2%	—	10%	—
Dyspnea	49%	—	12%	35.6%	12%	2.4%
Headache	33.7%	—	6.2%	—	13%	—
Diarrhea	25.7%	4.1%	3.8%	—	8%	3.2%
Weary	—	—	10.6%	—	21%	22.2%
Length of hospital stay	12.1±7.5	18.0	17.5±8.2	20.7	12	21
Death	15.4%	1%	1%	11%	4.3%	1%

MuLBSTA score of 13.5±3.2 indicates deterioration of the patient's condition.[19]

One study indicated that the comorbidity, age, lymphocyte, and lactate dehydrogenase (LDH) (CALL) score were based on a nomogram for clinical use and further evaluation.[2,15] The CALL score mainly evaluates comorbidity, age of more than 60 years, lymphocyte count of less than or equal to 1000, and LDH value.[2,15] Ji *et al*.[15] divided 208 patients into the control group (*n* = 168; 80.8%) and experimental group (*n* = 40; 19.2%) and evaluated whether the disease worsened during hospitalization. The CALL score is divided into three risk levels according to their probability: 4–6 points with less than 10% risk of progression as low risk (level A), 7–9 points with 10%–40% risk of progression as intermediate risk (level B), 10–13 points with a risk of progression more than 50%, and high risk (Grade C).[15] Comorbidities, older age, lower lymphocyte count, and higher LDH are high-risk factors for COVID-19. Clinicians used the CALL scoring models to more accurately and efficiently assess COVID-19 treatment outcomes and reduce mortality and healthcare resources.[2,15] García Clemente *et al*.[2] revealed that the CALL score has an area under the curve (AUC) of 0.874 (95% confidence interval [CI]: 0.808–0.939), and the CURB-65 score has an AUC of 0.852 (95% CI: 0.794–0.909). Studies revealed that the CALL score has a good predictive value for mortality, as shown in Table 1.

COVID-19 clinical symptoms

COVID-19 is a cluster of infections and symptoms that vary from person to person and from asymptomatic infection to severe infection and even respiratory failure.[6]

Symptoms are very similar to seasonal flu infection.[1,22] The most common symptoms are fever (70%–80%), cough (50%), sore throat (7%), headache (20%), difficulty breathing (22%), diarrhea (9%), fatigue, etc. (18%), with a length of hospital stay of 16.8±7.8) and a mortality rate of 2.6%,[6,22] as shown in Table 2.

Studies by Amasiri *et al*.[23] revealed that approximately 3213 (87.2%) cases were asymptomatic, and 62.3%–75% were identified as positive and asymptomatic and mildly symptomatic cases; approximately 10% of those with symptoms develop dyspnea, severe pneumonia, ARDS, and multiple organ dysfunction.[22-24] Spinato *et al*. included a large number of outpatients in the southeastern United States and revealed that 11.9% of patients with detected SARS-CoV-2 RNA virus had a loss of taste or smell.[24]

Xu *et al*.[10] included 98 patients hospitalized for COVID-19 in Zhuhai, China, from January 17 to February 13, 2020. The study found that age of more than 60 years, C-reactive protein, and peripheral capillary oxygen saturation of less than 97% were associated with COVID-19.[10] However, prothrombin time (PT) of more than 12.3 s is a new risk factor. Previous studies revealed that coagulopathy is common in critically ill patients with COVID-19 and is associated with an increased risk of acute infection with respiratory distress syndrome. Early PT monitoring is recommended to predict the likelihood of progression.[10]

COVID-19 prevention

The WHO and the United States Centers for Disease Control and Prevention have confirmed that airborne transmission is an important route for the spread of COVID-19.[24-26] Somsen *et al*. revealed that the SARS-CoV-2 in aerosols can survive and remain infectious for a long time,[27] and the suspension time of aerosols increases tenfold in poorly ventilated spaces.[28-30] The epidemic could recur if indoor ventilation is not properly addressed even in countries with adequate levels of vaccination. Governments should acknowledge scientific evidence and take steps to develop official regulations and guidelines for indoor space ventilation to reduce the spread of COVID-19.[30]

Discussion

The present review emphasizes that the higher risk of the CALL score has a good predictive value for mortality in COVID-19 than the CURB-65 score. The 2021–2022

SARS-CoV-2 Omicron variant is a global concern due to its rapid spread to displace the main Delta and Alpha variants.[31] Hence, establishing appropriate standard assessment forms and admission criteria and preparing medical resources for critically ill patients as much as possible are necessary.[32]

Long *et al*.[33] revealed that risk scores may assist in prognostication, including the Coronavirus Clinical Characterization Consortium score, quick COVID severity index, NEWS2, and the PRIEST score, but these should only supplement and not replace clinical judgment.[33-35] These are useful for predicting the prognosis to dynamically measure the APACHE II, CURB-65, SOFA, and respiratory frequency.[36-39] A higher age, more days from the beginning of symptoms to hospital admission, and lower oxygenation at admission were preadmission determining factors for the risk of death.[40] Thus, we analyzed 40 studies and revealed that COVID-19 risk SCORE, including the CALL score, MuLBSTA score, APACHE II, and MuLBSTA, should only supplement clinical judgment.

Conclusion

The study analysis of 40 research reports revealed COVID-19 risk SCORE, including the CALL score, MuLBSTA score, APACHE II, and MuLBSTA. This review highlights the higher predictive value of the CALL score for higher risk COVID-19 mortality than the CURB-65 score. This scoring system has been designed to categorize based on the systemic involvement of the disease and, thus, would serve as a reliable indicator for prognostic assessment in patients. Prognosis scores routinely used the COVID score model. This suggestion is not to replace clinical professional judgment or expert advice.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Conflicts of interest

H.-C.F., the Executive Editor, and C.-W.H., an editorial board member at *Tungs' Medical Journal*, had no roles in the peer review process of or decision to publish this article. For the remaining authors, there are no conflicts of interest.

References

1. Esakandari H, Nabi-Afjadi M, Fakkari-Afjadi J, Farahmandian N, Miresmaeili S-M, Bahreini E. A comprehensive review of COVID-19 characteristics. Biol Proced Online 2020;22:19.
2. García Clemente MM, Herrero Huertas J, Fernandez Fernandez A, De La Escosura Munoz C, Enriquez Rodriguez AI, Perez Martinez L, *et al*. Assessment of risk scores in COVID-19. Int J Clin Pract 2021;75:e13705.
3. Xiao LS, Zhang WF, Gong MC, Zhang YP, Chen LY, Zhu HB, *et al*. Development and validation of the HNC-LL score for predicting the severity of coronavirus disease 2019. EBioMedicine 2020;57:102880.
4. Shi Q, Zhang X, Jiang F, Zhang X, Hu N, Bimu C, *et al*. Clinical characteristics and risk factors for mortality of COVID-19 patients with diabetes in Wuhan, China: A two-center. Diabetes Care 2020;43:1382-91.
5. Acter T, Uddin N, Das J, Akhter A, Choudhury TR, Kim S. Evolution of severe acute respiratory syndrome coronavirus 2(SARS-CoV-2) as coronavirus disease 2019 (COVID-19) pandemic: A global health emergency. Sci Total Environ 2020;730:138996.
6. Pascarella G, Strumia A, Piliego C, Bruno F, Del Buono R, Costa F, *et al*. COVID-19 diagnosis and management: A comprehensive review. J Intern Med 2020;288:192-206.
7. Xu R, Hou K, Zhang K, Xu H, Zhang N, Fu H, *et al*. Performance of two risk-stratification models in hospitalized patients with coronavirus disease. Front Med 2020;7:518.
8. Ning W, Lei S, Yang J, Cao Y, Jiang P, Yang Q, *et al*. Open resource of clinical data from patients with pneumonia for the prediction of COVID-19 outcomes via deep learning. Nat Biomed Eng 2020;4:1197-207.
9. Ayres JS. A metabolic handbook for the COVID-19 pandemic. Nat Metab 2020;2:572-85.
10. Xu J, Wang W, Ye H, Pang W, Pang P, Tang M, *et al*. A predictive score for progression of COVID-19 in hospitalized persons: A cohort study. NPJ Primary Care Respir Med 2021;31:33.
11. World Health Organization Regional Office for Europe. About Pandemic Phases. https://www.euro.who.int/en/health-topics/communicable-diseases/influenza/data-and-statistics/pandemic-influenza/about-pandemic-phases (WHO, 2020). [Last accessed on 08 Jul 2022].
12. Centers for Disease Control and Prevention. Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19), https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html#clinical-course (Centers for Disease Control and Prevention, 2020). [Last accessed on 25 Jun 2022].
13. Whitmore KA, Laupland KB, Vincent CM, Edwards FA, Reade MC. Changes in medical scientific publication associated with the COVID-19 pandemic. Med J Aust 2020;213:496-499.e1.
14. Van Bavel JJ, Cichocka A, Capraro V, Sjåstad H, Nezlek JB, Pavlović T, *et al*. National identity predicts public health support during a global pandemic. Nat Commun 2022;13:517.
15. Ji D, Zhang D, Xu J, Chen Z, Yang T, Zhao P, *et al*. Prediction for progression risk in patients with COVID-19 pneumonia: The CALL score. Clin Infect Dis 2020;71:1393-9.
16. Guo L, Wei D, Zhang X, Wu Y, Li Q, Zhou M, *et al*. Clinical features predicting mortality risk in patients with viral pneumonia: The MuLBSTA score. Front Microbiol 2019;10:2752.
17. Preetam M, Anurag A. MuLBSTA score in COVID-19 pneumonia and prediction of 14-day mortality risk: A study in an Indian cohort. J Family Med Prim Care 2021;10:223-7.
18. Cheng PF, Wu H, Yang J, Song X, Xu M, Li B, *et al*. Pneumonia scoring systems for severe COVID-19: Which one is better. Virol J 2021;18:33.
19. Iijima Y, Okamoto T, Shirai T, Mitsumura T, Sakakibara R, Honda T, *et al*. MuLBSTA score is a useful tool for predicting COVID-19 disease behavior. J Infect Chemother 2021;27:284-90.
20. Kodama T, Obinata H, Mori H, Murakami W, Suyama Y, Sasaki H, *et al*. Prediction of an increase in oxygen requirement of SARS-CoV-2 pneumonia using three different scoring systems. J Infect Chemother 2021;27:336-41.
21. Feng Z, Yu Q, Yao S, Luo L, Zhou W, Mao X, *et al*. Early prediction of disease progression in COVID-19 pneumonia

patients with chest CT and clinical characteristics. Nat Commun 2020;11:4968.
22. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, *et al*. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. Lancet 2020;395:507-13.
23. Amasiri W, Warin K, Mairiang K, Mingmalairak C, Panichkitkosolkul W, Silanun K, *et al*. Analysis of characteristics and clinical outcomes for crisis management during the four waves of the COVID-19 pandemic. Int J Environ Res Public Health 2021;18:12633.
24. Spinato G, Fabbris C, Polesel J, Cazzador D, Borsetto D, Hopkins C, *et al*. Alterations in smell or taste in mildly symptomatic outpatients with SARS-CoV-2 infection. JAMA 2020;323:2089-90.
25. WHO. Vol. 2021. World Health Organization; 2020. Coronavirus disease (COVID-19): How is it transmitted? https://www.who.int/news-room/q-a-detail/coronavirus-disease-covid-19-how-is-it-transmitted. [Last accessed on 28 Jun 2022].
26. Chung-Yen C, Ping-Hui C, Chen JK, Su TC. Recommendations for ventilation of indoor spaces to reduce COVID-19 transmission. J Formos Med Assoc 2055120:e2060.
27. Somsen GA, vanRijn C, Kooij S, Bem RA, Bonn D. Small droplet aerosols in poorly ventilated spaces and SARS-CoV-2 transmission. Lancet Respir Med 2020;8:658-9.
28. Kampf G, Todt D, Faender SP, Steinmann E. Persistence of coronaviruses on inanimate surfaces and their inactivation with biocidal agents. J Hosp Infect 2020;104:246-51.
29. Bazant MZ, Bush JWM. A guideline to limit indoor airborne transmission of COVID-19. Proc Natl Acad Sci U S A 2021;118:e2018995118.
30. Wohl DA, Barzin AH, Napravnik S, Davy-Mendez T, Smedberg JR, Thompson CM, *et al*. COVID-19 symptoms at time of testing and association with positivity among outpatients tested for SARS-CoV-2. PLoS One 2021;16:e0260879.
31. Chaguza C, Coppi A, Earnest R, Ferguson D, Kerantzas N, Warner F, *et al*. Rapid emergence of SARS-CoV-2 Omicron variant is associated with an infection advantage over Delta in vaccinated persons. Med 2022;3:325-334.e4.
32. Jing Y, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, *et al*. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: A systematic review and meta-analysis. Int J Infect Dis 2020;94:91-5.
33. Long B, Carius BM, Liang SY, Chavez S, Brady WJ, Koyfman A, *et al*. Clinical update on COVID-19 for the emergency clinician: Presentation and evaluation. Am J Emerg Med 2022;54:46-57.
34. Qu R, Ling Y, Zhang YH, Wei LY, Chen X, Li XM, *et al*. Platelet-to-lymphocyte ratio is associated with prognosis in patients with coronavirus disease-19. J Med Virol 2020.
35. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, *et al*. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet 2020;395:1054-62.
36. Wang H, Sun B, Li X, Wang Y, Yanga Z. Clinical analysis of severe COVID-19 patients. Technol Health Care 2022;30:225-34.
37. Ayvat P, Omeroglu SK. Mortality estimation using APACHE and CT scores with stepwise linear regression method in COVID-19 intensive care unit: A retrospective study. Clin Imaging 2022;88:4-8.
38. Asmarawati TP, Suryantoro SD, Rosyid AN, Marfiani E, Windradi C, Mahdi BA, *et al*. Value of sequential organ failure assessment, quick sequential organ failure assessment, acute physiology and chronic health evaluation II, and new early warning signs scores estimate mortality of COVID-19 patients requiring intensive care unit. Indian J Crit Care Med 2022;26:464-71.
39. Ganar A, Potey S. To evaluate and compare ability of two prognostic scoring systems in predicting the mortality of critically ill patients in adult intensive care unit. IJCMR 2019;6.
40. López-Valdés JI, Ponce-Mendoza RA, Solís-Barraza M, Trevizo-Díaz JL, Nevarez-Campos JR. Clinical characteristics related to mortality by COVID-19 in intensive care. Rev Med Inst Mex Seguro Soc 2022;60:249-57.

Original Article

L-glutamate can protect the oxidative stress injuries of the fetal lung cells

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Abstract

Background: Bronchopulmonary dysplasia (BPD) is one of the major complications of prematurity resulting in significant mortality and morbidity. Reactive oxygen species, which are highly reactive molecules that can cause oxidative damage to lung tissue and trigger inflammatory reactions, are associated with pathophysiological changes in many lung diseases, such as BPD. Hydrogen peroxide (H_2O_2), which is a strong oxidant, is widely used in simulating cellular oxidative damage. Whether glutamine can protect lung cells from oxidant damages is not known. **Objectives:** To explore the cytotoxic mechanisms of H_2O_2 on lung cells, including A549 and HEL299 cells, and investigate the effects of L-glutamine in the protection of oxidative damage on the lung cells. **Methods:** Cytotoxic effects of H_2O_2 and the protective effects of glutamine against H_2O_2 on lung cells were accessed by the cell viability assay. The underlying mechanisms for H_2O_2 damaging lung cells were analyzed by the flow cytometry to quantify changes in mitochondrial membrane potential before and after H_2O_2 and L-glutamine were added into lung cells. Pulmonary alveolar epithelial cells line, A549, and human embryonic bronchial fibroblast cell line, HEL 299, were grown in the incubator. H_2O_2 with and without L-glutamine was added in the lung cells, and cell viability was measured by the water-soluble tetrazolium 1 (WST-1) assay and the changes of mitochondrial membrane potential by the flow cytometry. Statistical analysis used is as follows: data comparisons from cell proliferation studies were analyzed by one-way analysis of variance. The quantification data of the mitochondrial potential assay was analyzed by Student's *t* tests. A *P*-value of less than 0.05 was considered statistically significant. **Results:** A total of 100-μM H_2O_2 significantly decreased the viability of A549 and HEL299 cells; 8-mM L-glutamine rescued lung cell death caused by the H_2O_2 toxicity; and 100 μM of mitochondrial membrane potential was significantly elevated in HEL299 cells, except A549 cells in the application of H_2O_2 and L-glutamine. **Conclusion:** H_2O_2-induced cytotoxicity in A549 and HEL299 cells was associated with mitochondria. The different effects of L-glutamine on A549 and HEL299 cells in response to the 100 μM of H_2O_2-induced cytotoxicity suggest that these two cell lines may have different mechanisms against oxidative stress.

Keywords: Bronchopulmonary dysplasia (BPD), hydrogen peroxide, L-glutamine, mitochondria, reactive oxygen species (ROS)

Introduction

In general, preterm infants are defined as neonates born at less than 37 weeks of gestational age. Preterm birth has been recognized as a serious global health issue because it is the second largest direct cause of child deaths in children younger than 5 years.[1] Preterm infants with lung immaturity are unable to adequately oxygenate and ventilate, and, therefore, always require prolonged oxygen supplementation often with positive pressure ventilation.[2] However, oxygen may cause various oxygen toxicities in multiple organs, including the lungs and brain,[2] leading to an increased risk of adverse physical morbidity and mortality compared

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with full-term delivery, although supplemental oxygen for preterm infants is critical for their survival.[3] Therefore, oxygen therapy should be judiciously used to avoid oxygen toxicity in the perinatal care of infants with prematurity.[4]

Bronchopulmonary dysplasia (BPD) remains a major complication of prematurity, resulting in significant mortality and morbidity.[5,6] Survivors of prematurity and BPD are at increased risk for respiratory disease, including respiratory infection, asthma-like disease, and pulmonary artery hypertension.[7] A typical BPD is characterized by wide-ranging and serious inflammation in lung tissue and extensive fibrosis in various respiratory tracts.[8] BPD is associated with an increased risk for neurodevelopmental disability.[6,9,10] Moreover, infants with severe BPD have a higher risk of mortality than unaffected infants.[11-13] No wonder families, especially mothers of preterm infants with BPD, experience substantially more psychological distress than others.[14]

The BPD pathogenesis is multifactorial. The risk factors include (1) prematurity, (2) respiratory distress, (3) mechanical ventilation, (4) infection and inflammation, (5) pulmonary edema as a result of patent ductus arteriosus or fluid overloading, (6) nutritional deficiencies, (7) genetic factors, and (8) oxygen supplementation.[15,16] The principle mechanism involves the univalent reduction of molecular oxygen and the formation of reactive oxygen species (ROS), which are highly reactive chemicals formed from oxygen, such as peroxides, superoxide, hydrogen peroxide (H_2O_2), singlet oxygen, and alpha-oxygen.[17] These oxygen-free radicals are highly reactive molecules that can cause oxidative damage to lung tissue and trigger inflammatory reactions.[18] Premature infants have inadequate antioxidant defense systems because their antioxidant enzymes, such as superoxide dismutase, catalase, and glutathione peroxidase, are not mature; thus, they are vulnerable to develop lung injury from oxygen toxicity.[19]

Oxygen is a double-edged sword and is used to prevent hypoxemia, whereas oxygen-associated hypoxemia and hyperoxemia can have detrimental effects on the health of infants with prematurity.[20] Advanced interventions in perinatal care have not dramatically changed the incidence of BPD[21]; thus, understanding the cellular mechanisms of BPD is fundamental given the therapeutic strategies to manage such diseases. H_2O_2 is a strong oxidant that can penetrate the cell membrane and form highly reactive free radicals to directly damage cell membrane lipids, proteins, and nuclear DNA, thereby causing extensive oxidative injuries. Hence, H_2O_2 has been widely used in simulating cellular oxidative damage.[22] Glutamine is the most abundant amino acid in the body and is an important respiratory substrate for rapidly dividing cells.[23,24] However, some studies revealed that lung cells exposed to hyperoxia have improved survival when supplemented with higher concentrations of glutamine although the role of the glutamine in the lung is unclear.[25,26] This idea inspired us to hypothesize that glutamine may protect the lungs against oxidative stress. We developed an *in vitro* model using human alveolar epithelial and fetal bronchial cells using H_2O_2 to determine the effects of glutamine on these lung cells under oxidative stress to investigate our hypothesis.

Materials and Methods

Culture of lung cells

Pulmonary alveolar epithelial cells immortalized from the human lung carcinoma cell line, A549, and lung cells immortalized from the human embryonic bronchial fibroblast cell line, HEL 299, were purchased from the American Type Culture Collection (Manassas, Virginia). All cells were detected negative for *Mycoplasma* contamination before all experiments were performed in this study. Based on our previous publication,[27] we grew these cells in monolayers at 37°C in 5% CO_2 and 100% humidity using tissue culture dishes. A549 cells were maintained on RPMI1640 (Gibco BRL, Grand Island, New York). HEL299 cells were maintained on Modified Eagle's Medium (MEM; Gibco BRL). Both media were supplemented with penicillin (1×10^5 U/L), streptomycin (100 mg/L), amphotericin B (0.25 mg/L), L-glutamine (2 mM, Invitrogen, Carlsbad, California), and 10% (*v*/*v*) fetal bovine serum (FBS, Hyclone Laboratories, Logan, Utah). The same batch of FBS was used for all experiments. The culture medium was renewed every 2–3 days.

Cell viability with hydrogen peroxide stimulation and concurrent L-glutamine treatment

A549 and HEL 299 cells were plated into 96-well culture plates at a concentration of 1×10^5 cells/mL and incubated at 37°C in 5% CO_2 for 24 h. After washing, A549 and HEL299 cells were incubated for an additional 24 h with serum-free RPMI1640 and MEM, respectively. Cell viability was analyzed by measuring the activity of mitochondrial malate dehydrogenase using the water-soluble tetrazolium 1 (WST-1) assay.[28] A549 and HEL299 cells were plated in 96-well plates, treated with or without meconium stimulation, and incubated with 10 μL of WST-1 reagent (BioVision, Milpitas, California) for 3 h at 37°C. The amount of formazan generated, which was proportional to the number of viable cells, was calculated using a Microplate Photometer (MultiSkan FC, Thermo Fisher Scientific K.K., Tokyo, Japan) based on the absorbance signal at 440 nm. The absorbance was corrected using a background reading. Cells were treated with 0, 10, 25,

50, 100, 150, and 200 μM of H_2O_2 (Sigma, St. Louis, Missouri) and 8, 80, 800, and 8-mM L-glutamine for 24 h to investigate the dose effect of H_2O_2 and concurrent L-glutamine treatment. Control cells were incubated in an H_2O_2- or L-glutamine-free medium in the same condition. The supernatant was collected at each time point and used to determine cell viability.

Mitochondrial membrane potential assay

The experiment protocols followed the manufacturer's instructions and were modified by our previous experiment.[29] Briefly, 5,5′,6,6′-tetrachloro-1,1′,3,3′-tetraethylbenzimidazolcarbocyanine iodide (JC-1) (MitoProbe JC-1 Assay Kit, Catalog number: M34152, Thermo Fisher Scientific Inc., Waltham, Massachusetts) is a mitochondrial-specific and lipophilic cationic dye that undergoes potential-dependent accumulation in the mitochondria. JC-1 monomers convert to J-aggregates that emit red light (590 nm) following excitation with green light (540 nm) at a higher membrane potential. It exists as a monomer when the membrane potential ($\Delta\Psi$) is less than 140 mV and emits green light (540 nm) following blue light excitation (490 nM).

JC-1 has no effects on living cells, including their respiration. A stock solution of JC-1 of 100 μmol/L was prepared in dimethyl sulfoxide. A549 and HEL299 cells (1×10^5) were seeded into 75 cm^3 of flasks. Cells were treated with 100 μM of H_2O_2 with and without 8 mM of L-glutamine on day 3 in an incubator with 5% CO_2, 21% oxygen, and 100% humidity at 37°C for 24 h. Then, cells were loaded with JC-1 (10 μg/mL) in PBS at 37°C for 20 min in the dark. Fluorescence was measured using a FacsCalibur flow cytometer (Becton–Dickinson, Mountain View, California). Changes in the ratio between the red (590 nm) (FL2) and green (540 nm) (FL1) fluorescence intensities indicate the changes in the mitochondrial membrane potential. The ratio of red to green fluorescence is dependent only on the membrane potential but not on other factors, including mitochondrial size, density, cell number, and shape. Data were analyzed with the CellQuest 5.1 software (Becton–Dickinson).

Statistical analysis

All values were expressed as mean ± standard deviation. Data comparisons from cell proliferation studies were analyzed by one-way analysis of variance. The quantification data of the mitochondrial potential assay was analyzed by Student's *t* tests. A *P*-value of less than 0.05 was considered statistically significant.

Ethical approval

This study was approved by the institutional review board at Tungs' Taichung MetroHarbor Hospital, Taiwan (IRB approval No.: 107059 and date of approval: December 6th, 2018).

Results

Effect of H_2O_2 on lung cell viability

H_2O_2 cytotoxicity assessment through the WST-1 assay exhibited the dose-dependent toxic effects on the viability of A549 and HEL299 cells in a concentration range of 0–200 μM for 24 h [Figure 1A and B]. The A549 cells treated with 100 μM of H_2O_2 revealed a significant decrease in percent viability compared with the untreated control cells (83.51% ± 3.47% vs. 100, respectively; $P < 0.05$; Figure 1A). The cell viability

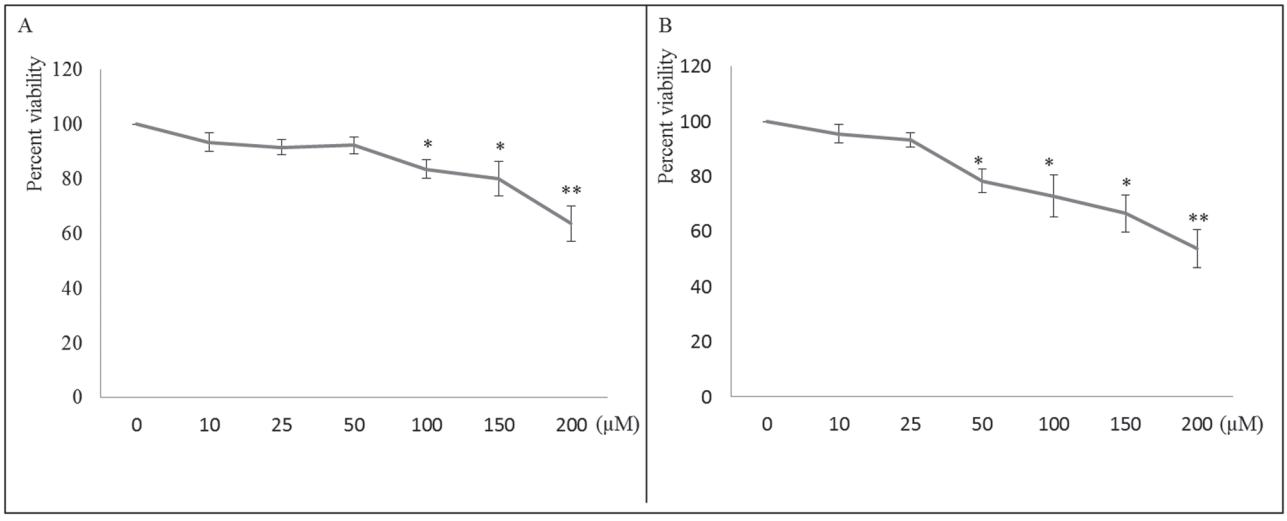

Figure 1: Effects of hydrogen peroxide (H_2O_2) on the growth of A549 cells (A) and HEL299 cells (B). The A549 cells and HEL299 cells were treated with various H_2O_2 concentrations (0–200 μM), and the cell viability was estimated by WST-1 assay. Data are presented as mean ± standard deviation when treated with increasing H_2O_2 concentrations ($n = 6$). Data were considered as statistically significant at $^*P < 0.05$, $^{**}P < 0.005$ when H_2O_2 treated cells were compared with untreated controls

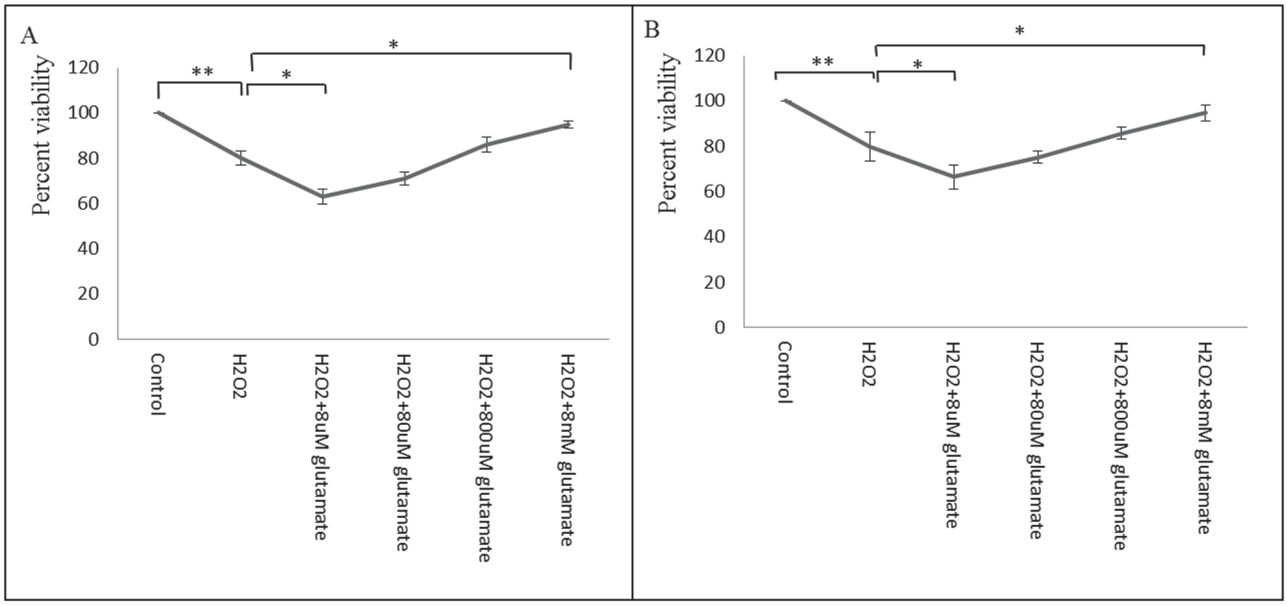

Figure 2: Biphasic protecting effects of L-glutamine on the H_2O_2-induced cytotoxicity on the A549 cells (A) and HEL299 cells (B). Cells were initially seeded at equal densities and supplemented with L-glutamine and grown in 100 μM of H_2O_2. L-glutamine at 8 μM significantly enhanced 100 μM of H_2O_2 cytotoxicity in A549 cells and HEL299 cells (*$P < 0.05$). L-glutamine at 8 mM rescued the H_2O_2 that induced cytotoxicity on A549 cells and HEL299 cells (*$P < 0.05$). The cell viability was estimated by WST-1 assay. Data are presented as mean ± standard deviation when treated with 100 μM of H_2O_2 concomitantly with and without L-glutamine from 0, 8, 80, 800, and 8 mM of L-glutamine ($n = 4$). Data were considered statistically significant at *$P < 0.05$, **$P < 0.005$ when cells treated with H_2O_2 concomitantly with L-glutamine were compared with cells treated with 100 μM of H_2O_2 alone

of the A549 cells revealed a significant decline when the H_2O_2 concentration increased to 200 μM compared with untreated control cells (63.58% ± 6.43% vs. 100, respectively; $P < 0.005$). The HEL299 cells treated with 50 μM of H_2O_2 revealed a drastic decrease in percent viability compared with the untreated control cells (78.43% ± 4.26% vs. 100, respectively; $P < 0.05$). The cell viability of the HEL299 cells significantly fell in the concentration of H_2O_2 increased to 200 μM compared with untreated control cells (53.87% ± 6.85 vs. 100, respectively; $P < 0.005$). We selected 100 μM of H_2O_2 concentration as an oxidative stress inducer in all lung cells in further experiments, because A549 and HEL299 cells revealed different responses to H_2O_2.

Biphasic effects of L-glutamine on the H_2O_2 inducing cytotoxicity on lung cell viability

The protecting effects of L-glutamine H_2O_2 were evaluated by treating A549 and HEL299 cells with 100 μM of H_2O_2 concomitantly with and without L-glutamine from 0, 8, 80, 800, and 8 mM of L-glutamine for 24 h [Figure 2]. H_2O_2 treatment at 100 μM significantly decreased the viability of A549 and HEL299 cells. However, 8-μM L-glutamine application enhanced the 100 μM of H_2O_2 toxicity on A549 cells (63.17% ± 3.45% vs. 80.13% ± 3.01%, respectively; $P < 0.05$) and HEL299 cells (66.43% ± 5.12% vs. 79.94% ± 6.40%, respectively; $P < 0.05$). The cell viability of the A549 (94.94% ± 1.48% vs. 80.13% ± 3.01%, respectively; $P < 0.05$) and HEL299 cells (94.81% ± 3.57% vs. 79.94% ± 6.40%, respectively; $P < 0.05$) significantly increased when the concentration of the additional L-glutamine increased to 8 mM.

Mitochondria is one of the targets for the cytotoxic effect of H_2O_2 on lung cells

Mitochondrial membrane potential quantification with flow cytometry was conducted to investigate the underlying mechanisms of the cytotoxic effects of H_2O_2 on A549 and HEL299 cells. The mitochondrial membrane potentials of A549 (82.63% ± 5.28% vs. 9.87% ± 2.931%, respectively; $P < 0.005$; Figure 3) and HEL299 cells (93.75% ± 2.57% vs. 7.20% ± 1.54%, respectively; $P < 0.005$; Figure 4) were both significantly decreased in the application of 100 μM of H_2O_2, suggesting mitochondria as main targets for the cytotoxic effect of H_2O_2 on lung cells.

L-glutamine significantly attenuates oxidative stress injuries in A549 and HEL299 cells

The application of 8 mM of L-glutamine did not increase the mitochondrial membrane potential, which was decreased by 100 μM of H_2O_2, although H_2O_2-induced cytotoxicity in A549 cells was through the mitochondrial membrane potential changes [Figure 3]. Similarly, H_2O_2-induced cytotoxicity in HEL299 cells

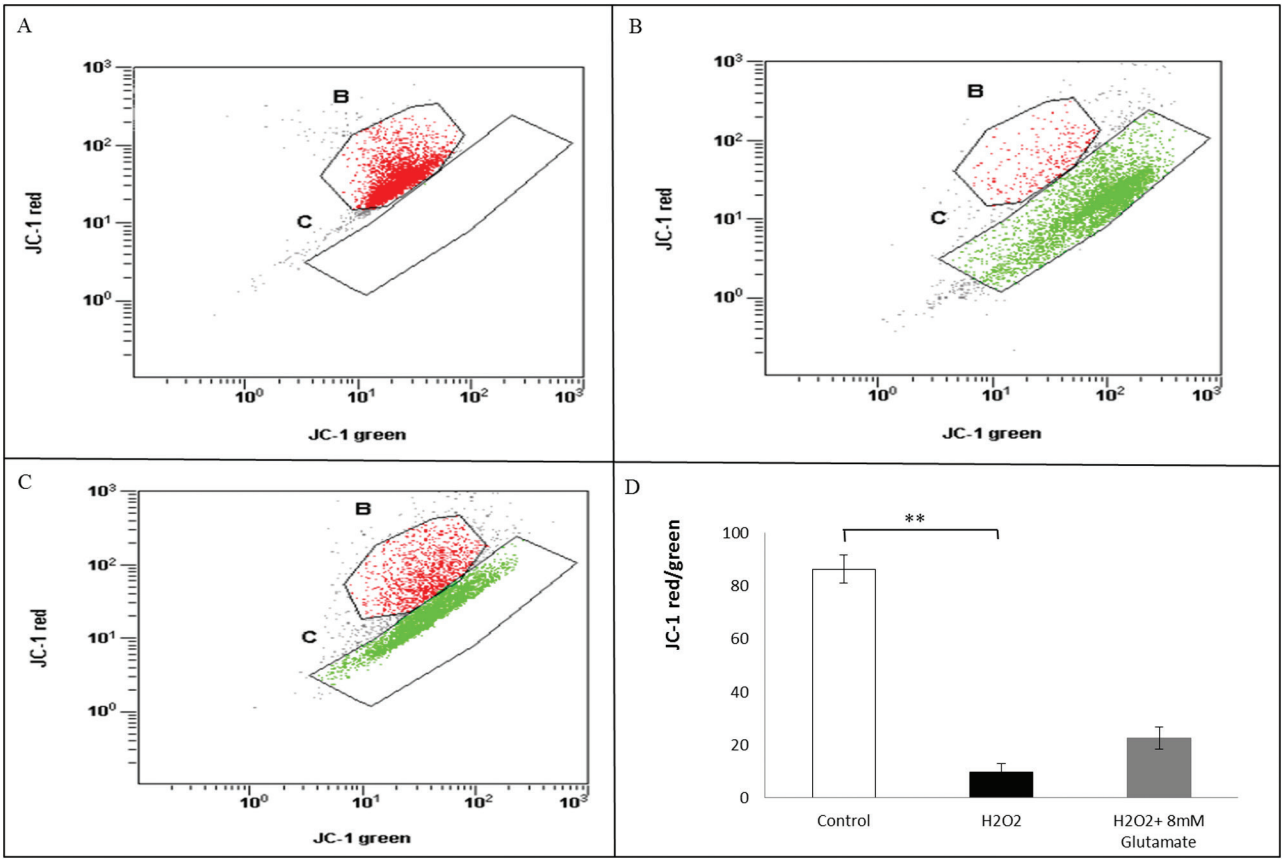

Figure 3: Flow cytometry analysis of the JC-1 assay (mitochondrial membrane potential) in H_2O_2-treated A549 cells. The protective effect of L-glutamine on alveolar epithelial cells was further investigated by examining mitochondrial depolarization. Mitochondria of the A549 cells stained with JC-1 emitted red and/or green fluorescence. JC-1 accumulated into normal mitochondria appeared in the JC-1 aggregate form (red fluorescence) (A). H_2O_2 at 100 μM decreased the mitochondrial potential and produced obvious green fluorescence compared with the control group (B). The application of 8 mM of L-glutamine did not significantly neutralize the cytotoxic effect of 100 μM of H_2O_2 on A549 cells (C). Collected results analyzed from three experiments and presented (D). Data were considered statistically significant at $^{**}P < 0.005$ when the ratio of the red/green of the cells treated with H_2O_2 was compared with untreated cells

was through the mitochondrial membrane potential changes. Mitochondrial membrane potential was significantly elevated in HEL299 cells after exposure to 8 mM of glutamate for 24 h compared with the control group (49.15% ± 2.84% vs. 7.20% ± 1.54%, respectively; $P < 0.05$; Figure 4). Therefore, H_2O_2-induced cytotoxicity in A549 and HEL299 cells was associated with mitochondria. The different effects of L-glutamine on A549 and HEL299 cells in response to the 100 μM of H_2O_2-induced cytotoxicity suggest that these two cell lines may have different mechanisms against oxidative stress.

Discussion

Advances in obstetric medicine have not decreased the incidences of preterm births, especially extremely preterm infants.[30] Even most extremely preterm infants can survive when these premature babies are receiving suboptimal perinatal care or facing major antenatal events that cause severe respiratory failure at birth, but they often develop BPD.[16] ROS is believed as one of the main causes of BPD development.[31] ROS, including the superoxide ($O_2^{-\bullet}$) and hydroxyl ($^{\bullet}OH$) radicals, and H_2O_2, are derived from activated neutrophils, mitochondria, the xanthine oxidase system, and the cyclooxygenase pathway.[32] $O_2^{-\bullet}$ has been implicated as a mediator of hypoxemia/hyperoxemia/reperfusion-induced leukocyte adhesion-related damages[33] and increased microvascular permeability.[34] $^{\bullet}OH$ possesses the most damaging effects.[34] Increased ROS levels cause growth inhibition, adenosine triphosphate (ATP) depletion, DNA damage, and cell death by apoptosis or necrosis.[35] An ROS overproduction undermines the oxidation-antioxidant balance and triggers an oxidative stress response that can lead to inflammatory reactions and tissue damage, eventually leading to cell death.[31] H_2O_2 is an important tool for inducing ROS.[22] All the above-mentioned mechanisms may explain the drastic decrease in the viability of both lung cells exposing H_2O_2 in this study.

ROS is a highly active oxidant that directly damages all biological molecules, including proteins, nucleic acids,

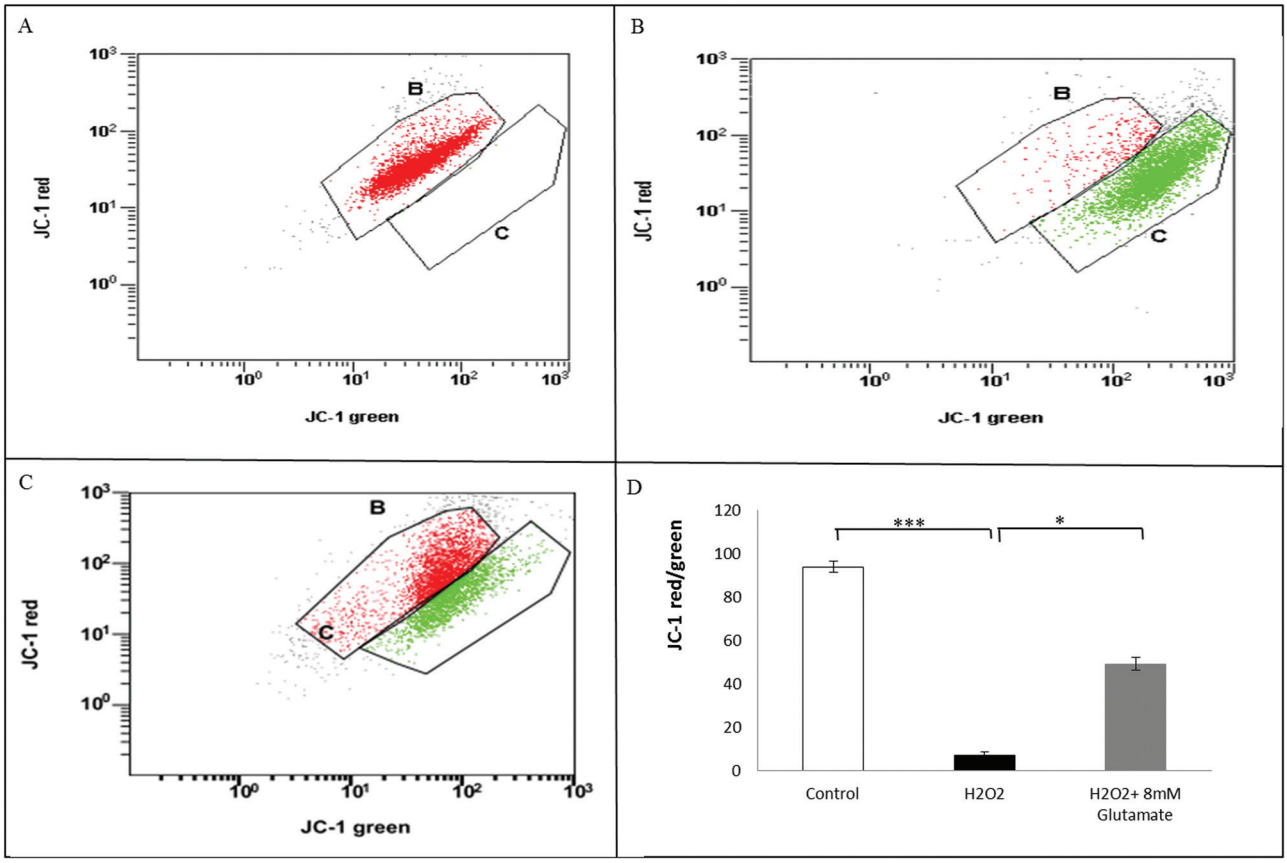

Figure 4: Flow cytometry analysis of the JC-1 assay (mitochondrial membrane potential) in H_2O_2-treated HEL299 cells. The protective effect of L-glutamine on fetal lung cells was further investigated by examining mitochondrial depolarization. Mitochondria of the HEL299 cells stained with JC-1 emitted red and/or green fluorescence. JC-1 accumulated into normal mitochondria appeared in the JC-1 aggregate form (red fluorescence) (A). H_2O_2 at 100 μM decreased the mitochondrial potential and produced obvious green fluorescence compared with the control group (B). The application of 8 mM of L-glutamine significantly attenuated the cytotoxic effect of 100 μM of H_2O_2 on HEL299 cells (C). Collected results analyzed from three experiments and presented (D). Data were considered statistically significant at $^*P < 0.05$, $^{**}P < 0.005$ when the ratio of the red/green of the cells was compared with cells with 100 μM of H_2O_2

carbohydrates, and membrane lipids.[31] Cells need to eradicate excessive ROS for survival. Glutathione is oxidized and forms glutathione-protein mixed disulfides during scavenging the ROS; hence, the glutathione redox system is part of the antioxidant defense mechanism against oxidative stress.[36,37] Thus, this study targeted glutamine. Interestingly, we initially revealed no cytotoxic effects of H_2O_2 on these lung cells. However, a further investigation revealed that it was the culture medium that contained serum, which could neutralize the cytotoxic effects of 100 μM of H_2O_2 on these lung cells. The use of a culture medium without serum was the resolution in H_2O_2 treatment. However, the findings that the application of 8 μM of L-glutamine did not increase, but decreased the viability of lung cells, were confusing.

Glutamine is known to enter the Krebs cycle via the α-ketoglutarate complex to provide energy requirements to tissues and cells.[38] The rate-limiting step in purine biosynthesis is catalyzed by glutamine 5-phosphoribosyl-1-pyrophosphate amidotransferase in the concentrations of glutamine at 0.5–2.5 mM.[39] Glutamine would not be rate-limiting for this reaction under normal conditions; however, glutamine depletion is expected to impact this rate-limiting step,[40] possibly because low glutamine levels prevent sufficient nucleotide biosynthesis. This might explain that the L-glutamine concentration less than the minimum requirement of the cells lead to a decrease instead of an increase in viability. Lung cells revealed a significant increase in viability percentage than cells without L-glutamine in the application of H_2O_2 when the L-glutamine concentrations reached 8 mM. Additionally, lung cells might undergo autophagy during serum starvation, leading to cell death, and low doses of L-glutamine might accelerate the phenomenon.[41]

ROS is associated with pathophysiological changes in many lung diseases, such as BPD.[31] That is because a given baby with BPD needs a high concentration of oxygen, which first increased the production of ROS in mitochondria, followed by an increased level of ROS in the cytoplasm, eventually leading to oxidative stress

damage caused by the overload of ROS in the cells.[42] Mitochondrial membrane potential is an important parameter reflecting the stability of the environment of the inner mitochondria and the oxidative phosphorylation pathway. The present study revealed that alternations of MMP were detected in A549 and HEL299 cells with 100 μM of H_2O_2. Our findings suggest that mitochondria are a target for the cytotoxic effect of H_2O_2 on lung cells. Moreover, L-glutamine possessed protective effects against H_2O_2-induced HEL299 cytotoxicity via mitochondrial mechanisms. Glutamine is used as a major energy source and drives mitochondrial ATP formation.[43] Sudden glutamine depletion from the culture medium results in a sharp decline in mitochondrial respiration in the cells,[44] suggesting a role of glutamine in the functions of mitochondria. L-glutamine did not show a positive effect against the cytotoxic effect of H_2O_2 on A549 cells, suggesting different antioxidative defense mechanisms of these two cell lines.

The limitations of the present study include the *in vitro* experimental design and relatively a wide range of doses of L-glutamine, and no measurement of ROS Additionally, the results of this study demonstrated A549 cells and HEL299 cells presented with different responses to the same H_2O_2 and L-glutamine exposure, suggesting that alveolar and bronchial cells might respond differently to these stimuli. Although A549 cells retain some characteristics of normal alveolar type II cells and are widely used for lung function studies, however, A549 cells are in fact an adult human lung carcinoma cell line.[45] Therefore, using cell lines of normal lung cells, primary lung cell cultures, or *in vivo* studies should be considered for future investigations.

Conclusion

In conclusion, significant cellular death of A549 and HEL299 cells can be induced by exposure to 100 μM of H_2O_2 for 24 h in this *in vitro* study. L-glutamine at 8 mM can rescue the decreased viability of these lung cells exposed to 100 μM of H_2O_2 for 24 h. The cytotoxic effects of H_2O_2 on these lung cells were probably through the mitochondrial pathway. L-glutamine can attenuate the cytotoxic effects of H_2O_2 on the fetal lung cells, instead of adult alveolar lung cells, through the mitochondrial pathway. L-glutamine may be beneficial on alveolar epithelial lung and bronchial cells to defend against cellular injury and inflammatory mediator release caused by oxidative stress. Further studies are required to clarify the role and mechanisms of L-glutamine in oxidative stress-injured lung tissues.

Data availability statement

The data are not publicly available due to privacy.

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Conflicts of interest

H.-C.F., the Executive Editor at *Tungs' Medical Journal*, had no role in the peer review process of or decision to publish this article. For the remaining authors, there are no conflicts of interest.

References

1. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, *et al*. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: A systematic analysis and implications. Lancet 2012;379:2162-72.
2. Vogel ER, Britt RD Jr, Trinidad MC, Faksh A, Martin RJ, MacFarlane PM, *et al*. Perinatal oxygen in the developing lung. Can J Physiol Pharmacol 2015;93:119-27.
3. Martinez-Nadal S, Demestre X, Raspall F, Alvarez JA, Elizari MJ, Vila C, *et al*. [Neonatal morbidity in early-term newborns]. An Pediatr (Barc) 2014;81:39-44.
4. Kapadia V, Wyckoff MH. Oxygen therapy in the delivery room: What is the right dose? Clin Perinatol 2018;45:293-306.
5. Mowitz ME, Ayyagari R, Gao W, Zhao J, Mangili A, Sarda SP. Health care burden of bronchopulmonary dysplasia among extremely preterm infants. Front Pediatr 2019;7:510.
6. Schmidt B, Asztalos EV, Roberts RS, Robertson CM, Sauve RS, Whitfield MF; Trial of Indomethacin Prophylaxis in Preterms (TIPP) Investigators. Trial of indomethacin prophylaxis in preterms I: Impact of bronchopulmonary dysplasia, brain injury, and severe retinopathy on the outcome of extremely low-birth-weight infants at 18 months: Results from the trial of indomethacin prophylaxis in preterms. JAMA 2003;289:1124-9.
7. Farrow KN, Steinhorn RH. Pulmonary hypertension in premature infants. Sharpening the tools of detection. Am J Respir Crit Care Med 2015;191:12-4.
8. Pesce C, Musi L, Belloli G. [Progress in the surgical treatment of congenital and acquired broncho-pulmonary pathology]. Pediatr Med Chir 1996;18:451-61.
9. Bauer SE, Schneider L, Lynch SK, Malleske DT, Shepherd EG, Nelin LD. Factors associated with neurodevelopmental impairment in bronchopulmonary dysplasia. J Pediatr 2020;218:22-27.e2.
10. Walsh MC, Morris BH, Wrage LA, Vohr BR, Poole WK, Tyson JE, *et al*; National Institutes of Child Health and Human Development Neonatal Research Network. Extremely low birthweight neonates with protracted ventilation: Mortality and 18-month neurodevelopmental outcomes. J Pediatr 2005;146:798-804.
11. Guaman MC, Pishevar N, Abman SH, Keszler M, Truog WE, Panitch H, *et al*. Invasive mechanical ventilation at 36 weeks post-menstrual age, adverse outcomes with a comparison of recent definitions of bronchopulmonary dysplasia. J Perinatol 2021;41:1936-42.
12. Overstreet DW, Jackson JC, van Belle G, Truog WE. Estimation of mortality risk in chronically ventilated infants with bronchopulmonary dysplasia. Pediatrics 1991;88:1153-60.
13. Wheater M, Rennie JM. Poor prognosis after prolonged ventilation for bronchopulmonary dysplasia. Arch Dis Child Fetal Neonatal Ed 1994;71:F210-1.

14. Singer LT, Salvator A, Guo S, Collin M, Lilien L, Baley J. Maternal psychological distress and parenting stress after the birth of a very low-birth-weight infant. JAMA 1999;281:799-805.
15. Jobe AH, Abman SH. Bronchopulmonary dysplasia: A continuum of lung disease from the fetus to the adult. Am J Respir Crit Care Med 2019;200:659-60.
16. Thebaud B, Goss KN, Laughon M, Whitsett JA, Abman SH, Steinhorn RH, *et al*. Bronchopulmonary dysplasia. Nat Rev Dis Primers 2019;5:78.
17. Turrens JF. Mitochondrial formation of reactive oxygen species. J Physiol 2003;552:335-44.
18. Capasso L, Vento G, Loddo C, Tirone C, Iavarone F, Raimondi F, *et al*. Oxidative stress and bronchopulmonary dysplasia: Evidences from microbiomics, metabolomics, and proteomics. Front Pediatr 2019;7:30.
19. Perrone S, Tataranno ML, Negro S, Cornacchione S, Longini M, Proietti F, *et al*. May oxidative stress biomarkers in cord blood predict the occurrence of necrotizing enterocolitis in preterm infants? J Matern Fetal Neonatal Med 2012;25:128-31.
20. Weinberger B, Laskin DL, Heck DE, Laskin JD. Oxygen toxicity in premature infants. Toxicol Appl Pharmacol 2002;181:60-7.
21. Kalikkot Thekkeveedu R, Guaman MC, Shivanna B. Bronchopulmonary dysplasia: A review of pathogenesis and pathophysiology. Respir Med 2017;132:170-7.
22. Josephson RA, Silverman HS, Lakatta EG, Stern MD, Zweier JL. Study of the mechanisms of hydrogen peroxide and hydroxyl free radical-induced cellular injury and calcium overload in cardiac myocytes. J Biol Chem 1991;266:2354-61.
23. Grimble GK, Westwood OM. Nucleotides as immunomodulators in clinical nutrition. Curr Opin Clin Nutr Metab Care 2001;4:57-64.
24. Higashiguchi T, Hasselgren PO, Wagner K, Fischer JE. Effect of glutamine on protein synthesis in isolated intestinal epithelial cells. JPEN J Parenter Enteral Nutr 1993;17:307-14.
25. Ahmad S, White CW, Chang LY, Schneider BK, Allen CB. Glutamine protects mitochondrial structure and function in oxygen toxicity. Am J Physiol Lung Cell Mol Physiol 2001;280:L779-91.
26. McGrath-Morrow SA, Stahl J. Inhibition of glutamine synthetase in a549 cells during hyperoxia. Am J Respir Cell Mol Biol 2002;27:99-106.
27. Fan HC, Chang FW, Pan YR, Yu SI, Chang KH, Chen CM, *et al*. Approach to the connection between meconium consistency and adverse neonatal outcomes: A retrospective clinical review and prospective in vitro study. Children (Basel) 2021;8:1082.
28. Galas RJ Jr, Liu JC. Surface density of vascular endothelial growth factor modulates endothelial proliferation and differentiation. J Cell Biochem 2014;115:111-20.
29. Chang FW, Fan HC, Liu JM, Fan TP, Jing J, Yang CL, *et al*. Estrogen enhances the expression of the multidrug transporter gene ABCG2-increasing drug resistance of breast cancer cells through estrogen receptors. Int J Mol Sci 2017;18:163.
30. Zysman-Colman Z, Tremblay GM, Bandeali S, Landry JS. Bronchopulmonary dysplasia—Trends over three decades. Paediatr Child Health 2013;18:86-90.
31. Wang J, Dong W. Oxidative stress and bronchopulmonary dysplasia. Gene 2018;678:177-83.
32. Wu ML, Tsai KL, Wang SM, Wu JC, Wang BS, Lee YT. Mechanism of hydrogen peroxide and hydroxyl free radical-induced intracellular acidification in cultured rat cardiac myoblasts. Circ Res 1996;78:564-72.
33. Cook-Mills JM, Marchese ME, Abdala-Valencia H. Vascular cell adhesion molecule-1 expression and signaling during disease: Regulation by reactive oxygen species and antioxidants. Antioxid Redox Signal 2011;15:1607-38.
34. Kvietys PR, Granger DN. Role of reactive oxygen and nitrogen species in the vascular responses to inflammation. Free Radic Biol Med 2012;52:556-92.
35. Perillo B, Di Donato M, Pezone A, Di Zazzo E, Giovannelli P, Galasso G, *et al*. ROS in cancer therapy: The bright side of the moon. Exp Mol Med 2020;52:192-203.
36. Aukrust P, Svardal AM, Muller F, Lunden B, Berge RK, Ueland PM, *et al*. Increased levels of oxidized glutathione in CD4+ lymphocytes associated with disturbed intracellular redox balance in human immunodeficiency virus type 1 infection. Blood 1995;86:258-67.
37. Dumaswala UJ, Zhuo L, Mahajan S, Nair PN, Shertzer HG, Dibello P, *et al*. Glutathione protects chemokine-scavenging and antioxidative defense functions in human RBCs. Am J Physiol Cell Physiol 2001;280:C867-73.
38. Mazat JP, Ransac S. The fate of glutamine in human metabolism. The interplay with glucose in proliferating cells. Metabolites 2019;9:81.
39. Wyngaarden JB. Regulation of purine biosynthesis and turnover. Adv Enzyme Regul 1976;14:25-42.
40. Cory JG, Cory AH. Critical roles of glutamine as nitrogen donors in purine and pyrimidine nucleotide synthesis: Asparaginase treatment in childhood acute lymphoblastic leukemia. In Vivo 2006;20:587-9.
41. Tan HWS, Sim AYL, Long YC. Glutamine metabolism regulates autophagy-dependent mTORC1 reactivation during amino acid starvation. Nat Commun 2017;8:338.
42. Rosanna DP, Salvatore C. Reactive oxygen species, inflammation, and lung diseases. Curr Pharm Des 2012;18:3889-900.
43. Piva TJ, McEvoy-Bowe E. Oxidation of glutamine in HeLa cells: Role and control of truncated TCA cycles in tumour mitochondria. J Cell Biochem 1998;68:213-25.
44. Darmaun D. Role of glutamine depletion in severe illness. Diabetes Nutr Metab 2000;13:25-30.
45. Foster KA, Oster CG, Mayer MM, Avery ML, Audus KL. Characterization of the A549 cell line as a type II pulmonary epithelial cell model for drug metabolism. Exp Cell Res 1998;243:359-66.

Original Article

Exploring the self-control efficacy of risk factors using self-management program in patients with acute coronary

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Abstract

Background: Cardiovascular diseases are a major cause of death and disability. Research shows that self-management is better than routine care for improving patients' awareness of diseases, self-care, and self-efficacy, thereby reducing the recurrence and mortality rates of cardiovascular diseases. **Objectives:** This study examined the self-control efficacy of risk factors in patients with acute coronary syndrome (ACS) before and after a self-management program. **Methods:** Purposive sampling was used in this quasi-experimental study. Thirty-eight participants were enrolled from January 1, 2020, to June 30, 2020. The case manager utilized a self-management program as the intervention and developed the "Questionnaire on Self-management of ACS." Measurements were conducted for each sample before, during, and after the intervention. **Results:** Each participant in the sample had at least three risk factors for ACS, with an average of 5.3 risk factors. The overall self-management scores before and after the intervention were notably different ($F = 135.842$, $P < 0.001$), with significant differences in two dimensions: disease awareness ($F = 159.752$, $P < 0.001$) and behavior compliance ($F = 111.63$, $P < 0.001$). **Conclusion:** Controlling the risk factors for ACS requires continuous adjustment and maintenance of lifestyle. Exercise-related behaviors before and after the self-management program showed the worst compliance. Thus, appropriate interventions should be combined with intelligent devices to assist patients in integrating health management into their lifestyles, thereby reducing risk factors and preventing disease recurrence.

Keywords: Acute coronary syndrome, cardiovascular diseases, risk factors, self-care, self-efficacy

Introduction

Cardiovascular diseases are a major cause of death and disability. It is estimated that 22.2 million people will die annually due to cardiovascular diseases by 2030.[1] According to statistics from the Ministry of Health and Welfare in Taiwan, cardiovascular diseases are the second leading cause of death in Taiwan since 2007. Among them, acute coronary syndrome (ACS) has the highest mortality rate, and its recurrence rate has continued to increase annually.[2] In recent years, the mortality rate and prognosis have significantly improved due to the progress of drugs and vascular reperfusion therapy in the acute phase. Nevertheless, patients with hypertension, hyperglycemia, and hyperlipidemia have continued to increase due to increased burdens in daily life, Westernization of dietary habits, and lack of regular exercise, which has further accelerated the recurrence

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of cardiovascular diseases.[3-6] Moreover, the morbidity rate has gradually shifted toward a younger trend. Thus, there is a need to help these patients survive for a longer period. Deterioration due to cardiovascular diseases can be prevented or avoided by making healthier changes in one's lifestyle and reducing risk factors. Empowering patients to manage themselves is a necessary measure to achieve the best quality of life.[7] The key factor for making healthier changes in one's lifestyle is self-management. To achieve optimum self-management, the self-efficacy of patients must be combined with the professional knowledge of medical personnel.[8-10]

In a large-scale study, patients with cardiovascular diseases were the least likely to have risk factors controlled than those without.[11] However, patients' self-care behavior is positively correlated with disease awareness. Among cases with poor control of risk factors after discharge, 50% of patients did not receive health education guidance or could not accept or comply with the advice after consultation.[12-15] Consistent with the clinical care findings, researchers conducted telephone follow-ups regarding the control of risk factors among discharged patients. Their results showed that patients often could not maintain control over risk factors due to various reasons, such as returning to work or busy life, thereby resulting in a significant gap between disease awareness and behavior compliance.

ACS has two types of risk factors: unmodifiable (e.g., gender, age, and family history)[12,16] and modifiable (e.g., obesity, lack of exercise, smoking, and history of chronic diseases). Increased risk factors indicate higher chances of development or recurrence of cardiovascular diseases.[8] A cross-sectional survey of patients with coronary heart disease undergoing percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG) in 27 European countries showed that 55% of patients with a smoking habit continued to smoke 6 months after the operation, 82% of patients had a body mass index (BMI) higher than 25 kg/m^2, and 66% of patients did not exercise regularly. The results showed that these behaviors continued because the patients had not received professional knowledge guidance or could not accept or comply with the advice after consultation.[12]

Self-management is a process wherein patients take the initiative to participate in health-care activities, establish partnerships with health-care providers, learn problem-solving, continuously modify their lifestyle, and continue to live with chronic diseases.[9,17,18] Kuo and Wang[18] and Palacios *et al*.[10] found that self-management is better than routine care for improving patients' awareness of diseases, self-care, and self-efficacy, thereby reducing the recurrence and mortality rates of cardiovascular diseases. A 1-month follow-up after intervention can help reflect the effectiveness of education and training.[1] The American Heart Association proposed Life's Simple 7 (controlling blood pressure, blood lipid, blood glucose, quitting smoking, controlling body weight, increasing physical activity, and eating a healthy diet) to prevent cardiovascular diseases.[8] To enable patients to achieve optimal self-care and management, sufficient disease awareness must be provided to ensure proper compliance with health behaviors.[13]

Therefore, this study aimed to examine the effectiveness of self-control for risk factors in patients with ACS before and after intervention by a self-management program by using evaluation tools to provide a reference basis for case management and future care.

Materials and Methods

This quasi-experimental study was approved by the Institutional Review Board of Tungs' Taichung MetroHarbor Hospital (IRB Certificate No.: 108066). Purposive sampling was used in this study. The patients were referred to our hospital by a regional hospital in central Taiwan after being diagnosed with ACS by a cardiologist during hospitalization. After obtaining written consent, 38 participants were enrolled from January 20, 2020, to June 30, 2020.

The inclusion criteria were as follows: (1) the patient or primary caregiver was willing to participate and had filled in the consent form, (2) the patient was aged between 20 and 80 years, and (3) the patient was scheduled to be discharged from the hospital after undergoing PCI or CABG. Patients who could not perform activities of daily living and instrumental activities of daily living after discharge and those who could not be contacted or passed away during the study duration were excluded. Patients were allowed to withdraw consent or from the study at any time, without providing any reason and affecting their medical care.

The "self-management program" used in this study aimed to enhance patients' awareness of ACS and improve their self-care and self-efficacy to help them introduce positive changes in their lifestyle. The program comprises interventional activities in three periods, with each instance lasting approximately 20–30 min. In the first period, face-to-face health education consultation was conducted with patients during hospitalization. Patients' learning motivation for disease care was assessed and detected through the "Questionnaire on Demographic Variables and Self-management of ACS." Furthermore, accurate disease awareness was provided according to the "Disease Care Handbook," and self-management goals were formulated with the patients after discharge. In the second period, telephone calls and questionnaires were used to discuss patient experiences of risk factor control 1 month after the

patients were discharged. This task aimed to improve their problem-solving ability and reduce obstacles in their self-management. In the third period, a follow-up was conducted with patients through a telephone call 3 months after the patients were discharged, and their responses were evaluated to determine their self-management efficacy after returning home.

The self-designed questionnaire included demographic variables and two dimensions: disease awareness and behavior compliance. These dimensions were further divided into five categories: disease, medication, diet, exercise, and tobacco harm. The questionnaire was scored by five experts to verify its validity based on the content. The content validity index test results ranged from 0.98 to 1.0. The Cronbach's α value of 30 patients in the pilot experiment was 0.787, and that of the formal experiment was 0.791, indicating that the questionnaire had good internal consistency. The researchers personally enrolled the participants, intervened using the "self-management program," and administered the "Questionnaire on Self-management of ACS" during hospitalization, 1 month after discharge, and 3 months after discharge. Data were analyzed using Statistical Package for the Social Sciences, 17.0 software package (SPSS, USA). Statistical significance was considered at $P < 0.05$. Measurement data with a normal distribution were expressed as mean ± standard deviation, and categorical variables were expressed as percentages.

Results

Demographic variables of patients with ACS

Thirty-eight participants were enrolled in this study. They had an average of 5.3 ± 1.0 factors among the seven risk factors for ACS and an average of 2.2 ± 0.7 factors among the three unmodifiable risk factors. Approximately 92.1% of participants were male, and 7.9% were female. The average age at disease onset was 61.5 ± 10.8 years, and 57.9% of participants experienced disease onset at 64 years or earlier. Approximately 52.6% of participants had a family history of cardiovascular diseases. Among the four modifiable risk factors, participants had an average of 3.2 ± 0.7 factors. The average BMI was 25.6 ± 2.6 kg/m^2, and 68.4% of participants were overweight. Approximately 76.3% of participants had no exercise habits. Approximately 47.4% of participants smoked, and 21.1% had quit smoking before the disease onset. Approximately 73.7% of participants had a history of chronic diseases, among which 60.7% had continuous control. In terms of education level, 55.3% of participants had junior high school education or below, and 44.7% had senior (vocational) high school education or above. Approximately 21.1% of participants lived alone, whereas 78.9% lived with family members or friends. In terms of dining style, 50.0% of participants dined out. Moreover, 68.4% of participants were hospitalized for the first time,

Table 1: Analysis of demographic variables in patients with ACS ($N = 38$)

Variable	Mean ± SD	*n* (%)
Seven risk factors for ACS		
3 factors	5.3 ± 1.0	1 (2.6)
4 factors		7 (18.4)
5 factors		13 (34.2)
6 factors		12 (31.6)
7 factors		5 (13.2)
Three unmodifiable risk factors		
1 factor	2.2 ± 0.7	5 (13.5)
2 factors		20 (54.1)
3 factors		12 (32.4)
Gender		
Male		35 (92.1)
Female		3 (7.9)
Age		
64 years or below	61.5 ± 10.8	22 (57.9)
65 years or above		16 (42.1)
Family history		
No		14 (36.8)
Yes		20 (52.6)
Unknown		4 (10.5)
Four modifiable risk factors		
1 factor	3.2 ± 0.7	1 (2.6)
2 factors		4 (10.5)
3 factors		20 (52.6)
4 factors		13 (34.2)
BMI (kg/m^2)		
18.5–24	25.6 ± 2.6	12 (31.6)
24–27		15 (39.5)
Above 27 kg/m^2		11 (28.9)
Exercise habit		
No		29 (76.3)
Yes		9 (23.7)
Smoking history		
No		12 (31.6)
Quit before disease onset		8 (21.1)
Yes		18 (47.4)
History of chronic diseases		
No		10 (26.3)
Yes		28 (73.7)
Chronic disease control		
Controlled		17 (60.7)
Not controlled		11 (39.3)
Level of education		
Junior high school or below		21 (55.3)
Senior (vocational) high school or above		17 (44.7)
Living status		
Living alone		8 (21.1)
Living with family members or friends		30 (78.9)
Dietary status		
Cook for oneself		9 (23.7)
Dine out		10 (26.3)
Both		19 (50)

Table 1: Continued

Variable	Mean ± SD	*n* (%)
Hospitalization status		
Hospitalization for the first time	1.7 ± 1.4	26 (68.4)
Hospitalization not for the first time		12 (31.6)
Cardiac catheterization		
Treatment for the first time	1.2 ± 0.7	34 (89.5)
Treatment not for the first time		4 (10.5)
Days of hospital stay		
4 days or less	5.4 ± 4.5	24 (63.2)
5 days or more		14 (36.8)

SD = standard deviation

and 89.5% received cardiac catheterization treatment for the first time. The average length of hospital stay was 5.4 days [Table 1].

Correlation of demographic variables of ACS patients with measurements before and after intervention by the self-management program

After enrollment, the questionnaire was evaluated on three occasions (i.e., before intervention, 1 month after intervention, and 3 months after intervention) with the self-management program. During the 3-month intervention period, one participant died, and two participants could not be contacted. Thus, they were excluded from the study sample. A total of 35 questionnaires were completed. The results of a Pearson product-moment correlation analysis showed that before the intervention, self-management was negatively correlated with the seven risk factors for ACS ($r = -0.348$*, $P < 0.05$), modifiable risk factors ($r = -0.340$*, $P < 0.05$), smoking history ($r = -0.463$**, $P < 0.01$), and dietary status ($r = -0.345$*, $P < 0.05$), and positively correlated with gender ($r = 0.440$**, $P < 0.01$), exercise habit ($r = 0.523$**, $P < 0.01$), and hospitalization status ($r = 0.341$*, $P < 0.05$). One month after intervention, self-management was negatively correlated with residence type ($r = 0.408$*, $P < 0.05$) and not correlated with other demographic variables. Three months after the intervention, self-management was positively correlated with exercise habits ($r = 0.421$*, $P < 0$ 0.05) and negatively correlated with hospitalization status ($r = -0.388$*, $P < 0.05$). Other demographic variables did not show significant correlation. The details are presented in Table 2.

Correlation and efficacy of self-management before and after the intervention management plan for patients with ACS

The "Questionnaire on Self-management of ACS" was divided into two dimensions: disease awareness and behavior compliance. The results of Pearson product-moment correlation analysis showed a positive correlation between disease awareness and behavior compliance before ($r = 0.332$, $P < 0.05$) and 3 months after the intervention program ($r = 0.401$, $P < 0.05$). A positive correlation was also found in behavior compliance between 1 month and 3 months after the intervention program ($r = 0.742$, $P < 0.01$; [Table 3]). Repeated measures analysis of variance was used to compare the self-management efficacy before, 1 month after, and 3 months after the intervention program. Self-management efficacy before and after the intervention program showed an overall significant difference ($F = 135.842$, $P < 0.001$). Significant differences were also noted in disease awareness ($F = 159.752$, $P < 0.001$) and behavior compliance ($F = 111.63$, $P < 0.001$). Furthermore, significant differences were noted in disease awareness ($F = 97.083$, $P < 0.001$), drug awareness ($F = 42.663$, $P < 0.001$), diet awareness ($F = 9.672$, $P < 0.001$), exercise awareness ($F = 14.987$, $P < 0.001$), smoking harm awareness ($F = 9.593$, $P < 0.001$), disease compliance ($F = 109.305$, $P < 0.001$), drug compliance ($F = 14.603$, $P < 0.001$), diet compliance ($F = 28.191$, $P < 0.001$), exercise compliance ($F = 21.682$, $P < 0.001$), and smoking harm compliance ($F = 28.794$, $P < 0.001$).

Discussion

Demographic variables of patients with ACS

In this study, seven risk factors for ACS were classified into three unmodifiable factors (i.e., gender, age, and family history) and four modifiable factors (i.e., obesity, lack of exercise, smoking history, and history of chronic diseases). Thirty-eight patients with ACS were enrolled in this study. Each patient had more than three risk factors, with an average of 5.3 factors. This is consistent with literature showing that increased risk factors indicate higher chances of cardiovascular disease development or recurrence.[8] Participants had an average of 2.2 factors among the three unmodifiable factors, and approximately 86.5% of participants had more than two factors. Moreover, participants had an average of 3.2 factors among the four modifiable factors. Among them, 97.4% had more than two factors, and 86.8% had more than three factors. If patients with ACS remain unwilling to adjust their lifestyle after discharge to reduce the risk factors, they will have a high probability of cardiovascular disease recurrence.[8]

In this study, 92.1% of participants were male, which is consistent with literature showing that the incidence of ACS was higher in men than in women.[4,12,18] A study showed that estrogen plays a protective role in coronary atherosclerosis, and thus, the disease incidence is higher among young men than young women.[9] In this study, the average age and minimum age of disease onset were 61.5 and 42.7 years, respectively. Approximately 57.9% and 42.1% of participants experienced disease onset at 64 years or earlier and 65 years or later, respectively. The morbidity ratio of both groups was nearly 1:1.

Table 2: Correlation analysis of demographic variables in ACS patients with self-management before and after the intervention program (*N* = 38)

Three periods of Self-management	Seven risk factors	Unmodifiable factors	Age	Modifiable factors	BMI
A. Total self-management score	−0.348[a]	−0.195	0.243	−0.340[a]	−0.171
B. Total self-management score	−0.168	−0.010	−0.120	−0.228	−0.138
C. Total self-management score	−0.207	0.013	−0.235	−0.307	−0.256

(A) Before, (B) 1 month after, and (C) 3 months after the intervention program

[a]The correlation was significant when the significance level was ≤0.05 (two-tailed)

Table 3: Correlation analysis of demographic variables in ACS patients with self-management before and after the intervention program (continued) (*N* = 38)

Three periods of Self-management	Chronic disease control	Living status	Level of education	Instances of hospitalization	Instances of cardiac catheterization	Dietary status	A. Total self-management score	B. Total self-management score
A. Total self-management score	−0.200	0.036	0.006	0.341[a]	0.197	−0.345[a]		
B. Total self-management score	0.095	0.408[a]	−0.238	−0.309	−0.240	0.176	0.265	
C. Total self-management score	−0.124	0.071	−0.036	−0.388[a]	−0.204	0.249	0.269	0.731[b]

(A) Before, (B) 1 month after, and (C) 3 months after the intervention program

[a]The correlation was significant when the significance level was ≤0.05 (two-tailed)

[b]The correlation was significant when the significance level was ≤0.01 (two-tailed)

Table 4: Data analysis of the correlation between disease awareness and behavior compliance (*N* = 35)

Three periods of Self-management	A. Disease awareness	A. Behavior compliance	B. Disease awareness	B. Behavior compliance	C. Disease awareness
A. Behavior compliance	0.332[a]				
B. Disease awareness	0.13	−0.17			
B. Behavior compliance	0.14	0.27	0.19		
C. Disease awareness	−0.17	0.01	0.06	0.20	
C. Behavior compliance	0.08	0.29	0.20	0.742[b]	0.401[a]

(A) Before, (B) 1 month after, and (C) 3 months after the intervention program

[a]The correlation was significant when the significance level was 0.05 (two-tailed)

[b]The correlation was significant when the significance level was 0.01 (two-tailed)

This is consistent with literature showing that blood vessels gradually harden after 40 years of age, and the morbidity rate has gradually shifted toward a younger trend.[8,9] The average BMI (25.6 kg/m^2) in this study is higher compared with the healthy BMI defined by the National Health Administration in Taiwan (18.5–24 kg/m^2). This finding is consistent with the average BMI of 26.6 kg/m^2 in patients with coronary heart disease in southern Taiwan.[9] In this study, 68.5% of patients with ACS had smoked once, 47.4% of participants smoked, and 21.1% of participants had quit smoking before disease onset. These findings are consistent with those of a study in southern Taiwan, wherein 65.8% of patients had smoked once.[9] Moreover, these findings are consistent with those of a US study, wherein 71% of 4003 participants had smoked once.[19] Regarding the modifiable risk factors of ACS, understanding the causes of noncompliance among patients and actively intervening by using a self-management program are crucial tasks.

Efficacy and correlation of self-management in patients with ACS

The self-management scores before and after the self-management program were significantly different (F = 135.842, $P < 0.001$). This finding is consistent with that of Erskine *et al*.[1] and Kuo and Wang,[18] who found that follow-up 1 month after intervention by a self-management program could reflect the effectiveness of education and training. In this study, disease awareness was positively correlated with behavior compliance before ($r = 0.332$, $P < 0.05$) and 3 months after the intervention program ($r = 0.401$, $P < 0.05$), which is consistent with the positive correlation between disease awareness and self-care behavior ($r = 0.48$, $P < 0.01$) noted by Chen and Dai.[9] This indicates that patients need sufficient disease awareness to comply correctly with healthy behaviors [Table 4].[18]

Significant differences were noted in degrees of diet (F = 28.191, $P < 0.001$) and exercise (F = 21.682, $P < 0.001$) compliances in self-management before

and after the intervention program. This finding is consistent with that of Kuo and Wang,[18] who found that exercise and diet control in diabetic patients were significantly improved 1 month after the self-management program.[17] Smoking status before and after the intervention was negatively correlated with the number of hospitalizations. This showed that more hospitalizations or continuous smoking indicates a lower self-management score, and longer hospitalization days indicate a higher probability of successful smoking cessation. The analysis results showed that among 18 patients who smoked, eight patients successfully quit smoking for 3 months after the intervention, and the average days of hospitalization were 7 days. The remaining 10 patients continued to smoke after discharge, and the average days of hospitalization were 3.4 days. According to Wang *et al*.,[20] the chance of successful smoking cessation is consistent with patients who have no past hospitalization experience due to heart diseases and longer hospitalization. Smoking or smoking cessation awareness would affect smoking cessation behavior. Therefore, patients did not strongly feel the correlation between smoking and their cardiovascular hazards before hospitalization. However, once they understood that smoking brings more disadvantages than advantages, the patients experienced higher motivation to quit smoking and a higher chance of successful smoking cessation.[20]

Conclusion

This study explored the correlation and efficacy of self-management in patients with ACS before and after intervention with a self-management program. The results show a significant difference in self-management before and after the intervention program ($F = 135.842$, $P < 0.001$). Moreover, the scores recorded 3 months after the intervention program were better than those recorded 1 month after and before the intervention program. A positive correlation was noted between disease awareness and behavior compliance before ($r = 0.332$, $P < 0.05$) and 3 months after the intervention program ($r = 0.401$, $P < 0.05$). Therefore, the findings indicate that providing individualized health education consultation through intervention by a self-management program has a positive effect on improving the self-management of patients with ACS.

To control the risk factors and avoid recurrence of ACS, patients must constantly adjust and maintain a healthy lifestyle. Significant differences were noted in the five types of compliance behaviors before and after the intervention. Exercise had the lowest degree of compliance, followed by diet. Walking is an aerobic exercise beneficial for increasing physical activity. It is also a living habit that is inherent, suitable for individuals of all ages, economical, safe, and relatively easy to perform.[21-23] Walking for 30 min is equivalent to taking nearly 3000–4000 steps, and it can be gradually increased to 5400–7000 steps or more without experiencing discomfort. Walking 6500 steps a day is equivalent to 150 min of moderate physical activity per week.[24] Research has highlighted that enabling a smartphone application (pedometer) to record one's daily steps automatically can help promote goal setting to encourage daily physical activity. Those who used the application walked 1000 steps more every day than those who did not.[9] Physical activity has many benefits in lowering low-density cholesterol, blood pressure, and fasting blood glucose while simultaneously maintaining weight loss and improving mental health.[8] Although this study showed significant findings, the number of patients is small. Therefore, further studies are warranted to explore the self-control efficacy of risk factors using a self-management program in patients with ACS. Intelligent devices can also be used in combination to improve the self-efficacy of patients' exercise behaviors and enhance the intensity of daily physical activity in the future.

Data availability statement

The datasets generated during the current study are available from the corresponding author on reasonable request.

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Conflicts of interest

There are no conflicts of interest.

Author contributions

Conceptualization, methodology, resources, project administration, and funding acquisition: Y.-C. Y. and T.-I C.; software and investigation: Y.-C. Y., K.-H. C., and T.-I C.; validation: Y.-C. Y., H.-P. W., B.-T. W., T.-I C., and K.-H. C.; formal analysis: Y.-C. Y. and K.-H. C.; data curation, writing—original draft preparation, writing—review and editing, visualization, and supervision: Y.-C. Y., K.-H. C., and T.-I C. All authors have read and agreed to the published version of the manuscript.

References

1. Erskine NA, Gandek B, Waring ME, Kinney RL, Lessard DM, Devereaux RS, *et al*. Survivors of an acute coronary syndrome with lower patient activation are more likely to experience declines in health-related quality of life. J Cardiovasc Nurs 2018;33:168-78.
2. Statistical Analysis of Death Causes in 2020. 2020. Available from: https://www.mohw.gov.tw/cp-16-61533-1.html. [Last accessed on 01 Aug 2023].
3. Davidson KW, Burg MM, Kronish IM, Shimbo D, Dettenborn L, Mehran R, *et al*. Association of anhedonia with recurrent major

adverse cardiac events and mortality 1 year after acute coronary syndrome. Arch Gen Psychiatry 2010;67:480-8.
4. Fosco MJ, Ceretti V, Agranatti D. Systemic inflammatory response syndrome predicts mortality in acute coronary syndrome without congestive heart failure. West J Emerg Med 2010;11:373-8.
5. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med 2005;353:487-97.
6. Ford ES, Greenlund KJ, Hong Y. Ideal cardiovascular health and mortality from all causes and diseases of the circulatory system among adults in the United States. Circulation 2012;125:987-95.
7. Kao C-W, Chuang H-W, Chen T-Y. The utilization of health-related applications in chronic disease self-management. J Nurs Res 2017;64:19-25.
8. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, *et al*. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: A report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. Circulation 2019;140: e596-646.
9. Kelli HM, Witbrodt B, Shah A. The future of mobile health applications and devices in cardiovascular health. Euro Med J Innov 2017;2017:92-7.
10. Palacios J, Lee GA, Duaso M, Clifton A, Norman IJ, Richards D, *et al*. Internet-delivered self-management support for improving coronary heart disease and self-management-related outcomes: A systematic review. J Cardiovasc Nurs 2017;32:E9-E23.
11. Rodriguez F, Lee UJ, Barone N, Swett K, Lopez L, Cheng S, *et al*. Risk factor control across the spectrum of cardiovascular risk: Findings from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). Am J Prev Cardiol 2021;5:100147.
12. Kotseva, K, De Backer G, De Bacquer D, Ryden L, Hoes A, Grobbee D, *et al*. Lifestyle and impact on cardiovascular risk factor control in coronary patients across 27 countries: Results from the European Society of Cardiology ESC-EORP EUROASPIRE V registry. Eur J Prev Cardiol 2019;26:824-35.
13. Chen H-F, Tai M-K. To explore disease knowledge, disease attitude, physical symptom distress and self-care behaviors in patients with coronary artery disease: An example from a medical center in Southern Taiwan. Kaohsiung J Nurs 2017;34:14-27.
14. Gyarfas I, Keltai M, Salim Y. [Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries in a case-control study based on the INTERHEART study]. Orv Hetil 2006;147:675-86.
15. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, *et al*. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case-control study. Lancet 2004;364:937-52.
16. Tan YC, Sinclair H, Ghoorah K, Teoh X, Mehran R, Kunadian V. Gender differences in outcomes in patients with acute coronary syndrome in the current era: A review. Eur Heart J Acute Cardiovasc Care 2016;5:51-60.
17. Song Y-C, Chen S-F, Lin C-C. A concept analysis of self-management in chronic diseases. New Taipei J Nurs 2008;10:49-56.
18. Kuo C-C, Wang H-H. Applying self-management intervention studies to patients with chronic illness: A systematic review. J Nurs Healthcare Res 2012;8:50-60.
19. Buchanan DM, Arnold SV, Gosch KL, Jones PG, Longmore LS, Spertus JA, *et al*. Association of smoking status with angina and health-related quality of life after acute myocardial infarction. Circ Cardiovasc Qual Outcomes 2015;8:493-500.
20. Wang H-L, Wang P-C, Wu Y-W, Shyu K-G. Factors associated with successful smoking cessation in male patients with coronary artery disease at 3 months after hospital discharge. J Nurs Res 2017;64:34-43.
21. Boyne P, Welge J, Kissela B, Dunning K. Factors influencing the efficacy of aerobic exercise for improving fitness and walking capacity after stroke: A meta-analysis with meta-regression. Arch Phys Med Rehabil 2017;98:581-95.
22. Morris JN, Hardman AE. Walking to health. Sports Med 1997;23:306-32.
23. Devasahayam AJ, Downer MB, Ploughman M. The effects of aerobic exercise on the recovery of walking ability and neuroplasticity in people with multiple sclerosis: A systematic review of animal and clinical studies. Mult Scler Int 2017;2017:4815958.
24. Grace SL, Turk-Adawi KI, Contractor A, Atrey A, Campbell N, Derman W, *et al*. Cardiac rehabilitation delivery model for low-resource settings. Heart 2016;102:1449-55.

Original Article

Situational analysis of medical care for heart failure patients in a regional hospital in central Taiwan

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Abstract

Background: Heart failure (HF) is a complex clinical syndrome and a leading cause of morbidity and mortality worldwide. Its symptoms are the ultimate severe results of all heart diseases. **Objectives:** To assess the situation of medical care for patients with HF in a regional hospital in central Taiwan. **Methods:** This retrospective study was conducted from June 1, 2019, to September 30, 2021, collecting basic information of patients, hospitalization and medication after discharge, emergency room visit, readmission, and mortality. **Results:** This study included 101 patients with HF with reduced ejection fraction, of which 71.3% were males. Their mean age was 64.9 ± 15.4 years, and the mean body mass index was 26.4 ± 5.6 kg/m^2. Moreover, 89.1% of them had chronic diseases, such as hypertension, diabetes, and heart disease; the mean left ventricular ejection fraction was 27.4% ± 7.7%. During hospitalization and at 1, 6, and 12 months after discharge, the administration rates were 61.4%, 39.6%, 26.7%, and 22.8% for angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker/angiotensin-neprilysin inhibitor; 64.4%, 41.6%, 27.7%, and 35.6% for beta-blocker; 47.5%, 26.7%, 14.9%, and 17.8% for mineralocorticoid receptor antagonist; and 4.9%, 2.0%, 1.0%, and 3.0% for sodium-glucose cotransporter-2 inhibitor, respectively. The rates of emergency room visit, readmission, and mortality due to cardiac reasons within 12 months after discharge were 18.8%, 20.8%, and 8.9%, respectively. **Conclusion:** Given that HF is a complex disease, the underlying causes must be treated, and the guideline-directed medical therapy must be applied to prevent the recurrence of an acute attack. Given the complexity of this high-functioning disease, it is essential to have a dedicated case manager who can ensure comprehensive integration of care.

Keywords: Guideline-directed medical therapy, heart failure, heart failure with reduced ejection fraction, retrospective research

Introduction

Heart failure (HF) is a leading cause of morbidity and mortality globally.[1] It is a complex clinical syndrome characterized by the structural or functional impairment of ventricular filling or ejection of blood. Its common causes include cardiovascular disease, hypertension, obesity, diabetes, valvular heart disease, hereditary cardiomyopathy, arrhythmia, and endocrine or metabolic problems.[1] HF has many documented risk factors, such as age, blood pressure, blood sugar, weight, cholesterol, and smoking. Brain natriuretic peptides (BNP) are frequently used to assess HF severity and predict mortality and readmission. Echocardiography is the most useful initial diagnostic test, and identifying the left ventricular ejection fraction (LVEF) is a fundamental step to classifying HF for an effective treatment. Patients with HF with reduced ejection fraction (HFrEF) generally have LVEF of ≤40%.[1,2]

Guideline-directed medical therapy (GDMT) for HFrEF includes four major drug classes, namely, angiotensin-converting enzyme inhibitor (ACE-I)/angiotensin II receptor blocker (ARB)/angiotensin-neprilysin inhibitor (ARNI), beta-blocker, mineralocorticoid

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receptor antagonists (MRA), and sodium-glucose cotransporter-2 inhibitors (SGLT2i), and the titrate dose of the target value. The goals of HF treatment are as follows: to reduce the heart load, to ameliorate the symptoms, to improve the quality of life without recurrence, and to prevent readmission caused by acute HF.[1,3] However, management is effective only if the clinicians and patients follow the guidelines. This study retrospectively explored the profiles of patients with HFrEF at our hospital to formulate recommendations for future HF management.

Materials and Methods

The institutional review board of Tungs' Taichung MetroHarbor Hospital (IRB Certificate No.: 110031) and a regional hospital in central Taiwan approved this retrospective study, collecting basic information of patients, hospitalization and medication after discharge, emergency room visit, readmission, and mortality. We recruited 101 inpatients diagnosed with HF with LVEF of ≤40% in echocardiography from June 1, 2019, to September 30, 2021. The patient was waived by the IRB.

Results

Demographic characteristics

Of the 101 patients, 71.3% were male, 28.7% were female, and 90.1% were married. The mean age was 64.9 ± 15.4 years (range: 27–91 years), and the mean body mass index (BMI) was 26.4 ± 5.6 kg/m^2. Smoking and drinking were observed in 23.8% and 8.9%, respectively. The mean inpatient LVEF was 27.4% ± 7.7%. Furthermore, 89.1% had a history of chronic diseases, of which hypertension was the most common (62.4%), followed by heart disease (57.8%), diabetes (43.6%), and kidney disease (10.9%). During hospitalization, 25.7% had atrial fibrillation (AF) [Table 1].

Examination, laboratory tests, and medication in patients with HF

During hospitalization and 6 and 12 months after discharge, the LVEF examination rates were 96.1%, 6.8%, and 5.8%, whereas the BNP blood test rates were 68.3%, 8.9%, and 5.9%, respectively. During hospitalization and 1, 6, and 12 months after discharge, the dosing rates were 61.4%, 39.6%, 26.7%, and 22.8% for ACE-I/ARB/ARNI; 64.4%, 41.6%, 27.7%, and 35.6% for beta-blocker; 47.5%, 26.7%, 14.9%, and 17.8% for MRA; and 4.9%, 2.0%, 1.0%, and 3.0% for SGLT2i, respectively [Table 2].

Rates of emergency room visit, readmission, and mortality in patients with HF

The rate of emergency room visit within 12 months was 25.7%, of which 18.8% was due to cardiac reasons. For the same reasons, the rates were 7.9% and 16.8% at 1 and 6 months after discharge, respectively. The readmission rate within 12 months was 27.7%, and 20.8% was for cardiac reasons. At 1 and 6 months after discharge, the readmission rates were 7.9% and 16.8%, respectively, also for cardiac reasons. Moreover, the cardiac-related mortality rate within 12 months was 8.9%, and at 1 and 6 months after discharge, it was 2.0% and 5.9%, respectively [Figure 1].

Discussion

This study investigated the medical care provided for patients with HF in a regional hospital in central Taiwan. A total of 101 patients with HFrEF were analyzed, with a mean age of 64.9 ± 15.4 years, a male proportion of 71.3%, and a mean inpatient LVEF of 27.4% ± 7.7%, consistent with the findings of a 2016 study published by the Taiwan Society of Cardiology (TSOC; 64.0 ± 15.8 years, 72.4%, and 28.2% ± 8.2%, respectively) and of the 2018 US study (66 ± 13 years,

Table 1: Demographic characteristics of the patients (n = 101)

Demographic variables	Mean ± SD	*N* (%)
Sex		
Male		72 (71.3)
Female		29 (28.7)
Age (years)		
≤40	64.9 ± 15.4	6 (5.9)
40–60		34 (33.7)
61–80		45 (44.6)
≥81		16 (15.8)
Married		91 (90.1)
Smoking		24 (23.8)
Alcohol		9 (8.9)
BMI (kg/m^2)		
<18.5	26.4 ± 5.6	7 (7.1)
18.5–24		27 (27.3)
24–27		27 (27.3)
>27		38 (38.4)
Hospitalized EF levels (%)		
≤10	27.4 ± 7.7	2 (2.1)
11–20		16 (17.0)
21–30		35 (37.2)
31–40		41 (43.6)
Past history		90 (89.1)
Hypertension		63 (62.4)
Diabetes		44 (43.6)
Hyperlipidemia		1 (1.0)
Stroke		9 (8.9)
Heart disease		59 (57.8)
Arrhythmia		2 (2.0)
Kidney disease		11 (10.9)
ECG showing AF		26 (25.7)

AF = atrial fibrillation, BMI = body mass index, ECG = electrocardiogram, EF = ejection fraction, SD = standard deviation

Table 2: Prescribed drug percentage during hospitalization and 1, 6, and 12 months after discharge in patients with heart failure (*N* = 101)

Prescribed drug	Hospitalization	1 month	6 months	12 months
ACE-I/ARB/ARNI	61.4	39.6	26.7	22.8
Beta-blocker	64.4	41.6	27.7	35.6
MRA	47.5	26.7	14.9	17.8
SGLT2i	4.9	2.0	1.0	3.0

ACE-I/ARB/ARNI = angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker/angiotensin-neprilysin inhibitor, MRA = mineralocorticoid receptor antagonist, SGLT2i = sodium-glucose cotransporter-2 inhibitor

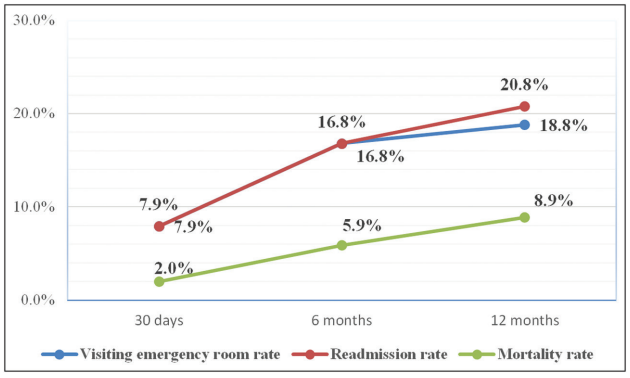

Figure 1: Rates of emergency room visit, readmission, and mortality caused by cardiac reasons in patients with heart failure

71%, and 29% ± 8%, respectively).[4,5] However, our results do not entirely agree with those of the 2018 meta-analysis published in Australia (mean age, 76.3 years; male proportion, 51%).[3]

Consistent with our findings, the 2016 study by TSOC reported that the mean BMI was 25.4 ± 6.5 kg/m^2, with smoking and AF prevalence rates of 23.2% and 26.7%, respectively.[4] Moreover, most of our patients (89.1%) had a history of chronic diseases, with diabetes, hypertension, and heart disease as the leading diseases. Diabetes prevalence is consistent with the TSOC's 2016 study, which obtained a prevalence rate of 43.6%. Conversely, the TSOC study reported a considerably lower prevalence of hypertension (34.5%), followed by coronary artery disease (41.8%), HF (40.4%), and AF (26.0%).[4] However, the "heart disease" in the statistical results is too general, considering the retrospective medical records used to verify patients' medical history records. Hence, the disease type (cardiovascular, valvular, cardiomyopathy, arrhythmia, etc.) should be clearly defined in future care manager visits.

GDMT for HFrEF now includes four major medication classes, namely ACE-I/ARB/ARNI, beta-blocker, MRA, and SGLT2i.[1] In the 2016 TSOC study, the administration rates of ACE-I/ARB/ARNI, beta-blocker, and MRA during hospitalization were 62.1%, 59.6%, and 49.0%, respectively, similar to our study.[4] However, their rates were 56.8%, 67.3%, and 43.9% at 6 months and 57.5%, 66.3%, and 40.8% at 12 months after discharge, respectively, which are considerably different from ours.[6] Compared with the US study published in 2018, the rates of the same medications in outpatient surveys were 73%, 67%, and 33%,[5] respectively, which are considerably higher than our results. One reason for the considerably lower maintenance usage rate in the present study could be the high comorbidity rate of 89.1%. The multitude and complexity of medication types often cause drug-to-drug interactions, which can cause side effects such as hypotension and renal dysfunction, thereby limiting drug administration. The physician may also not have followed the guidelines for medication administration completely. GDMT refers to the continuous administration of medications at target doses to improve patient outcomes.[1] Our results indicate that the rate of medication administration at discharge needs to be further strengthened and that the target dosages of these medications have not been audited. These points will be the focus of our future research.

Regarding readmission, our study shows lower rates at 1 month (7.9%) and 12 months (20.8%) after discharge than the Australian meta-analysis published in 2018 (20% and 56%, respectively).

Readmission rates at 6 months (16.8%) and 12 months (20.8%) after discharge are also lower than those reported in TSOC's 2017 study (31.9% and 38.5%, respectively).[6] Moreover, the mortality rate 1 month after discharge is lower in our study (2.0%) than in the 2018 Australia Meta-Analysis study (8%) and the 2021 Heart Failure Reviews study (7.4%).[2,3] Likewise, our study has a lower mortality rate at 6 months after discharge (5.9%) than the 2017 TSOC study (9.5%); our study also had a lower mortality rate at 12 months after discharge (8.9%) than the 2017 TSOC study (15.9%) and the 2018 Australian meta-analysis study (25%).[3,6] In addition, the rates of cardiac mortality in the present study at 6 and 12 months after discharge (5.9% and 8.9%, respectively) were similar to those in the 2017 TSOC study (6.8% and 10.5%, respectively).[6]

Conclusion

In conclusion, the readmission and mortality rates improved in inpatients with HF in our hospital, possibly

attributed to the presence of case managers who focus on patient-centered care and coordinate comprehensive care across multiple specialties at our hospital. However, the absence of improvement in cardiac mortality rates highlights the challenges in HF treatment. In the future, we will continue to collect and monitor our care indicators as a basis for ongoing review and improvement.

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Conflicts of interest

There are no conflicts of interest.

Data availability statement

All data generated or analyzed during this study are included in this published article.

References

1. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, *et al*. 2022 AHA/ACC/HFSA guideline for the management of heart failure: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2022;145:e895-1032.
2. Altibi AM, Prousi G, Agarwal M, Shah M, Tripathi B, Ram P, *et al*. Readmission-free period and in-hospital mortality at the time of first readmission in acute heart failure patients-NRD-based analysis of 40,000 heart failure readmissions. Heart Fail Rev 2021;26:57-64.
3. Al-Omary MS, Davies AJ, Evans TJ, Bastian B, Fletcher PJ, Attia J, *et al*. Mortality and Readmission following hospitalisation for heart failure in Australia: A systematic review and meta-analysis. Heart Lung Circ 2018;27:917-27.
4. Wang CC, Chang HY, Yin WH, Wu YW, Chu PH, Wu CC, *et al*. TSOC-HFrEF registry: A registry of hospitalized patients with decompensated systolic heart failure: Description of population and management. Acta Cardiologica Sinica 2016;32:400–411.
5. Greene SJ, Butler J, Albert NM, DeVore AD, Sharma PP, Duffy CI, *et al*. Medical therapy for heart failure with reduced ejection fraction: The CHAMP-HF registry. J Am Coll Cardiol 2018;72:351-66.
6. Chang HY, Wang CC, Wu YW, Chu PH, Wu CC, Hsu CH, *et al*. One-year outcomes of acute decompensated systolic heart failure in Taiwan: Lessons from TSOC-HFrEF registry. Acta Cardiol Sin 2017;33:127-38.

Case Report

A late-preterm infant with hypocalcemic tetany caused by traditional soy milk feeding: A case report and literature review

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Abstract

Hypocalcemia may cause numerous symptoms, including neuromuscular irritability, prolonged QT interval, apnea, cyanosis, tachypnea, vomiting, or laryngospasm. Here, we reported a late-preterm 3-month-old infant presenting general involuntary twitches caused by hypocalcemic tetany. Laboratory data revealed hypocalcemia–hyperphosphatemia, high parathyroid hormone, normal magnesium, and low vitamin D(25-OH). Calcium intake deficiency was suspected. The infant was cured after calcium supplementation through the intravenous route and standard infant formula.

Keywords: Hypocalcemia, infant, nutrition, soy milk

Introduction

Hypocalcemia is defined as a total serum calcium level of <7 mg/dL in preterm infants and <8 mg/dL in term neonates.[1] Early-onset hypocalcemia occurs within the first 72 h of life and is often asymptomatic, whereas, late-onset hypocalcemia occurs after the first 72 h and toward the end of the first week of life and is usually symptomatic. Symptoms associated with hypocalcemia include neuromuscular irritability, prolonged QT interval, apnea, cyanosis, tachypnea, vomiting, or laryngospasm.[1]

Healthy-term infants reach a physiological nadir in serum calcium levels by 24–48 h of age, and the serum calcium levels may be lower in high-risk neonates, including infants of mothers with diabetes, preterm, and perinatal asphyxia.[1] The calcium level is regulated by parathyroid hormone (PTH)-related peptide in fetus, and the calcium level depends on PTH secretion, dietary calcium intake, renal reabsorption, skeletal stores, and vitamin D status.[1]

The nutritional requirement of calcium was higher in late-preterm infants than in full-term infants because their bones contain smaller mineral stores. The calcium requirement was approximately 120–140 mg/kg/day for gestational age of 34–36 weeks and 70–120 mg/kg/day for full-term infants.[2] The recommended dietary allowance of calcium for 0–6-month-old infants was 200 mg/day by the American Academy of Pediatrics, and 300 mg/day by the Taiwan Food and Drug Administration.[3,4] Infants who do not meet the daily calcium intake recommendation may present hypocalcemia-associated manifestations or even death.

Herein, we report a late-preterm 3-month-old infant presenting general involuntary twitches. A further investigation proves that the traditional soy milk that did

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not contain enough calcium caused her hypocalcemic tetany.

Clinical Case

A 3-month-old (postmenstrual age of 49 weeks and 3 days) female infant was born at a gestational age of 35 weeks and 3 days with a birth body weight of 2724 g (75–90th percentile). No abnormal findings were observed in the prenatal examination, with no specific family histories such as thyroid disease or DiGeorge's disease. The mother did not have gestational diabetes mellitus, preeclampsia, hypercalcemia, or hyperparathyroidism, but maternal vitamin D status was unknown. After birth, she was fed with infant formula within 1 month of age. Neonatal jaundice was noted at 10 days of age, which was relieved after phototherapy and adequate feeding. No medication intake histories were traced. The baby was exclusively fed on traditional soy milk at 180–200 mL/5 h/day. Traditional soy milk was regularly purchased from a restaurant when the baby was 1 month old. Her parents preferred that kind of milk because they thought the soy milk was healthier for their baby. Decreased appetite and activity had occurred for 3 days before admission. Frequent general and focal tonic seizures with upward gazing were found for 2 h, and each seizure persisted for approximately 10 min. Increased muscle tone and poor weight gain (4.2 kg, 3–10th percentile) were found. Laboratory data revealed total serum calcium of 4.4 mg/dL, phosphorus of 8.0 mg/dL, magnesium of 1.7 mg/dL, alkaline phosphatase of 1041 U/L, intact PTH of 130.6 pg/mL, vitamin D(25-OH) of 9.9 ng/mL, and albumin of 3.8 g/dL. The cerebrospinal fluid analysis revealed negative findings. The cardiac sonography demonstrated an atrial septal defect and no coarctation of the aorta. The electroencephalography revealed normal findings. The serum calcium level 6 h after intravenous calcium chloride (20 mg/mL) administration at 4 mL increased from 4.4 to 5.1 mg/dL. Vitamin D was prescribed, and she was fed with standard infant formula since the second day of admission. Her serum calcium level was gradually corrected, and no seizure recurred. The serum calcium level was 7.7 mg/dL before discharge, and she was discharged with a full recovery. A 2-month follow-up laboratory data revealed calcium, phosphorus, intact PTH, and vitamin D(25 OH) levels within a normal range at 9.8, 5.6 mg/dL, 44.2 pg/mL, and 24.9 ng/mL, respectively.

Discussion

Many causes induced late-onset hypocalcemia in infants, such as increased phosphate load, hypomagnesemia, vitamin D deficiency, PTH resistance, hypoparathyroidism, metabolic syndromes, or iatrogenic causes.[1] Lee *et al.*[5] reported five infant cases with late-onset hypocalcemia caused by transient pseudohypoparathyroidism due to delayed renal maturation or magnesium deficiency.

Calcium concentrations in human milk vary from 25 to 35 mg/dL.[6] The standard infant formula contained 35–54 mg/dL of calcium and 70–80 mg/dL in the postdischarge formula.[3] The bioavailability of calcium was higher in human milk than in low birthweight formula.[7] The lactose-containing formula could increase the percentage absorption of calcium compared with the lactose-free formula, but the mechanisms are not fully understood.[8]

Traditional soy milk contained approximately 13 mg/dL of calcium, so it could not satisfy the daily calcium requirement of infants. Anil *et al.*[9] reported one 14-week-old infant with hypocalcemia–hyperphosphatemia due to soy milk feeding, with similar initial laboratory profiles as our case. Traditional soy milk was different from soy-based protein formula. Phytic acid is found in soybeans as phytin salts, which do not exist in humans and can chelate a series of minerals, including zinc, calcium, magnesium, and iron. Hence, soy-based protein formula was added with additional phosphorus and calcium of approximately 20% higher than those in cow's milk formula. The clinical role of soy-based protein formula was used in infants with severe cow's milk protein allergy.

Body calcium exists in two major compartments: skeleton (99%) and extracellular fluid (1%), and the skeletal calcium stores were less in preterm infants.[1,2,10] The bone mineralization was rapidly improved during the first months of life, and the preterm infants reached healthy terms between 6 and 12 months of age.[10] Bone turnover was stimulated after birth, and calcium and phosphorous would be released into the mineral pool.[2] The need for exogenous calcium was higher in preterm infants because the skeletal calcium sores were less than in term infants.

Here, the data revealed hypocalcemia–hyperphosphatemia, high PTH, normal magnesium, and low vitamin D(25-OH). However, vitamin D deficiency is usually presented with elevated PTH and normal or low serum inorganic phosphorus levels. Hence, calcium intake deficiency or high-phosphate load was considered the possible cause, and these could be differentiated by calculating the fractional excretion of inorganic phosphorus (FEiP). A high phosphate load was more likely if the FEiP was elevated. The drawback of this case report is that we did not check urine creatinine and urine phosphate with the onset of her symptoms. In addition, the baby had been exposed to traditional soy milk, and her blood test revealed hypocalcemia. Evidence supports that these two events are highly connected to each other. Therefore, primary caregivers and practitioners should keep in mind that

a history of traditional soy milk consumption may be important to the diagnosis of this condition when they are facing any infants presenting involuntary twitches, because severe hypocalcemia may cause neuromuscular and cardiac problems and even death.

Declaration of patient consent

The author certify that he have obtained appropriate patient's guardian consent form. In the form, the guardian has given the consent for the child's images and other clinical information to be reported in the journal. The guardian understands that the child's name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Data availability statement

All data generated or analyzed during this study are included in this published article.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 Jain A, Agarwal R, Sankar MJ, Deorari A, Paul VK. Hypocalcemia in the newborn. Indian J Pediatr 2010;77:1123-8.
2 Lapillonne A, O'Connor DL, Wang D, Rigo J. Nutritional recommendations for the late-preterm infant and the preterm infant after hospital discharge. J Pediatr 2013;162(3 Suppl):S90-S100.
3 Golden NH, Abrams SA. Committee on nutrition. Optimizing bone health in children and adolescents. Pediatrics 2014;134: e1229-43.
4 Shaw NS, Hsu SC. Dietary Reference Intakes for Calcium, Iodine, Vitamin D, and Carbohydrate. 8th ed. Taiwan: Healthy Promotion Administration; 2020.
5 Lee CT, Tsai WY, Tung YC, Tsau YK. Transient pseudohypoparathyroidism as a cause of late-onset hypocalcemia in neonates and infants. J Formos Med Assoc 2008;107:806-10.
6 Jenness R. The composition of human milk. Semin Perinatol 1979;3:225-39.
7 Salle BL, Putet G. Calcium, phosphorus and vitamin D requirements in premature infants. In: Salle BL, editor. Nutrition of the Low Birth Weight. Nestle´ Nutrition Workshop Series, Belgium; 1993. p. 125-35.
8 Abrams SA, Griffin IJ, Davila PM. Calcium and zinc absorption from lactose-containing and lactose-free infant formulas. Am J Clin Nutr 2002;76:442-6.
9 Anil M, Demirakca S, Dotsch J, Kiess W. Hypocalcemia–hyperphosphatemia due to soy milk feeding in early infancy. Klin Pädiatr 1996; 208:323-26 [In Germanese: English abstract].
10 ESPGHAN Committee on Nutrition, Aggett PJ, Agostoni C, Axelsson I, Curtis MD, Goulet O, Hernell O, *et al*. Feeding preterm infants after hospital discharge. JPGN 2006;42:596-603.

Moyamoya disease caused frequent transient ischemic attack and focal epilepsy in a Taiwanese child: A case report

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Abstract

We report a case of a 4-year-old boy with a history of global developmental delay presenting with recurrent sudden onset of weakness and spontaneous recovery and refractory focal seizures. The findings of his brain magnetic resonance imaging revealed that the underlying cause of his unexplained neurological deficits was moyamoya disease (MMD). Revascularization can cure MMD-associated transient ischemic attacks and seizures. Proper control of seizures and blood pressure and early use of antiplatelet treatment before the surgery may lead to better outcomes.

Keywords: Case report, child, epilepsy, moyamoya disease, transient ischemic attack

Introduction

Unlike in adults, acute strokes and transient ischemic attacks (TIAs) are uncommon in children. The etiologies of childhood strokes include cardiac abnormalities, vascular abnormalities, hematological problems, infection, and trauma. Moyamoya disease (MMD), a rare cerebrovascular disorder caused by chronic progressive stenosis of the main intracranial arteries, especially the terminal portion of the internal carotid arteries (ICA), and the small collateral vessels, is one of the causes of these conditions. These collateral vessels produce a characteristic smoky appearance on angiography, contributing to the name "moyamoya," which means "hazy-like" in Japanese. MMD can cause varying manifestations, including ischemic stroke, TIAs, intracranial hemorrhage (ICH), seizure, and epilepsy, and may lead to developmental delay in children.

The annual incidence of MMD is 0.5–1.5 per 100,000 individuals in East Asia but as low as 0.1 per 100,000 in other regions, including North America.[1] In Taiwan, the annual incidence is 0.15 per 100,000 person-years based on 12-year statistical data from the Universal Health Insurance System.[2]

A previous study in Japan reported that the incidence of MMD has a bimodal age distribution with peaks at approximately 2 and 40 years of age.[3] A nationwide study also showed a similar bimodal age distribution, with the highest peak at 5–14 years of age and a second peak at 40–44 years.[2] The age of our case is compatible with these reports.

This case report presents a typical MMD in childhood and may remind us to consider the diagnosis of MMD in cases of unexplained neurologic deficits, such as recurrent weakness, TIAs, or stroke, in children.

Case Report

A 4-year-old boy was born prematurely at 30 1/7 weeks of gestation. He had a history of global developmental delay, including gross motor function, cognition, and

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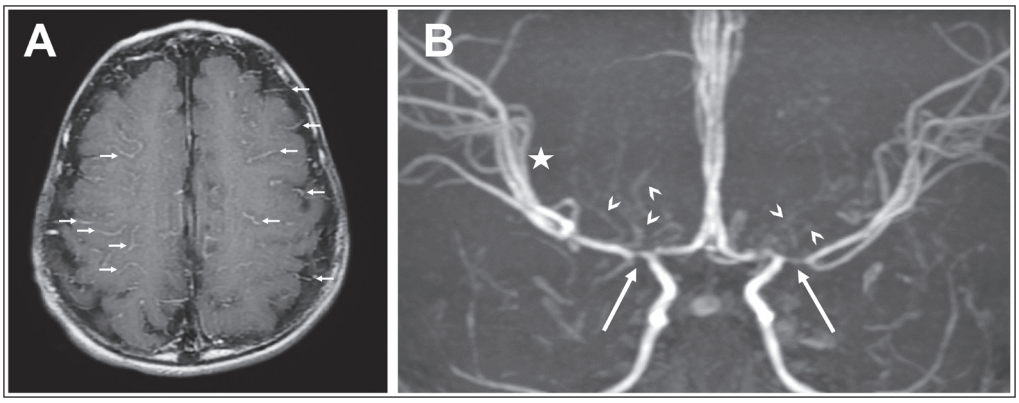

Figure 1: (A) Diffuse sulcal hyperintensity in bilateral cerebral hemispheres (arrows) on contrast-enhanced T1-weighted magnetic resonance imaging (MRI). This is caused by the vivid enhancement of the prominent leptomeningeal collaterals, suggestive of the "ivy sign." (B) Magnetic resonance angiography (MRA) showing bilateral internal carotid artery (ICA) bifurcation stenosis (arrows) with moyamoya changes (arrowheads) and a mildly dilated right middle carotid artery (asterisk)

language, for which he received a regular rehabilitation program. In the beginning, his family noted weakness in his right upper and lower limbs after an exertional cry. He could not grasp with his right hand, and a right foot drop was noted. Otherwise, the sensation of bilateral limbs was not affected. He presented to our pediatric emergency department (ED) when he was 3 years and 9 months old. Tracing his history, his mother reported no history of head trauma. On admission, his blood pressure was 92/56 mmHg, and the capillary refilling time was less than 2 s.

His neurological examination revealed a mild unsteady gait, alert consciousness and mentality, normal deep tendon reflexes, and no facial asymmetry or tone deviation. Muscle power was 4/5 and 5/5 in the right and left limbs, respectively. Hematological and biochemical laboratory results were within the normal range. Emergent brain computed tomography without contrast was normal. Surprisingly, all his symptoms spontaneously disappeared, and he completely recovered without neurological sequelae at the pediatric ED. He was discharged and followed up at our clinic. Unexpectedly, at 3 years and 10 months of age, the boy suddenly developed tonic movements over the right limbs for approximately 10 min after an exertional cry, followed by right limb weakness. No loss of consciousness was noted during this episode. He presented to our pediatric ED again. His neurological examination revealed muscle power of 2/5 in the right limbs, unstable gait, and asymmetric facial appearance with right facial droop. Similar to his previous episode, all these abnormalities vanished when we finished his examinations at our ED. An electroencephalogram was performed and showed amplitudes of intermittent high voltage, intermixed with diffuse θ and δ slow sharp waves on both sides with right-side dominance. Based on the above findings, levetiracetam 10 mg/kg/day was initiated for his suspected focal seizures or epilepsy with Todd's paralysis after the examination and titrated to 30 mg/kg/day a few days later. He was shifted to oxcarbazepine 20 mg/kg/day because of his recurrent seizures and the occurrence of impulsivity and titrated to 30 mg/kg/day in the following days. Even with dose adjustment and changes or additions of antiepileptic drugs, his seizures worsened.

Contrast-enhanced T1W magnetic resonance imaging (MRI) of the brain at 4 years and 1 month of age showed diffuse sulcal hyperintensity in the bilateral cerebral hemispheres, compatible with the "ivy sign" [Figure 1A]. Magnetic resonance angiography (MRA) showed bilateral ICA bifurcation stenosis with adjacent small collateral vessels and a mildly dilated right middle cerebral artery [Figure 1B]. Additionally, mild enlargement of the cerebral ventricles was observed, potentially due to brain atrophy. No evidence of an ischemic or hemorrhagic stroke was observed. Based on these findings, he was diagnosed with MMD. We initiated antiplatelet treatment with aspirin 5 mg/kg/day for his persistent and recurrent seizures. Under the treatment, focal seizures still occurred, but the frequency decreased under the medical control with antiepileptic drugs and antiplatelet treatment. His muscle power also became normal in the usual time. He was referred to another medical center for cerebral revascularization. His seizures and weakness significantly improved after the operation. He is continually receiving a rehabilitation program and follow-up at the neurosurgical clinic.

Discussion

The clinical presentation of MMD in children differs from that in adults. In children, the initial manifestations are ischemic symptoms, including TIAs and ischemic stroke, especially after hyperventilation, crying, agitation, and playing. A retrospective study of MMD in childhood showed that the most common

initial attack type was TIAs (up to 54.4%) with limb weakness.[4] Furthermore, symptoms such as hemiplegia, monoplegia, sensory abnormalities, seizures, and headaches can occur paroxysmally and recurrently on the same side.[5] Repeated cerebral ischemic attacks may also lead to cerebral atrophy, mental dysfunction, and cognitive delay. In comparison, TIA is not so common in adults, but ICH is more common in adults than in children. A previous study revealed a high prevalence of hemorrhage, up to 62.4%, in patients with adult-onset MMD.[6]

MMD is classified into six stages based on the angiographic findings, from Suzuki stage I, which reveals narrowed carotid bifurcation, to Suzuki stage VI, which presents as the disappearance of the moyamoya vessels with cerebral blood flow derived only from the external carotid artery and vertebrobasilar artery systems. However, another classification system was proposed based on MRA findings from MRA stages 1 to 4 by summarizing the assigning scores. This staging system corresponds well to the Suzuki stages: MRA stage 1 to Suzuki stages I and II, stage 2 to stage III, stage 3 to IV, and stage 4 to stages V and VI. The advanced Suzuki stages of MMD tend to be associated with preoperative, intraoperative, and postoperative complications.[5]

Surgical revascularization is effective for MMD presenting with ischemic symptoms and has become the standard treatment for MMD. Many studies have demonstrated that children with MMD who undergo cerebral revascularization have lower stroke recurrence, reduced frequency of TIAs, and better long-term prognosis.[7]

Initial medical management before surgery included proper control of seizures and blood pressure. A large, nationwide, population-based cohort of 25,978 patients with newly diagnosed MMD revealed that receiving antiplatelet therapy was associated with two-thirds lower mortality in patients with MMD.[8] Additionally, even after revascularization surgery, antiplatelet therapy can reduce the rate of postoperative major strokes and postoperative hemorrhage complications.[9] Based on these reports and our experience in this case, we recommend long-term aspirin (2–5 mg/kg/day) for all pediatric patients with MMD.

In conclusion, this case highlighted the possibility of recurrent weakness and recurrent and refractory seizures in MMD presenting with stroke-like symptoms, even without evidence of acute strokes. Moreover, children with MMD tend to present with ischemic symptoms, including ischemic stroke and TIAs. However, adults with MMD tend to present with hemorrhage strokes. Consequently, frequent ischemic attacks may lead to cognitive and neurodevelopmental delays. Early recognition and proper treatment not only cease the exacerbation of ongoing and recurrent strokes but also improve developmental delay in all entities. Therefore, first-line clinicians should consider MMD when diagnosing cases with acute subtle and unexplained neurologic deficits, such as recurrent and refractory seizures, recurrent weakness with spontaneous recovery, and acute strokes.

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We would like to thank the patient and his family members who agreed to give his consent for his images and other clinical information to be reported in the journal.

Ethical approval

This study was approved by the Institutional Review Board of Tri-Service General Hospital (Protocol no. A202215216, dated December 22, 2022).

Declaration of patient consent

The authors certify that they obtained all appropriate patient consent forms. In this form, the patient and his legal representative gave their consent for the images and other clinical information to be reported in the journal. The patient and his legal representative understands that the name and initials will not be published, and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Data availability statement

All data generated or analyzed during this study are included in this published article.

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Conflicts of interest

There are no conflicts of interest.

References

1. Ihara M, Yamamoto Y, Hattori Y, Liu W, Kobayashi H, Ishiyama H, *et al*. Moyamoya disease: Diagnosis and interventions. Lancet Neurol 2022;21:747-58.
2. Chen PC, Yang SH, Chien KL, Tsai IJ, Kuo MF. Epidemiology of moyamoya disease in Taiwan: A nationwide population-based study. Stroke 2014;45:1258-63.
3. Sato Y, Kazumata K, Nakatani E, Houkin K, Kanatani Y. Characteristics of Moyamoya Disease Based on National Registry Data in Japan. Stroke 2019;50:1973-80.
4. Wang Y, Kong H, Wang Y, *et al*. A Retrospective Study on Clinical Features of Childhood Moyamoya Disease. Pediatr Neurol 2023;138:17-24.
5. Research Committee on the Pathology and Treatment of Spontaneous Occlusion of the Circle of Willis, Health Labour Sciences Research Grant for Research on Measures for Infractable Diseases. Guidelines for diagnosis and treatment of moyamoya disease (spontaneous occlusion of the circle of Willis). Neurol Med Chir (Tokyo) 2012;52:245-66.

6. Han DH, Kwon OK, Byun BJ, Choi BY, Choi CW, Choi JU, *et al*. Korean Society for Cerebrovascular Disease. A co-operative study: clinical characteristics of 334 Korean patients with moyamoya disease treated at neurosurgical institutes (1976-1994). The Korean Society for Cerebrovascular Disease. Acta Neurochir (Wien). 2000;142:1263-73; discussion 1273-4.
7. Lee S, Rivkin MJ, Kirton A, deVeber G, Elbers J. International Pediatric Stroke Study. Moyamoya Disease in Children: Results from the International Pediatric Stroke Study. J Child Neurol 2017;32:924-9.
8. Seo WK, Kim JY, Choi EH, Kim YS, Chung JW, Saver JL, *et al*. Association of Antiplatelet Therapy, Including Cilostazol, With Improved Survival in Patients With Moyamoya Disease in a Nationwide Study. J Am Heart Assoc 2021;10: e017701.
9. Yamada S, Oki K, Itoh Y, Kuroda S, Houkin K, Tominaga T, *et al*. Effects of Surgery and Antiplatelet Therapy in Ten-Year Follow-Up from the Registry Study of Research Committee on Moyamoya Disease in Japan. J Stroke Cerebrovasc Dis 2016;25:340-9.

Small-cell neuroendocrine carcinoma of ampulla of Vater

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A 58-year-old woman presented to our emergency department with abdominal pain, chills, and fever for 2 weeks. Computed tomography of the abdomen showed obstructive common bile duct dilatation and gallbladder distension [Figure 1, right upper panel]. Multiple liver tumors were observed, consistent with liver metastases

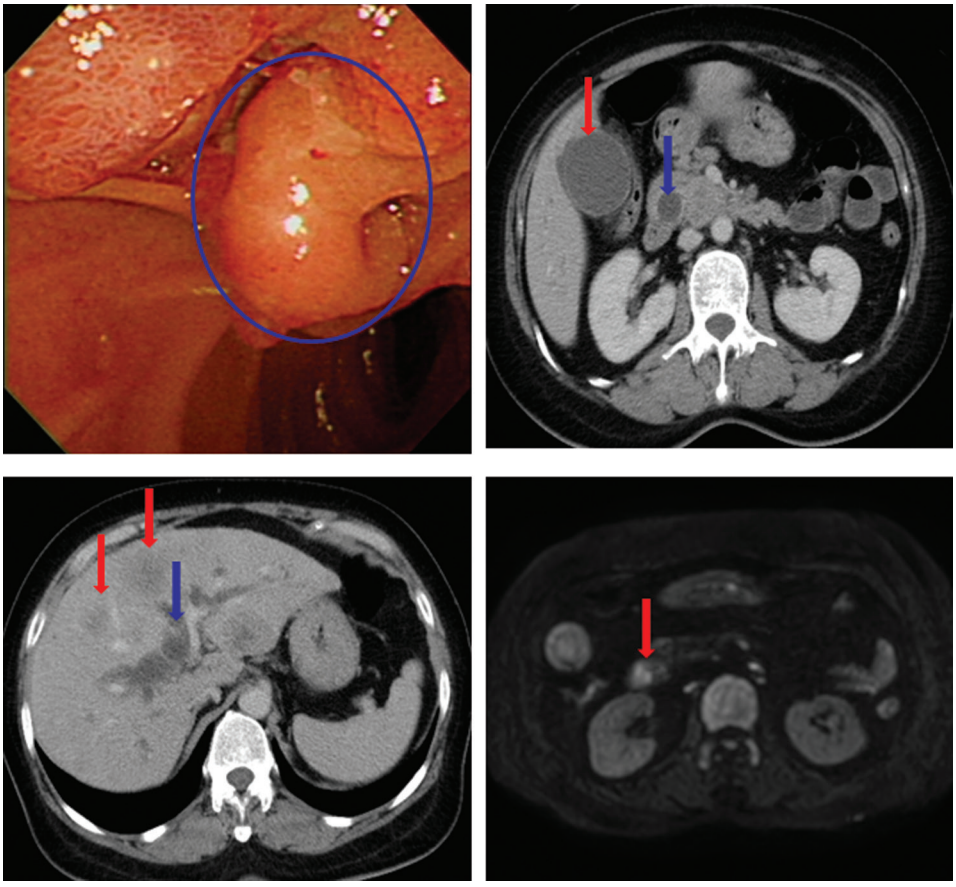

Figure 1: Gastroscopy findings of the polypoid tumor in the region of the ampulla of Vater (left upper panel, blue encircle area indicating tumor). Computed tomography of the abdomen showed gallbladder distension (red arrow, right upper panel) and common bile duct dilation (blue arrow, right upper panel). Computed tomography of the abdomen showed multiple liver metastases (red arrow, left lower panel) and intrahepatic bile duct dilation (blue arrow, left lower panel). Magnetic resonance imaging of the abdomen showed a high-signal-intensity tumor in the ampulla of Vater (red arrow, right lower panel)

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[Figure 1, left lower panel]. The patient had a history of uterus myoma, for which she underwent myomectomy 5 years ago, and acute appendicitis, for which she underwent appendectomy 10 years ago. On admission, the laboratory data revealed an increased CA199 level to 153 units/mL, and the CA125 and carcinoembryonic antigen levels were within the normal range. The upper gastrointestinal endoscopy showed a polypoid tumor in the region of the ampulla of Vater [Figure 1, left upper panel]. Magnetic resonance imaging showed a high-signal-intensity tumor in the ampulla of Vater [Figure 2, right lower panel]. Biopsy, endoscopic sphincterotomy, and endoscopic retrograde biliary drainage were performed. The histopathologic analysis of the biopsy specimen revealed a sheet of tumor cells. The tumor cells showed round-to-ovoid nuclei with scanty cytoplasm and salt and pepper chromatin [Figure 2, upper panel]. The immunohistochemical staining revealed a Ki-67 index [Figure 2, right lower panel] of 60%, and tumor cells were positive for CK (AE1/AE3) [Figure 2, right upper panel], synaptophysin [Figure 2, left lower panel], and chromogranin A and negative for cytokeratin 7, CK20, caudal-related homeobox gene 2, and thyroid transcription factor-1. Based on these findings, the patient was diagnosed with small-cell neuroendocrine carcinoma of the ampulla of Vater.

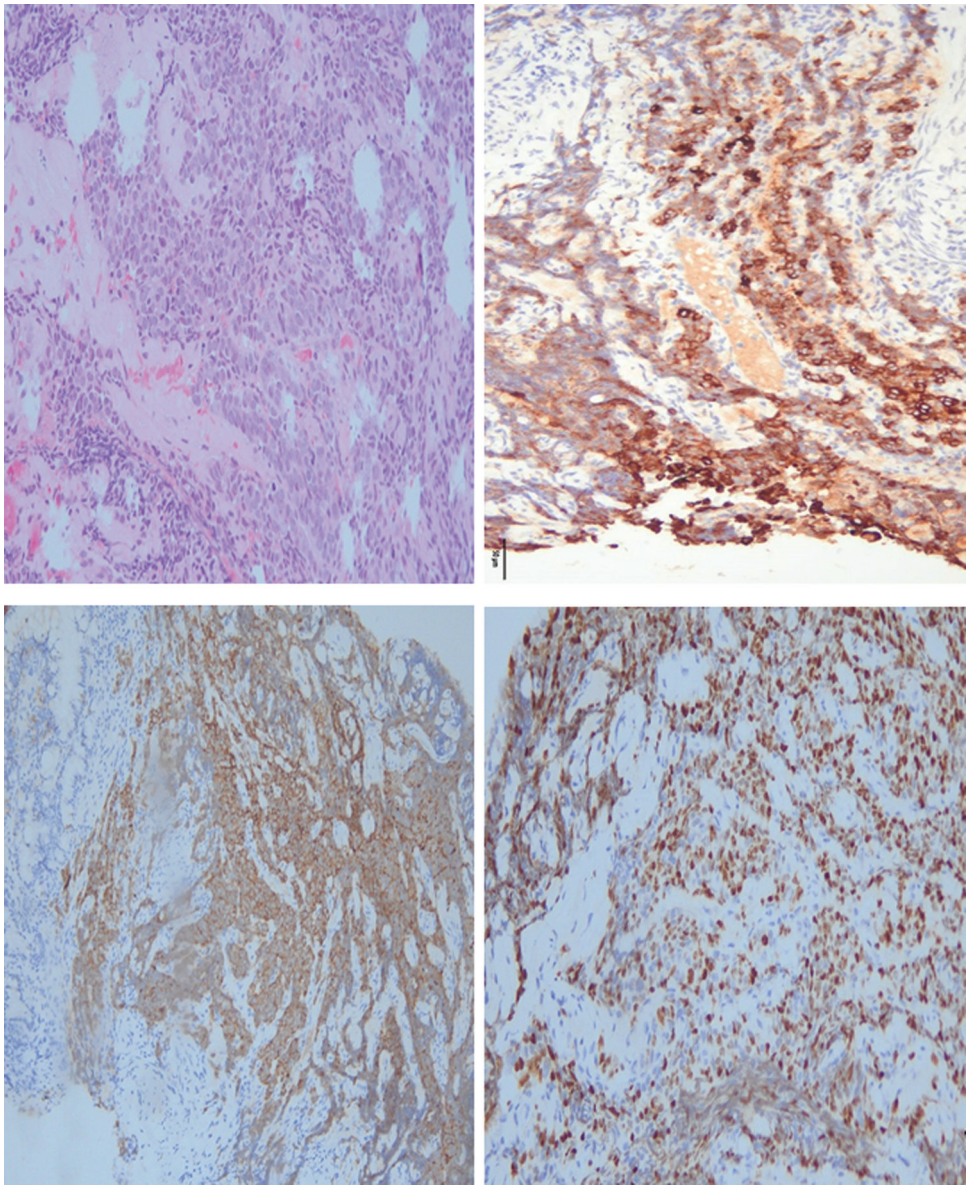

Figure 2: Histopathologic analysis revealed a sheet of tumor cells with closely packed uniform cells with round uniform nuclei, salt and pepper chromatin, and scanty cytoplasm (upper panel, H&E stain, 400×). Immunohistochemically, the tumor cells showed membranous and positive cytoplasmic staining for cytokeratin (AE1/AE3, right upper panel, 400×) and synaptophysin (left lower panel, 400×) and positive nuclear staining for Ki-67 (right lower panel, 400×). H&E = hematoxylin and eosin

The patient received platinum-based chemotherapy, followed by triweekly cyclophosphamide + adriamycin + vincristine. Fifteen months after histopathologic diagnosis, the patient died of disease progression with multiple liver tumors, consistent with liver metastases. The maximum diameter of the liver tumor was more than 10 cm. The patient also developed Klebsiella pneumonia and acute bacteremia with a blood culture showing *Escherichia coli*.

Neuroendocrine tumors are very rare tumors of the ampulla of Vater. In total, less than 150 cases have been reported. The ampulla of Vater is highly vascularized, which contributes to liver dissemination and lymph node metastases. Regardless of tumor size, published data showed that tumors metastasized in half of the cases in a retrospective case series of 20 patients. Overall, the 10-year survival for resected ampulla of Vater neuroendocrine tumors is 71% for well-differentiated tumors but only 15% for poorly differentiated neuroendocrine carcinoma.[1]

According to the World Health Organization Classification of Tumors of the Digestive System (fifth edition) for poorly differentiated neuroendocrine carcinoma, the diagnostic criteria include Ki-67 index of more than 20% or mitotic index of more than 20 mitoses/2 mm^2, equaling 10 high-power fields. Previous studies showed that pancreatic poorly differentiated neuroendocrine carcinoma responded to platinum-based chemotherapy. However, its prognosis was very poor. The Japanese guidelines for the management of pancreatic and gastrointestinal tract neuroendocrine carcinoma recommend chemotherapy instead of surgery.[2] Generally, the prognosis of small-cell neuroendocrine carcinomas is very poor, because early metastasis to the liver and regional lymph nodes is common. The 5-year survival rate was 8% for small-cell neuroendocrine carcinoma of the gall bladder and 0% for small-cell neuroendocrine carcinoma of the extrahepatic bile duct.[3]

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Data availability statement

All data generated or analyzed during this study are included in this published article.

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Nil.

Conflict of interest

Dr. Hong-Wei Gao, an section editor at *Tungs' Medical Journal*, had no role in the peer review process of or decision to publish this article. The other authors declared no conflicts of interest in writing this paper.

References

1. Zheng Z, Chen C, Li B, Liu H, Zhou L, Zhang H, *et al*. Biliary neuroendocrine neoplasms: Clinical profiles, management, and analysis of prognostic factors. Front Oncol 2019;9:38.
2. Ito H, Wada Y, Takami Y, Ryu T, Ureshino H, Imamura H, *et al*. A case of small cell neuroendocrine carcinoma of the ampulla of Vater. Surg Case Rep 2020;6:150.
3. Albores-Saavedra J, Batich K, Hossain S, Henson DE, Schwartz AM. Carcinoid tumors and small-cell carcinomas of the gallbladder and extra hepatic bile ducts: A comparative study based on 221 cases from the surveillance, epidemiology, and end results program. Ann Diagn Pathol 2009;13:378-83.