ISSN 2071-3592

Tungs' Taichung MetroHarbor Hospital

Tungs' Medical Journal

An Official Journal of the Tungs' Taichung MetroHarbor Hospital

Volume 16 • Issue 2 • July-December 2022

https://journals.lww.com/TMJ

Wolters Kluwer

Medknow

Print ISSN: 2071-3592

Tungs' Medical Journal

Print ISSN: 2071-3592

Tungs' Medical Journal (TMJ)

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Published by
Wolters Kluwer India Private Limited
A-202, 2nd Floor, The Qube, C.T.S. No.1498A/2 Village Marol,
Andheri (East), Mumbai - 400 059, India.
Phone: 91-22-66491818
Website: www.medknow.com

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Printed by
Nikeda Art Printers Pvt. Ltd.,
Building No. C/3 - 14,15,16, Shree Balaji Complex, Vehele Road,
Village Bhatale, Taluka Bhiwandi, District Thane - 421302, India.

Tungs' Medical Journal

Volume 16 - Issue 2 - July-December 2022

Contents

Medical care and research: Two wings of a great eagle in critical care

Two important events highlight the crucial role of Tungs' Taichung MetroHarbor Hospital in providing critical care medical services in Taiwan:

Chiu (邱小妹), a little girl who had been severely beaten by her father, was forced to travel to our hospital for treatment after being turned away by other Taipei City Hospitals.

Chin Liang-Feng (秦良丰), a 26-year-old male from the Army Aviation and Special Forces Command, jumped from a C-130 aircraft flying at an altitude of approximately 396 m on May 17, 2018, at the annual Han Kuang drill rehearsal. His parachute failed to open completely, and after falling to the ground, he lost consciousness and was paralyzed. While staying in our hospital, he regained consciousness and has since recovered dramatically from critical injuries.

These headline news stories drew the entire nation's attention to the philanthropic support and high-quality medical care provided by our hospital. To effectively utilize the ever-expanding diagnostic and therapeutic technologies and techniques developed by the research–industrial complex to care for a wide spectrum of patients, health-care providers must overcome various challenges associated with clinical practice. *Tungs' Medical Journal* is a conduit for publishing these priceless experiences and substantial findings and results.

In nephrology, end-stage renal disease (ESRD) is a major public health issue in Taiwan. Patients with ESRD require hemodialysis, peritoneal dialysis, and kidney transplants to enjoy an improved quality of life. Although kidney transplants provide good outcomes for patients with ESRD, the survival rate of transplant recipients remains lower than that of the general population. Chen *et al*.[1] discovered that delayed graft function and age were the prognostic factors associated with the survival of patients with ESRD in their cohort. Liu *et al*.[2] suggested that measuring grip strength using the "Timed Up and Go" test during initial screening can be a reliable indicator of weak muscle strength and mobility among elderly patients with ESRD that are on hemodialysis. Pruritus is an annoying problem, especially in patients with ESRD. Wu *et al*.[3] investigated patients on hemodialysis with and without uremic pruritus and found that patients' serum biochemistry, such as C-reactive protein (CRP) level, is related to uremic pruritus. Therefore, they encourage all health-care professionals to regularly assess these factors, along with itching status, to provide early and proper treatment. Chen[4] reviewed hyperuricemia through an introduction of the mechanisms underpinning the overproduction of uric acid, the disease course of gout, and the risks associated with cardiovascular diseases, metabolic syndrome, chronic kidney disease, urolithiasis, diabetes mellitus, thyroid dysfunction, and psoriasis.

In cardiology, Hsu *et al*.[5] reported on a young patient with intermittent chest pain whose characteristic electrocardiographic T-wave changes and clinical manifestations led to the diagnosis of Wellens syndrome. After an urgent coronary angiography, the patient was found to have left anterior descending coronary artery stenosis. Early identification and emergent intervention saved his life.

Guillain–Barré syndrome (GBS) is a life-threatening, acute, and immune-mediated demyelinating peripheral neuropathy. GBS typically manifests progressive ascending weakness and sensory loss from distal to proximal muscles. Hu *et al*.[6] reported a 14-year-old boy presenting with right lower limb weakness and sensory loss which were relieved by intravenous immunoglobulin treatment. His upper gastrointestinal endoscopy showed a typical pattern of gastritis and *Helicobacter pylori* infection. His weakness and sensory loss did not recur after a complete therapeutic course targeting *H. pylori* with a triple therapy of lansoprazole, amoxicillin, and clarithromycin.

No one can live without respiration, but too much air in the mediastinum may cause agony. Spontaneous pneumomediastinum is an uncommon disorder that primarily affects young adult males. Its prognosis varies from very benign to fatal. Huang *et al*.[7] characterized spontaneous pneumomediastinum and found that chest pain and dyspnea were the most common clinical presentations. The clinical course of spontaneous pneumomediastinum is generally very benign and the disease is self-limiting. Therefore, unnecessary aggressive therapy and invasive diagnostic procedures should be limited. Interestingly, the air in the biliary tract (pneumobilia) is relatively rare and suggests abnormal communication between the biliary and gastrointestinal tracts. Wu *et al*.[8] reported a 6-month-old female infant that presented with intermittent bilious vomiting. Her abdominal plain film imagery showed typical features of pneumobilia. These were attributed to a previous intestinal operation with a gas leak, which led to the X-ray findings.

In neurology, while strokes are not rare, especially in the elderly, cerebral venous thrombosis as the initial presentation of hematological malignancy is very unusual. Chen *et al*.[9] presented a 49-year-old woman complaining of progressive headaches for 3 weeks. Brain imaging studies revealed edema in the right thalamus and bilateral caudate nuclei, and acute

thrombosis in the straight and right transverse sinuses. Initial laboratory investigations revealed several negative findings excluding anemia. Her headache resolved after anticoagulation therapy; however, acute quadriparesis and coma occurred after warfarin treatment was stopped. Magnetic resonance imaging showed acute thrombosis of the basilar artery with brainstem infarction, which may have been associated with acute leukemia. Therefore, malignancies should be ruled out if patients are found to have cerebral venous thrombosis.

In conclusion, 10 additional papers consist of one editorial, one review, four research articles, two imaging cases, and two case reports. We sincerely thank all authors for their contributions and willingness to share insightful overviews and valuable experiences toward making proper diagnoses and developing and implementing appropriate therapeutic plans. Medical care and research, like the two wings of a great eagle, can help free patients from suffering through proper diagnoses and appropriate therapies. Moreover, the editorial board would like to invite our readers to publish the most influential and scientifically sound papers to help our journal become recognized as a high-impact journal of scholarly general and specialized medical care and research.

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Received: 07-Oct-2022 **Accepted:** 07-Oct-2022 **Published:** 13-Dec-2022

Access this article online

Quick Response Code:

Website: https://journals.lww.com/TMJ

DOI: 10.4103/ETMJ.TMJ-111026

How to cite this article: Tung MC, Ou YC, Fan HC. Medical care and research: Two wings of a great eagle in critical care. Tungs Med J 2022;16:41-2.

Review Article

Hyperuricemia – A narrative review

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Abstract

Gout is an inflammatory disease caused by the accumulation of monosodium urate crystals in joints, cartilage, synovial bursa, tendons, and soft tissues. Gout is highly associated with hyperuricemia. Gout is not a new disease, which was first documented nearly 5000 years ago. Tophi are solid nodules that develop in the joints of people with uncontrolled chronic gout. Recently, many studies have advocated that hyperuricemia and gout are associated with insulin resistance syndrome. Hyperuricemia is also an independent risk factor for cardiovascular diseases. Recently, the prevalence of gout has increased globally, imposing a great disease burden worldwide. Moreover, gout or hyperuricemia is associated with various comorbidities, including cardiovascular diseases, metabolic syndrome, chronic kidney disease, urolithiasis, diabetes mellitus, thyroid dysfunction, and psoriasis. Furthermore, research has shown a correlation between high uric acid levels and type 2 diabetes, high blood pressure, and fatty liver disease. High uric acid levels may lead to permanent bone, joint, and tissue damage, kidney disease, and heart disease.

Keywords: Cardiovascular disease, gout, hyperuricemia, uricosuric agents, urolithiasis

Introduction

In most cases, gout does not occur immediately when the serum uric acid concentration rises and exceeds the normal range (>7 mg/dL), a condition referred to as asymptomatic hyperuricemia.[1] Hyperuricemia occurs due to the abnormality of enzymes in the process of uric acid metabolism in the body, which leads to the decomposition of excessive nucleic acid, or intake of high-purine diets (seafood, red meat, beer, and animal offal). Other mechanisms may also include insufficient daily physical activity.[2] With the presence of a large amount of cell apoptosis in the body, as in systemic diseases such as leukemia and multiple myeloma the release of nucleic acid increases, which is metabolized into uric acid, leading to even higher levels of uric acid.[3] The American Rheumatology Association suggests that unless gout attack, tophi, or kidney disease is found, there is no need to treat patients with asymptomatic hyperuricemia.[4] In addition, uric acid may play an important role in the formation of cardiovascular diseases, and some evidence suggests that lowering uric acid affects the prognosis of cardiovascular diseases.[5]

Received: 07-Mar-2022 **Revised:** 08-Apr-2022 **Accepted:** 15-Apr-2022
Published: 13-Dec-2022

Access this article online

Quick Response Code:

Website: https://journals.lww.com/TMJ

DOI: 10.4103/ETMJ.TMJ-111008

Asymptomatic Hyperuricemia

Hyperuricemia may occur due to a decrease in the excretion of uric acid. The kidneys are responsible for removing uric acid from our bodies. In the case of decreased renal excretion of uric acid, it can easily accumulate in the body and cause hyperuricemia, which is often categorized as primary hyperuricemia.[6] For hyperuricemia, there is a possibility of familial inheritance, especially if the patient has the following symptoms: the onset of gout occurs before the age of 30 years, combined with urinary tract stones, but without other signs of gout when conducting behaviors such as drugs and alcohol drinking. Joint pain and high blood uric acid may not necessarily indicate gout, but conversely, a low uric acid level may be a case of gout.[7] Gout and uric acid nephrolithiasis have traditionally been considered the main complications of hyperuricemia. However, there is increasing evidence that hyperuricemia is a consequence of cardiovascular disease and an independent risk factor for recurrent urinary tract infection. Furthermore, lowering uric acid can be beneficial for people with high blood pressure and cardiovascular disease, and therefore,

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How to cite this article: Chen C. Hyperuricemia – A narrative review. Tungs Med J 2022;16:43-6.

lowering uric acid will lower the overall cardiovascular risk.[8] Recent epidemiological long-term follow-up studies have pointed out that asymptomatic hyperuricemia may also lead to death, particularly due to cardiovascular diseases such as stroke and myocardial infarction.[9] One article reported that the risk of death due to cardiovascular disease increases by about 8%–13% for every 1 mg/dL increase in uric acid concentration in patients with hyperuricemia.[10] Asymptomatic hyperuricemia (uric acid >7 mg/dL) is positively associated with overall mortality or death from cardiovascular diseases. This shows the predictive power of serum uric acid concentration on the risk of death, and the paper analyzed 26,341 patients with gout, the average age was 62 years, 75% were men, and the rest were women.[10] The increase in the prevalence of hyperuricemia and gout in Taiwan may be related to the increase in obesity and metabolic syndrome. A report from Taiwan in 2013 showed that hyperuricemia combined with metabolic syndrome (e.g., hypertension, obesity, and hyperlipidemia) significantly increased the incidence of gout, and this risk of metabolic syndrome and gout attack was more pronounced in men.[11] Patients with hyperuricemia had a 22% higher risk of death than those with normal uric acid (uric acid of 5–6 mg/dL), and the risk of death increased to 27% in patients with hyperuricemia who had insufficient physical activity.[12] Patients with hyperuricemia were followed up for 8.5 years, and the results showed that the percentage of death could be lowered by 11% if their physical activity exceeded 150 min per week.[13]

Definition and Prevalence of Asymptomatic Hyperuricemia

According to the epidemiological definition, hyperuricemia is defined as the blood uric acid concentration, i.e., two standard deviations higher than the average of normal people: 7 mg/dL for the male and 6 mg/dL for the female. If there is no development of arthritis, the condition can only be referred to as asymptomatic hyperuricemia,[14] during which, with such high blood uric acid concentration, no manifestation of clinical symptoms is seen but instead can only be detected by the measurement of the uric acid levels in the plasma. Asymptomatic hyperuricemia usually occurs after a period of time before the first attack of gouty arthritis.[15] Primary hyperuricemia accounts for 90%, mainly due to familial inheritance of specific constitution, causing overproduction of uric acid or decreased renal excretion of uric acid. Meanwhile, secondary hyperuricemia accounts for only 10% and is generally a complication of other diseases, such as obesity, hyperlipidemia, or renal failure, or the use of specific drugs.[16]

Many epidemiological studies reported that the modern lifestyle leads to an increase in the prevalence of hyperuricemia and gouty arthritis in Asians, and the same phenomenon is observed in Taiwan. According to the epidemiological survey from 1986 to 1989, the prevalence of gout in Taiwan was about 0.5%, and the following increase in the Asian was most likely caused by diet and insufficient physical activity in the modern lifestyle.[4] Among adults over 45 years old, 22% of male (uric acid >7.7 mg/dL) and 23% of female (uric acid >6.6 mg/dL) were diagnosed with hyperuricemia.[17] Although the prevalence of hyperuricemia also increases with age, the prevalence of gout is not the same as hyperuricemia (9% and 6% of men and women >80 years of age, respectively). Particularly, the prevalence of gout in postmenopausal women is gradually comparable to that of men, which may be due to the loss of the protective effect of estrogen in aged women, which is another factor of increased risk of cardiovascular disease.[18]

Nonpharmacological Treatment of Hyperuricemia

Other factors that can affect a gout attack include obesity, alcohol abuse, high blood pressure, use of drugs (e.g., diuretics), renal insufficiency, sedentary lifestyle, or hereditary gene. Therefore, nonpharmacology treatments for hyperuricemia generally involve dietary control (low-purine diet) and lifestyle adjustment.[19] In addition to diet control, the patient is encouraged to develop a habit of exercise, reduce body weight, and take adequate fluid.[20,21] Beer is the only alcohol known to contain a large number of purines, thus increasing the risk of exacerbating hyperuricemia and triggering gout attacks. Heavy alcohol drinking in a short period can also cause temporary lactic acidemia, which reduces renal urate excretion and increases uric acid formation.[22] Plant-based high-purine foods (tofu and mushrooms) have a slight effect on uric acid and gout.[23]

Drug Therapy for Gout

Uric acid-lowering drugs are divided into three categories according to their mechanism of action: (1) inhibiting uric acid synthesis (uricostatic), such as allopurinol and febuxostat; (2) promoting uric acid excretion (uricosuric) such as benzbromarone, sulfinpyrazone, and probenecid; and (3) enhancing the breakdown of uric acid (uricolytic), such as pegloticase.[24] Furthermore, allopurinol or febuxostat, which inhibits uric acid synthesis, is considered the first-line treatment choice according to the American College of Rheumatology recommendations.[25] Previous studies reported that patients with the HLA-B*5801 genotype have a higher chance of developing a severe allergic reaction to allopurinol,[26] and about 6%–12% of Asians have this gene; thus, it is recommended to test for the HLA-B*5801 genotype before the use of allopurinol.[27] Drugs that promote the excretion of uric acids such as benzbromarone, sulfinpyrazone, and probenecid, require special attention because of the possibility of urinary tract stones. Therefore, increasing water intake when taking these drugs is necessary to reduce the side effects.[28,29] Lowering uric acid may cause gout to recur, particularly during the first few months of treatment. Uric-acid-reducing medications may even increase the risk of gout attacks. This is because any uric acid crystals already present only break down gradually. Since lowering uric acid may cause gout to recur, clinicians always prescribe a combination of medications to prevent gout

recurrence, and the first choice will be low-dose colchicine or low-dose nonsteroidal anti-inflammatory drugs (NSAIDs) such as naproxen. Prednisolone is a good prescription medicine for relieving symptoms of acute inflammatory response. Therefore, 10 mg/day of prednisolone is suggested as second-line therapy. Medication for recurrence prevention is based on symptoms. If hyperuricemia is without symptoms, there is no need for medications. But for persistent gouty activity, manifestation of more than one tophus, recurrent acute gout flares, or chronic tophi arthritis, and the inability to control uric acid concentration within a normal range, it is still necessary to continue taking the drug and monitor the side effects of the drug.[30] When the uric acid concentration reaches the target values, the drug can only be used for another 3 months because of the steroid's general side effects.[31] Fenofibrate can also reduce the reabsorption of uric acid by the renal tubules and promote the excretion of uric acid. Fenofibrate can reduce blood uric acid concentration by 25%–30% in healthy people or people with gout and normal kidney function.[32] Studies indicated that treatment with allopurinol not only helped slow the progression of chronic kidney disease and reduce the risk of cardiovascular disease but also lowered systolic and diastolic pressure.[33]

If first-line drug therapy is ineffective, the addition of second-line drug combination therapy may be considered.[34] Combination therapy is an appropriate option for acute severe gout attacks, particularly those with multiple joints. Currently accepted drug combination therapies include (1) colchicine + NSAIDs, (2) oral steroids + colchicine, and (3) colchicine + acetaminophen. The use of NSAIDs accompanied by steroids is not recommended due to an increased risk of gastrointestinal bleeding.[35] In cases of poor response to oral NSAIDs, intraarticular corticosteroid injection may also be recommended. Half of the patients with gouty arthritis usually recede within 24 h following a single intra-articular injection of low-dose triamcinolone (8–10 mg).[36]

Oral steroid therapy is also recommended, with prednisolone at a starting dose of at least 0.5 mg/kg daily for 5–10 days or a full dose of prednisolone b.i.d. for 2–5 days.[37] Those who suffer from hyperuricemia and acute gouty arthritis are recommended to receive uric acid-lowering drugs to prevent tophi and cardiovascular complications.[38] It is generally recommended that uric acid-lowering drugs be for long-term use, even if there is no acute attack. The goal of urate-lowering drug therapy should be set to achieve a serum uric acid concentration of <6.0 mg/dL.[39]

Conclusion

Hyperuricemia causes inflammation of the joints, which can cause redness, heat, swelling, and pain. Some causes of gout include genes, overweight, drugs (e.g., cyclosporine), impaired kidney function, sedentary lifestyle, and habits such as high-purine diet of excessive consumption of beer, sugar drinks, and seafood. Purine in the body is metabolized by the liver to form uric acid, which is then excreted in the urine by the kidneys. If excessive uric acid is produced in the body or the excretory function of the kidneys is poor, clinical symptoms such as hyperuricemia or acute and chronic gouty arthritis, tophi, joint deformity, and kidney stones will manifest.[40] Studies have shown that an average increase of 1 mg/dL of uric acid can increase cardiovascular disease by 32%, which is a similar effect to that of an increase of 46 mg/dL in total cholesterol and a 10 mmHg increase in systolic blood pressure.[41,42] Studies also found that the risk of coronary artery disease and cardiovascular disease in patients with hypertension and high uric acid simultaneously was 3–5 times higher than that in people with a normal level of uric acid. Hyperuricemia is common in patients with hypertension, as one in four untreated patients with hypertension shows concurrent asymptomatic hyperuricemia. Asymptomatic hyperuricemia occurs in half of the patients receiving blood pressure-lowering drugs that contain diuretics. Furthermore, 75% of patients with malignant hypertension and renal insufficiency have high uric acid.[43] Gout can be treated with uric acid-lowering agents, such as benzbromarone, allopurinol, and febuxostat. Furthermore, tophi can be treated by surgical removal. The risk of developing gout increases with an increase in uric acid concentration. Because high uric acid levels can increase the risk of gout, the high concentration of uric acid in the blood will eventually convert the acid into urate crystals, which can then accumulate around the joints and soft tissues. Deposits of the needle-like urate crystals are responsible for the inflammation and the painful symptoms of gout. The health hazards of hyperuricemia have exceeded the traditional perception in the past. Hyperuricemia not only causes gout or kidney stones but also has a worldwide concern for the risk of death from cardiovascular diseases.[44,45] Therefore, we should urge the importance of routine screening of uric acid in middle-aged men or women without estrogen or other diseases leading to high uric acid levels because hyperuricemia may threaten our health and cause cardiovascular diseases.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Original Article

Graft and patient survival in kidney transplantation: A single-center experience

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Abstract

Background: Patients with end-stage renal disease need renal replacement therapy, including hemodialysis, peritoneal dialysis, and kidney transplant (KT), to live a relatively normal life. Compared with other dialysis modalities, KT remains the choice for better survival. **Objectives:** This study aimed to report the KT outcomes at our center and investigate risk factors for graft and patient survival. **Methods:** This is a retrospective chart review of 72 KT recipients cared for at our center between July 1, 2004, and June 30, 2017. Delayed graft function (DGF) was defined as the need for dialysis within 1 week after KT. The primary outcome is death after KT. The secondary outcome is graft failure, which is defined as a return to dialysis while the patient is alive. Patient death with functional graft was censored during the survival analysis. **Results:** Among the patients, 17 KT recipients had primary diabetic nephropathy (23.6%) with a mean age of 47.4 ± 11.8 years. Furthermore, 13 patients returned to dialysis and 12 died during the study period, with malignancy being the leading cause of death (n = 4). The 1-, 3-, and 5-year graft survival rates were 94.3%, 90.4%, and 85.4%, respectively. The 1, 3-, and 5-year patient survival rates were 97.1%, 92.1%, and 85.7%, respectively. A total of 24 patients (33%) encountered DGF after KT. Patients with DGF had significantly poorer graft survival than those without DGF (P = 0.002 by log-rank test). Cox-proportional hazard analysis revealed that only DGF increased the risk of graft failure (hazard ratio (HR) = 6.52, 95% confidence interval (CI): 1.4629.2), and age predicted patient survival (HR = 1.09, 95% CI: 1.021.17). **Conclusion:** This study showed that patients with DGF had significantly poor graft survival. Patient's age was the only prognostic factor for patient survival in our cohort.

Keywords: Delayed graft function, graft survival, kidney transplantation, patient survival

Introduction

End-stage renal disease (ESRD) is a major public health issue in Taiwan. The incidence and prevalence of ESRD in Taiwan remain the highest worldwide.[1] It is estimated that 7.2% of the healthcare expenditure in Taiwan was used to provide treatment for patients with ESRD, who accounted for only 0.23% of the local population, according to an annual report by the Bureau of National Health Insurance in 2007.[2] In addition, patients became older and sicker as they entered ESRD. In the United States, the mean age of the ESRD group increased from 47 to 58 years, and ESRD due to diabetes increased from 9.1% to 38.2% from 1997 to 2007.[3] A similar trend was observed in Taiwan in an annual report in 2019. The mean age of patients with ESRD increased from 59.766 to. 8 years, and ESRD due to diabetes increased from 34.6% to 45.4% from 2000 to 2017.[4,5] The increased hospitalization and death rates due to ESRD contribute significantly to the healthcare burden globally.[6,7]

Kidney transplant (KT) is the treatment of choice for many people with ESRD.[8] In Taiwan, the 5-year survival rate of patients with KT was 88.4%, which was higher than that of patients with dialysis (54.6%).[4] One single-center study showed that cadaveric KT reduced the risk of death by 64% compared to dialysis.[9] Another study using data from the United States Renal Data System (USRDS) also showed that cadaveric KT had survival advantages with 48%–82% lower mortality among KT recipients than patients on the waiting list.[10] KT is also a cost-effective treatment modality.[10]

Received: 29-Dec-2020 **Revised:** 21-May-2021 **Accepted:** 21-May-2021
Published: 13-Dec-2022

Access this article online

Quick Response Code:

Website: https://journals.lww.com/TMJ

DOI: 10.4103/ETMJ.TMJ-109030

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How to cite this article: Chen CH, Kuo YC, Wu TK, Chen HP, Tseng TY, Pai MA, *et al*. Graft and patient survival in kidney transplantation: A single-center experience. Tungs Med J 2022;16:47-53.

Furthermore, living KT provides more superior graft and patient survival than deceased KT.[11]

Although KT provides better outcomes for patients with ESRD, the survival of transplant recipients is still worse than that of the general population.[12] Cardiovascular disease, infection, and malignancy remain the major causes of death in patients with KT.[12,13] Several factors affect patient and graft survival after KT. An early analysis in the United Kingdom revealed that more mismatches for human leukocyte antigen (HLA), increased ages of donor and recipient, diabetic recipient, longer cold ischemic time, and causes of donor's death were associated with poor graft outcomes.[14] In addition, delayed graft function (DGF),[15] obesity,[16] prior sensitization with high panel-reactive antibody level, repeat transplantation,[17] and expanded criteria donors[18] affected graft survival. Regarding patient survival, one study in the Netherlands concluded that male patients, patients aged over 40 years at transplantation, smokers, and patients with hypertension or diabetes had an increased risk of mortality in the 1st year after transplantation.[19] Previous studies in the United States reported that, besides age and underlying diseases, ethnicity of donor and recipient, length of dialysis, DGF, acute rejection, and high panel-reactive antibody level were the significant predictors of patient death with graft function.[12,20]

DGF often refers to acute kidney injury that necessitates dialysis intervention in the 1st week after KT.[21,22] DGF was reported in about 25.5% of deceased-donor recipients and 3%–5% of living-donor recipients in the United States.[20] The need for dialysis also prolongs hospitalization and increases patient management costs.[21] Multiple donor and recipient factors contribute to DGF.[21-23] Several donor-related factors, such as age, donation after cardiac death, donor creatinine, history of hypertension or diabetes, and causes of death, were the major components of the Kidney Donor Risk Index/Kidney Donor Profile Index.[22,24,25] Other recipient risk factors included cold ischemic time, HLA mismatch, peak panel-reactive antibody level, duration of dialysis, recipient body mass index, sex, ethnicity, and underlying diseases.[26] DGF is a significant negative factor for graft outcomes. A previous meta-analysis reported that patients with DGF were associated with a 41% higher risk of graft loss.[15] However, current evidence showed a conflicting result regarding the relationship between DGF and patient survival.[15]

In 2004, we performed our first deceased KT at Tungs' Taichung MetroHarbor Hospital. Until now, we have cared for more than 70 KT recipients. Furthermore, living KT was successfully performed in 2016. This study aimed to describe the patient and graft outcomes and determine the correlation between patient factors and survival in adult KT recipients.

Materials and Methods

Study design

This is a retrospective cohort study conducted in Tungs' Taichung MetroHarbor Hospital. Patients with KT cared for at our center between July 1, 2004, and June 30, 2017, were enrolled. The baseline characteristics, including etiology of original kidney disease and hepatitis profile, were recorded.

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Medical Ethics Review Boards of Tungs' Taichung MetroHarbor Hospital (IRB No. 105029), and consent was waived due to the retrospective nature of the study and nondisclosure of patient information.

Patient characteristics and description of the dataset

Patients' demographics, including age, sex, body mass index, length of dialysis, primary etiology of ESRD, hepatitis B, and hepatitis C, were collected from the medical records and registry data.

Our hospital has adopted two clinical care pathways for KT. Physicians were free to implement either one according to their experiences and modify the treatment according to the patient's needs. The major differences between them were the type and amount of infusion fluid, dose of initial and following steroids, and schedule for laboratory tests. However, the main component of immunosuppressive medication was similar in both pathways. Before surgery, induction therapy with anti-interleukin-2 receptor antibody and induction doses of immunosuppressants was administered. We used a three-combined immunosuppressive regimen, including steroids, antiproliferative agents, for example, mycophenolate mofetil or mycophenolic acid, and either calcineurin inhibitor (CNI) or mammalian target of rapamycin inhibitor. CNI and mammalian target of rapamycin inhibitor were classified as backbone immunosuppressants. In our experience, we rarely changed the immunosuppressive regimen in each recipient. Therefore, we assumed that they took the same drug combination we recorded throughout the course.

DGF was recorded when patients necessitated dialysis within 1 week after KT. The presence of acute rejection was defined when patients were recorded using steroid pulse therapy during follow-up as a surrogate proxy.

Outcome assessment

The primary outcome is death after KT. The secondary outcome is graft failure, which is defined as a return to dialysis while the patient is alive. Patients were censored when they lost follow-up or death with functional graft during survival analysis.

Statistical analysis

Statistical analysis was performed using the R 3.6.1 software (The R Foundation for Statistical Computing, Vienna, Austria). A two-sided $P \leq 0.05$ was considered statistically significant. The distributional properties of continuous variables were expressed as mean (standard deviation), and categorical variables were presented by frequency and percentage. The Kaplan–Meier method was used to estimate the survival rates of survival outcomes.

Univariate analysis was performed to assess the differences in the distributions of continuous and categorical variables within groups stratified by DGF using two-sample t-test,

Wilcoxon rank-sum test, Chi-square test, and Fisher's exact test (if the expected values in any of the cells of a contingency table were <5). Logistic regression analysis was performed to determine the factors associated with DGF. In addition, multivariate analysis was performed by fitting Cox's proportional hazards model to estimate the effects of risk factors, prognostic factors, or predictors on graft, and patient survival.

Results

The baseline demographic data are shown in Table 1. A total of 72 patients, including 3 living kidney recipients, with a mean age of 47.4 ± 11.8 years, were included in the study. Patients aged 4564 years (n = 38) were the largest group, followed by those aged 1844 years (n = 31). The main primary etiology for ESRD was glomerulonephritis (40.4%) and diabetic nephropathy (23.6%). Acute rejection ever occurred in 12 patients. Tacrolimus was used more often than cyclosporin as the backbone of immunosuppressants.

Graft and patient outcomes are shown in Table 2. Of the patients, 12 died during the study period. The overall 1-, 3-, and 5-year patient survival rates were 97.1%, 92.1%, and 85.7%, respectively. Malignancy was the leading cause of death (n = 4), followed by cardiovascular disease (n = 3) and sepsis (n = 2). A total of 13 patients returned to dialysis. The average time from transplantation to cancer diagnosis was 4.26 years. The mean survival of recipients after cancer diagnosis was 11.85 months. The 1-, 3-, and 5-year graft survival rates were 94.3%, 90.4%, and 85.4%, respectively. Patients with DGF had patient survival similar to those without DGF, but significantly poorer graft survival than those without DGF [P = 0.9 for patient survival and P = 0.002 for graft survival by log-rank test, Figure 1].

DGF occurred in 24 (33.3%) patients and not in living kidney recipients. The baseline characteristics between patients with and without DGF were similar, except that more patients in the DGF group used tacrolimus. Furthermore, the logistic regression analysis showed that patients' not using tacrolimus had lower odds of DGF [Table 3].

The risk factors for the primary and secondary outcomes were determined using Cox proportional hazards models [Table 4]. Age was the only prognostic factor for patient survival (hazard ratio (HR) =1.09, 95% confidence interval (CI): 1.021.17). In addition, only DGF increased the risk of graft failure (HR = 6.52, 95% CI: 1.4629.2). Sex, diabetes, presence of acute rejection, and immunosuppressant types did not contribute to risks for both outcomes.

Discussion

In this study, we presented our first-hand experience of our center in KT. We demonstrated that age was the only prognostic

Table 1: Baseline characteristics in overall cohort and categorized according to delayed graft function

	Overall (n=72)	Patient without DGF (n=48)	Patient with DGF (n=24)	P
Age (years)	47.4±11.8	46.8±12.1	48.6±11.4	0.54
Male	37 (51.4)	26 (54.1)	11 (45.8)	0.68
Body height (cm)	163.3±8.7	163.4±9.0	162.7±8.2	0.73
Body weight (kg)	60.4±12.2	59.7±12.4	61.9±12.0	0.79
BMI (kg/m^2)	22.6±3.7	22.2±3.5	23.3±4.0	0.23
Dialysis modality				
Hemodialysis	51 (70.8)	31 (64.6)	20 (83.3)	0.17
Peritoneal dialysis	19 (26.4)	15 (31.3)	4 (16.7)	0.30
Length of dialysis (months)[#]	72.6±65.7	69.9±62.2	77.4±72.8	0.62
Preemptive[ł]	2 (2.8)	2 (4.2)	0	0.55
Primary etiology				
Glomerulonephritis	29 (40.35)	19 (39.6)	10 (41.6)	1
Diabetic nephropathy	17 (23.6)	12 (25)	5 (20.8)	0.93
Hypertension	18 (25)	12 (25)	6 (25)	1
Others[ł]	8 (11.1)	5 (10.4)	3 (12.5)	1
Co-morbidity				
Hepatitis B[ł]	5 (6.9)	3 (6.3)	2 (8.3)	1
Hepatitis C[ł]	7 (9.7)	4 (8.3)	3 (12.5)	0.68
Living kidney transplantation[ł]	3 (4.2)	3 (6.3)	0	0.55
Observation period (year)[#]	5.2±13.5	5.8±15.5	4.0±7.5	0.08
Acute rejection[ł]	12 (16.7)	9 (18.8)	3 (12.5)	0.74
Backbone immunosuppressants				
Tacrolimus	39 (54.2)	21 (43.8)	18 (75)	0.024*
Cyclosporin	27 (37.5)	21 (43.8)	6 (25)	0.20
Others[ł]	6 (8.3)	6 (12.5)	0	0.17

*P<0.05, [#]Wilcoxon rank sum test, [ł]Fisher's exact test. Chi-square test was used for categorical data and 2-sample t-test was used for numerical data. Mean±SD, n (%). SD: Standard deviation, BMI: Body mass index, DGF: Delayed graft function

Table 2: Outcomes among kidney transplant recipients stratified by delayed graft function

	Overall (*n*=72)	Patient without DGF (*n*=48)	Patient with DGF (*n*=24)	*P*
Death[ǂ]	12 (16.7)	9 (18.8)	3 (12.5)	0.74
Cardiovascular disease[ǂ]	3 (25)	3 (33.3)	0	0.55
Sepsis[ǂ]	2 (16.7)	1 (11.1)	1 (33.3)	1
Malignancy[ǂ]	4 (33.3)	3 (33.3)	1 (33.3)	1
Ureteral carcinoma	2	1	1	
Renal cell carcinoma	1	1	0	
Gastric adenocarcinoma	1	1	0	
Time from transplantation to diagnosis (years)	4.26±4.31			
Time from diagnosis to death (month)	11.85±14.76			
Others	3 (25)	2 (22.2)	1 (33.3)	1
Patient survival rates[†] (years) (%)				
1	97.1	100	91.3	0.94
3	92.1	95.1	85.9	
5	85.7	86.0	85.9	
Graft failure[ǂ]	13 (18.1)	6 (12.5)	7 (29.2)	0.11
Graft survival rates[†] (years) (%)				
1	94.3	100	82.6	0.02*
3	90.4	97.2	76.3	
5	85.4	93.2	68.7	

*P<0.05, [ǂ]Fisher's exact test, [†]Log rank test. Mean±SD, *n* (%). SD: Standard deviation, DGF: Delayed graft function

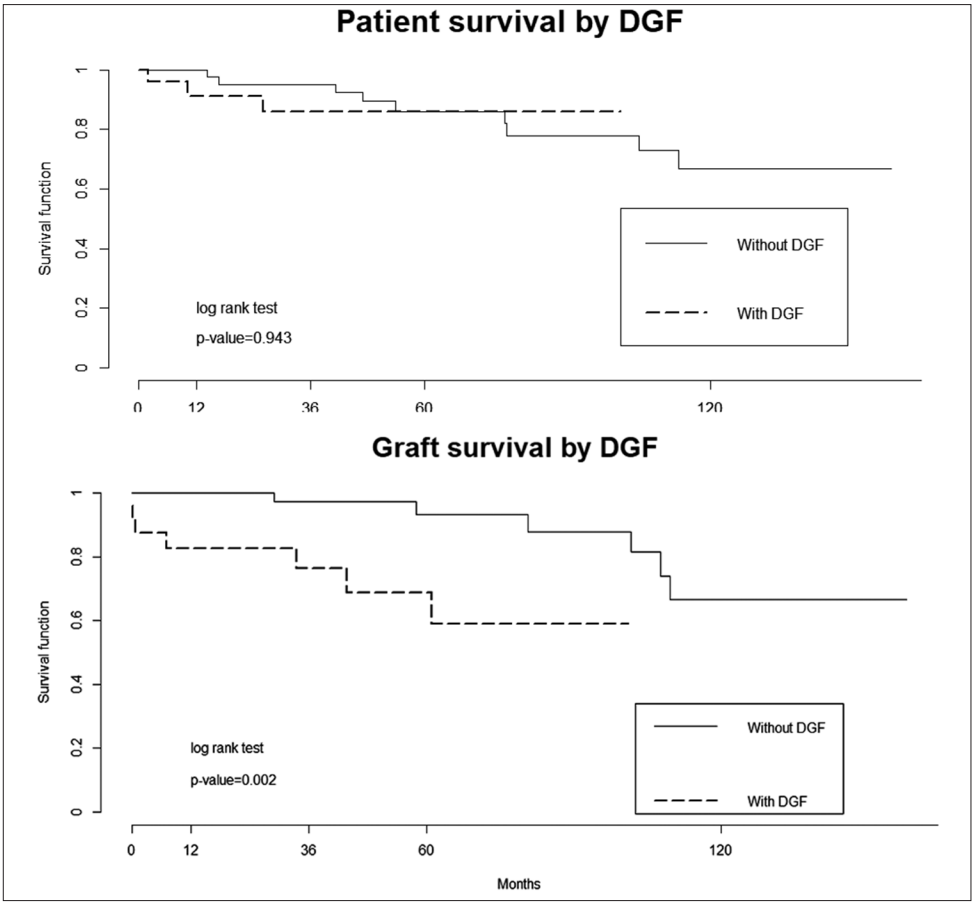

Figure 1: Kaplan-Meier estimates for patient survival and graft survival in patients with and without DGF. DGF: Delayed graft function

factor for patient survival. In addition, only DGF contributed to a higher probability of graft failure.

The overall KT outcomes in this study were acceptable compared with those in other reports.[4,17,27] In centers with 3099 KT cases between 2000 and 2012, the 5-year patient survival was 88.1%, according to an annual report in Taiwan.[4] The proportion of recipients under the age of 45 years was slightly greater in our cohort than in this national cohort.[4] After enrolling the patient transplanted only before 2012, we presented similar 5-year patient survival of 87.8%. It has been suggested that the transplant center's experience affects recipient outcomes. For example, in centers with more than 100 transplant recipients during the same period, 5-year patient survival was 89.9%.[4] However, a study in Europe reported 5-year patient survival of 84.4% in patients transplanted between 2006 and 2015.[17] The latest USRDS report revealed that 5-year graft and patient survival among deceased-donor transplant recipients were 79.7% and 76.7%, respectively.[27] Although our results were generally noninferior to those international data, we still need to make more efforts to catch up with those more experienced centers.

This study revealed that DGF in recipients largely increased the risk of graft failure. In this study, the incidence of DGF was similar to that reported in a recent report in the United States.[28] Current consensus suggests that DGF increases the risk of acute rejection and chronic allograft nephropathy, thus significantly worsening baseline transplant kidney function and graft survival.[21,22] However, the rate of acute rejection was not significantly different between groups with and without DGF, and acute rejection was not significantly associated with graft loss in our study. These findings might be due to the small cohort size, lack of immunosuppressive drug levels, and using surrogates instead of the histopathological definition of acute rejection. Moreover, since our protocol comprised anti-CD25 monoclonal antibody immunosuppressive induction therapy, our cohort had few acute rejection episodes. The complex mechanism for the development of DGF could be a key driver of acute and chronic rejection.[22,23] For example, increased expression of cell surface molecules and cytokine production caused by ischemic/reperfusion injury may expand allograft immunogenicity and trigger acute rejection.[23] A recent large cohort study showed that DGF remained a strong risk factor for acute rejection.[29] However, whether the effect of DGF on graft loss was influenced by acute rejection was still unknown.[20,30,31] Therefore, this study highlighted the importance of DGF prevention and management for improving graft outcomes.

Table 3: Factors associated with delayed graft function by logistic regression analysis

Covariates	OR (95% CI)	*P*
Age	1.01 (0.81–2.06)	0.31
Male	0.97 (0.78–1.21)	0.66
DM	0.95 (0.74–1.23)	0.88
Non-tacrolimus	0.74 (0.60–0.93)	0.017*

*P<0.05. OR: Odds ratio, CI: Confidence interval, DM: Diabetes mellitus

Both donor and recipient factors contribute to the development of DGF.[21,23] The most significant associated risk factors are cold ischemic time, donor terminal creatinine, donor body mass index, donation after cardiac death, and donor age, according to one predictive model for DGF.[26] However, a large portion of donor characteristics, such as cold ischemic time or donor creatinine, were missing in our cohort to explore these relationships. Nevertheless, we found that tacrolimus users had higher odds for DGF than cyclosporin users. In our clinical pathways, we initiated CNI during induction right before transplant surgery. In an early review, cyclosporin was considered a risk factor for DGF because such CNI may have a negative impact on the recovery from posttransplant acute tubular necrosis.[22,23] However, delayed CNI administration,[32,33] lowering CNI exposure,[34] or total CNI-free regimen[35] have been reported to be ineffective in reducing DGF in current studies. Therefore, we cannot infer that tacrolimus should be used less due to few patient numbers, missing important covariates, and selection bias in this study. Current guidelines suggest that tacrolimus should be the first-line CNI.[36]

In our study, age was the only prognostic factor for patient survival. According to the annual Taiwan report, trends toward better survival were found in younger age groups.[4] Several studies have shown similar results.[10,37,38] However, survival was significantly improved in older transplant recipients compared to similar patients on the waiting list.[38] Despite the shortage of organ resources and limited life expectancy, the elderly should not be precluded from KT due to survival benefits and some alternative allocation systems.[39-42] Recent guidelines also indicate that age alone should not be the main reason to exclude patients from being transplant candidates.[43]

This study showed that cancer is the most common cause of death. The average time from transplant surgery to malignancy diagnosis and mean survival time were also

Table 4: Multivariate cox regression analysis for graft and patient survival

Covariates	Graft survival, HR (95% CI)	*P*	Patient survival, HR (95% CI)	*P*
Delay graft function	6.52 (1.46–29.2)	0.014*	1.07 (0.19–5.88)	0.94
Age	1.04 (0.99–1.10)	0.12	1.09 (1.02–1.17)	0.009*
Male	0.58 (0.18–1.91)	0.37	0.49 (0.12–2.00)	0.32
DM	1.12 (0.26–4.85)	0.88	1.31 (0.30–5.83)	0.72
Acute rejection	1.21 (0.23–6.53)	0.82	0.63 (0.07–5.69)	0.68
Non-tacrolimus	0.36 (0.10–1.32)	0.12	0.39 (0.10–1.45)	0.16

*P<0.05. CI: Confidence interval, HR: Hazard ratio, DM: Diabetes mellitus

shorter than those in other studies.[44,45] It should be noted that the differences in our case number between malignancy, cardiovascular disease, and sepsis were trivial. In most studies, cardiovascular diseases remained the first cause of mortality,[12,13] and our different results might be related to small sample size, few cases suffering from events, and different clinical settings. Undoubtedly, KT recipients suffer from a twofold to fourfold higher risk of malignancy than the general population,[46] and the role of neoplasm becomes more important as longer life expectancy is achieved in KT recipients.[47] Oncogenic viral infection, immunosuppressive medication, and altered T-cell immunity contributed to cancer development.[46,47] Although general cancer screening is not recommended from the current evidence,[13,47] the development of such a cancer screening protocol might be considered reasonable due to the high incidence and poor patient prognosis in our center.

This study had several limitations. First, we could not retrieve some important covariates from both donors and recipients due to the retrospective study design. For example, the number of HLA mismatches, cold ischemic time, donor creatinine, and recipient panel-reactive antibody titer, which significantly contributed to DGF, acute rejection, graft, and patient survival, were missing in a large majority of study participants. The lack of adjusting these significant covariates may explain why DGF in this study showed a more tremendous effect on graft loss than others.[15] Besides, we could not provide a more comprehensive review and more targeted initiatives to improve the quality of care. Second, there were no established universal protocols in the early period. Although some clinical pathways were suggested, surgical techniques and posttransplant care were based on individual experience, thus confounding patient outcomes and hindering the analysis of care quality. Therefore, recently, we have adopted a generalized caring protocol and data collection system to improve our clinical practice. Third, we used a surrogate proxy for the definition of acute rejection instead of histopathology. Allograft biopsy remains the diagnostic standard for acute rejection and is strongly recommended when graft function worsens unexplainably.[36] Our imprecise and arbitrary definition may explain why acute rejection did not affect both outcomes.

This first report provided us with not only the results of our transplant program but also some valuable information regarding future quality improvement. Since the main etiologies of mortality include malignancy, cardiovascular disease, and sepsis, regular cancer surveillance protocols, cardiovascular disease management, and infection precaution measures should be implemented and educated. Despite the lack of an established treatment for DGF, some interventions can be adopted to minimize organ damage during donor preconditioning, surgical extraction, and organ preservation.[20] For example, we can reduce cold and warm ischemic time by modifying our transplantation program for more efficient teamwork and more standard surgical procedure and chart record. We hope these stepwise improvement processes will further improve clinical outcomes and enhance patients' quality of life.

Conclusion

This study showed that patient and graft survival in our transplant cohort were comparable to those in other reports. The main causes of death were malignancy, cardiovascular disease, and infection in our cohort. We found that age was the only prognostic factor for patient survival. Patients with DGF had patient survival similar to those without DGF, but significantly poorer graft survival than those without DGF. This study highlighted the priority of a more comprehensive transplant policy and guidelines in our center, including donor management, organ procurement, immunosuppressive regimen, and short-term and long-term recipient surveillance protocol, to reduce DGF and improve the quality of care and patient prognosis.

Financial support and sponsorship

Nil.

Conflicts of interest

Prof. Paik-Seong Lim, an editorial board member 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.

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Original Article

Handgrip strength as a predictor of mobility in patients with end-stage renal disease on hemodialysis

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Abstract

Background: The Timed Up and Go (TUG) test is commonly used to assess motor function and gait stability in the elderly, including patients with chronic kidney disease (CKD). Furthermore, the handgrip strength test is used to evaluate general muscle strength and may help identify weakness, a key element of frailty. **Objectives:** This study aimed to determine whether the handgrip strength test is a suitable screening tool before the TUG test because it requires less physical effort and likelihood of adverse events associated with falling during testing. **Methods:** A total of 120 patients with CKD on hemodialysis participated in the study. The associations or correlations among handgrip strength, TUG test, and routine nutritional biomarkers were analyzed. **Results:** A significant correlation was observed between handgrip strength and TUG test in all patients ($R = -0.39$, $P = 1*10\text{-}5$), even in patients with diabetic kidney disease ($n = 56$, $R = -0.36$, $P = 0.0065$). Interestingly, when dividing the patients into two groups according to hemoglobin A1c (HbA1c) levels (<7% vs. ≥7%), no significant differences in handgrip strength or completion time of the TUG test were observed between both groups. **Conclusion:** In patients on hemodialysis with decreased mobility, measuring grip strength can be a reliable marker as an initial screening to determine whether patients can exert the necessary physical effort to perform the TUG test. Furthermore, a HbA1c <7% did not provide additional benefits in terms of muscle strength and mobility to patients with diabetes on hemodialysis.

Keywords: Chronic kidney disease, handgrip strength test, timed up and go test

Introduction

With an increasing number of elderly patients with chronic kidney disease (CKD) and on dialysis,[1] there is a growing burden for physicians and healthcare providers to ensure safeguards are in place while administering this life-prolonging, but potentially harmful, treatment. Among the many potential complications of dialysis, falls can cause significant morbidity for patients.[2] Furthermore, it is of paramount importance for healthcare providers to routinely screen for risk factors in patients on dialysis due to the fact that those patients are predominantly older, which is an independent risk factor for falls.[3] The timed up and go (TUG) test is used to assess gait abnormalities in elderly patients, including patients with CKD.[4,5] Therefore, over the years, this test has been widely and routinely used in the settings of dialysis and primary care.

Multiple obstacles, including lines, poles, and dialyzers, are often found in hemodialysis centers, which put patients on hemodialysis at additional risk of falls. This fact was also reported in a previous article.[6] A multicenter cohort study on patients on hemodialysis reported that patients were already at risk of falls, and more than a quarter of patients suffered from one or more falls within a 12-month period, especially among patients who were categorized as frail.[7] Hence, if objective physical tests that involve ambulation

Received: 29-Oct-2021 **Revised:** 20-Jan-2022 **Accepted:** 20-Jan-2022
Published: 13-Dec-2022

Access this article online

Quick Response Code:

Website: https://journals.lww.com/TMJ

DOI: 10.4103/ETMJ.TMJ-110022

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How to cite this article: Liu WC, Chiu LS, Lim PS. Handgrip strength as a predictor of mobility in patients with end-stage renal disease on hemodialysis. Tungs Med J 2022;16:54-60.

were to be done on these patients already at risk of falls, then there need to be additional medical staff and allotted time for these assessments to be conducted.[8] This can further burden an already-overstretched workforce.[9] To solve this problem, we need to perform some form of assessment, which requires less physical effort before the TUG test to evaluate whether the patient is a suitable candidate for ambulation. We propose that the handgrip strength test can be a suitable screening tool to be performed before the TUG test since it does not require much physical effort from patients and can be performed while patients are in any position. A previous study involving community-dwelling women showed a correlation between handgrip strength and the TUG test.[10] Furthermore, multiple other studies showed that grip strength is inversely proportional to the number of falls sustained by elderly individuals,[11,12] which indicates the possibility of using the handgrip strength test instead of the TUG test when assessing the risk of falls in patients on hemodialysis.

Thus, this study aimed to evaluate whether handgrip strength correlates with the TUG test among patients on dialysis and compare to other serum markers of strength and mobility. Additionally, we analyzed this relationship between handgrip strength and the TUG test in a subset of patients with end-stage renal disease (ESRD) due to diabetes mellitus (DM) and whether strict glucose control will benefit patients with DM on dialysis.

Patients and Methods

Subjects

A total of 120 patients with CKD on hemodialysis in Tungs' Taichung MetroHarbor Hospital participated in this study (HD-10,708). Subjects must be treated in the hemodialysis room of this hospital for more than 6 months and do not need to use auxiliary tools to walk. Essentially, they can ambulate independently and complete all the actions to be tested in this experiment. Subjects with any neurological, orthopedic, visual, or mental impairment, which would hinder them from performing the whole tasks, were excluded from the study.

All subjects provided informed consent, and this study was approved by the hospital ethics committee (IRB: 10733). They all received the same instructions and conditions when testing.

Handgrip strength test

This test aims to measure the maximum isometric contraction of the hand and forearm muscles.

Equipment

A handgrip dynamometer (Model 503 L1, Lafayette Instrument, Lafayette, IN, USA).

Pretest

Explain the procedures to the subject. Calibrate the dynamometer, and adjust it to suit the subject. The subjects should not be allowed to know the experimental procedures before the experiment to reduce the potential "learning effect."

Procedure

The subjects' arms were relaxed on their thighs while sitting on a chair, and they were asked to flex the elbow joint of their dominant hand by 90° with the elbow by the side of the body in the natural position. Put the dynamometer handle into the palm of the subject with the proximal and distal interphalangeal joints of the four fingers showing 90° flexion and the thumb showing 90° abduction. The subjects hold the dynamometer in their hand to be tested, with the arm at right angles and the elbow by the side of the body. The handle of the dynamometer is adjusted if required. The base should rest on the first metacarpal (heel of palm), while the handle should rest on the middle of the four fingers. When ready, the subject performs the maximum isometric grip for 3 s two times with a rest interval of 1 min.[13] No other body movement was allowed. The better maximum handgrip strength (kg) was used for analysis.

Timed up and go test

This test aims to evaluate a person's functional mobility and ability of both static and dynamic balance. It is usually administered to the elderly because it is easy to be completed.

Equipment

A stopwatch, a standard armchair, and a 3-m line on the floor were used.[14]

Pretest

Subjects wear comfortable clothes and shoes. Explain the procedures to the subject.

Procedure

Subjects were given verbal instructions to rise from an armchair, walk 3.0 m as safely and as quickly as possible, cross the 3.0 m mark placed on the floor, turn around, and walk back to sit down in the chair. The test's score is the time (seconds) the subject takes to finish the test. Subjects were asked to complete the TUG test 2 times with resting for 5 min, and the shorter one[10] was used for analysis.

Laboratory evaluation

Routine laboratory tests (basic metabolic panel, calcium, phosphate, albumin, and complete blood count) were performed using an automated analyzer. Serum albumin was measured using the bromocresol green method. High-sensitivity C-reactive protein was measured using a particle-enhanced immunoturbidimetric assay.

Body composition measurements

Bioimpedance spectroscopy (BIS) measurements were performed using a Body Composition Monitor (BCM) (Fresenius Medical Care) before the midweek dialysis session, in a supine position after a 5-min rest. Electrodes were placed on the hand and foot contralateral to the arteriovenous fistula. Basic demographic data of the patient (sex, age, height, and weight) were entered into the BCM-BIS device. The BCM measures whole-body impedance over 50 frequencies (from 5 kHz to 1 MHz) and determines extracellular and total body resistance by Cole

modeling[15] to estimate extracellular water and intracellular water using the fluid volume model.[16,17] The 3-compartment body composition model uses these volumes to separate the body weight into normally hydrated lean tissue mass, normally hydrated adipose tissue mass, and excess fluid (or overhydration) (c). The data obtained from BIS measurements were as follows: Lean Tissue Index (LTI), a quotient of lean mass and height squared, and Fat Tissue Index (FTI), a quotient of fat mass and height squared. Patients with sarcopenia were defined as those with LTI lower than the 10th percentile for their age and gender (minus values of LTI). The reference values of LTI were defined as values between the 10th percentile and the 90th percentile for age and gender. The reference values of FTI were defined as values between the 10th percentile and the 90th percentile for age and gender.

Statistical analysis

Statistical analysis was performed to analyze the relationship between the common biomarkers and the physical characteristic variables, the handgrip strength test, and the TUG test using multilinear regression, Pearson's correlation, and Welch two-sample *t*-test (The R Project for Statistical Computing, available at https://www.r-project.org/). Continuous variables were expressed as their means and standard deviations, and categorical variables were expressed as their counts and composition of the participants. Additionally, the means and standard deviations for variables were calculated and summarized in a table format.

Results

Characteristics of the study participants and preliminary data

The baseline characteristics of the participants are shown in Table 1. The participants (n = 120) were divided into two groups: DM group (n = 56) and non-DM (n = 64). There were significant differences in the average of dialysis vintage (months), Kt/V (dialyzer clearance of urea × dialysis time/volume of distribution of urea), triglyceride, FTI, and LTI between the two groups. Additionally, the average of TUG and handgrip strength had significant differences between both groups [Table 1].

All patients in our cohort had ESRD and were on hemodialysis. The leading cause of renal failure among our cohort was DM (46.7%), followed by glomerulonephritis (35.8%) and hypertension (10.8%). The remaining causes of renal failure were interstitial nephritis, nephrolithiasis, polycystic kidney disease, kidney cancer, and systemic lupus erythematosus (6.7%) [Table 2].

Identifying potential confounding variables impacting the study's results

As the primary objective of this study was to study the relationship between the TUG test and handgrip strength, identifying potential confounding variables within our study results was important. The multilinear regression method was selected as the mode of multivariate analysis. Multilinear regression was performed on TUG and handgrip strength. Furthermore, the data were filtered across all patients on hemodialysis, DM patients and non-DM patients. The results are shown in Tables 3 (TUG) and 4 (handgrip strength).

Tables 3 and 4 show that albumin and LTI are significant predictor variables predicting TUG. In predicting handgrip strength, gender, and kt/V were meaningful predictor variables across its three groups (all patients, DM, and non-DM groups). However, no common variables could significantly predict both TUG and handgrip strength, which removes the possibility of confounding variables. Thus, the analysis and dataset did need adjustment.

Table 1: Baseline characteristics of the study participants

Variable	Mean±SD			*P*
	All (n=120)	DM (n=56)	Non-DM (n=64)	
Gender (number of male), *n* %	75 (62.5%)	38 (67.85%)	37 (57.81%)	0.409
Age (years)	57.7±10.4	60.5±9.5	55.2±10.5	0.005*
Dialysis vintage (months)	73.4±62.1	44.5±31.3	98.6±7	0.043*
Kt/V	1.7±0.2	1.6±0.2	1.8±0.2	0.001*
Hemoglobin (g/dL)	11.2±1.7	11.3±1.8	11.2±1.6	0.614
Albumin (g/dL)	4±0.3	3.9±0.3	4.0±0.3	0.268
Cholesterol (mg/dL)	164.1±37.7	163.4±38.0	164.8±37.7	0.842
Triglyceride (mg/dL)	170.6±127.2	196.6±127.6	147.9±123.4	0.036*
HbA1c (%)	7.3±1.6	7.4±1.7	6.7±1.3	0.251
BMI (kg/m^2)	24.8±3.9	25.5±4.1	24.3±3.7	0.104
FTI (kg/m^2)	14.5±2.7	10.7±4.4	8.8±3.9	0.016*
LTI (kg/m^2)	9.7±4.2	13.9±2.5	15.1±2.7	0.014*
TUG (s)	8.95±2.24	9.51±2.28	8.30±2.14	0.042*
Handgrip strength (kg)	38.5±23.1	35.9±20.8	43.8±24.02	0.039*

*: P<0.05, DM: Diabetes mellitus, HbA1c: Glycated hemoglobin A1c, Kt/V: Dialyzer clearance of urea×dialysis time/volume of distribution of urea, SD: Standard deviation, BMI: Body mass index, FTI: Fat tissue index, LTI: Lean tissue index, TUG: Time up and go

Relationship between handgrip strength and metabolic variables and walking speed

The correlation coefficient between handgrip strength and the TUG test was shown to be significant at − 0.39. This showed a strong negative correlation between the TUG test and strength, which indicated that the weaker the participant, the longer it took for the participant to complete the TUG test [Figure 1a]. Furthermore, we examined factors related to their nutritional status, including albumin [Figure 1b], or body composition, including body mass index (BMI) and LTI [Figure 1c and d], and their relationship to completing the TUG test. When assessing the association of these three variables with the TUG test, only BMI did not have any significant correlation with the TUG test [Figure 1c]. Furthermore, it is worth noting that the dialysis vintage was not associated with either the TUG test or grip strength.

Focusing on patients with diabetes mellitus

Focusing on the most common cause of renal failure in patients, that is, DM, we repeated the analysis in the previous section. Among the 47 participants with renal failure due to DM, we also found that grip strength and the TUG test had a significant negative correlation with each other [Figure 2a]. Interesting, the original variables that were shown to be significantly correlated with the TUG test (albumin and LTI) in the whole cohort did not show any significant correlation with the TUG test in this subset of patients [Figure 2b and d]. BMI continued to be not significantly correlated with the TUG test [Figure 2c].

Table 2: Causes of renal failure of the 120 hemodialysis patients

Causes of chronic renal failure	*n* (%)
DM	56 (46.7)
Glomerulonephritis	43 (35.8)
Hypertension	13 (10.8)
Kidney stone	2 (1.7)
Kidney cancer	2 (1.7)
Systemic lupus erythematosus	2 (1.7)
Polycystic kidney disease	1 (0.8)
Interstitial nephritis	1 (0.8)
All	120 (100)

DM: Diabetes mellitus

Table 3: Variable coefficients for predicting time up and go

Variables	Group (estimated coefficients)		
	All patients (*n* = 120)	DM (*n* = 56)	Non-DM (*n* = 64)
Gender (male)	−0.271	−0.119	0.383
Dialysis vintage	0.006	0.019	0.002
DM	1.138	-	-
Kt/V	−0.012	−0.220	−0.017
Hemoglobin	−0.068	0.242	−0.276
Albumin	−1.103*	−2.761*	−2.363*
Cholesterol	−0.007	−0.012	0.002
Triglyceride	−0.001	−0.002	−0.000
HbA1c	−0.029	−0.343	−0.219
BMI	0.139	−0.460	0.704
FTI	−0.047	0.581	−0.607
LTI	0.301*	0.418	−0.655*

*P<0.05. DM: Diabetes mellitus, HbA1c: Glycated hemoglobin A1c, Kt/V: Dialyzer clearance of urea × dialysis time/volume of distribution of urea, BMI: Body mass index, FTI: Fat tissue index, LTI: Lean tissue index

Tighter hemoglobin A1c control does not equate to better handgrip strength or timed up and go results

We examined whether a tighter glucose control among patients on hemodialysis with DM had any benefit in terms of grip strength and mobility. These patients (47 patients) were divided based on whether their glycated hemoglobin A1c (HbA1c) was below 7% (29 patients) or equal to or >7% (18 patients). No significant difference in our measured variables was observed between these two subsets of patients, as shown in Table 5.

Next, we compared grip strength and the TUG test between both groups. Grip strength and time to complete the TUG test did not differ significantly between these two groups [Figure 3a and b].

Discussion

This study investigated various biomarkers' association with the TUG test, a commonly used test to assess one's mobility, in patients with ESRD on hemodialysis. The study results showed that grip strength was significantly correlated with the TUG test. Additionally, LTI and albumin were also significantly correlated with the TUG test. However, the value of using grip strength as a surrogate marker to assess the TUG test became evident among patients with ESRD, whether or not caused by DM. In this stratified group of patients, grip strength remained the sole biomarker of the aforementioned three markers that had a significant correlation with the TUG test.

Among the many comorbidities that can develop in patients with CKD, gait abnormality can increase mortality rates by increasing the frequency of falls.[18,19] The TUG test is a well-established assessment of mobility in elderly patients.[5] The test has been shown to have a strong correlation with falls and has been commonly used among patients with CKD.[4] However, a previous article[8] showed that objective physical tests, similar to the TUG test, often require patients to exert physical energy and effort. Unfortunately, in some cases, patients cannot participate due to their chronic illnesses. Particularly in dialysis centers, where patients are already at an increased risk of falls,[6] there is a need to have an increased number of trained medical staff and allotted time for these assessments to minimize the risk of falls.

In patients with DM on hemodialysis, there is an even greater need for clinicians to assess patients' mobility status. DM is an independent risk factor for gait instability.[20] There have been multiple proposed theories as to why this is the case.[21] Other

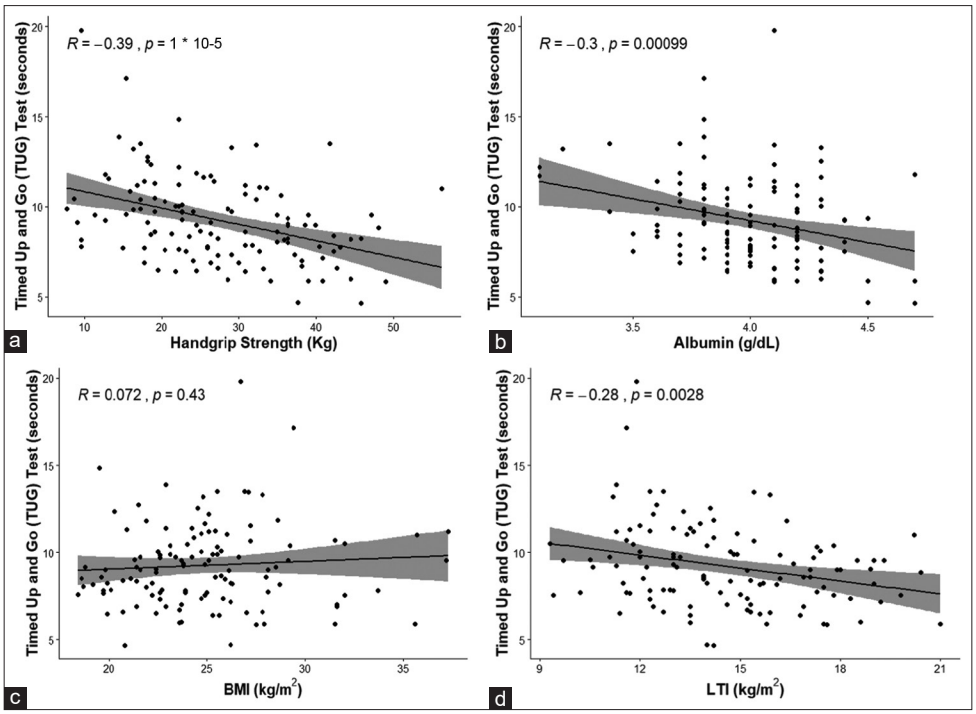

Figure 1: In all 120 patients, the TUG test versus (a) handgrip strength test ($R = -0.39$, $P = 1 * 10\text{-}5$), (b) albumin ($R = -0.3$, $P = 0.00099$), (c) BMI ($R = 0.072$, $P = 0.43$), and (d) LTI ($R = -0.28$, $P = 0.0028$). Handgrip strength, albumin, and LTI were shown to be significantly correlated with the TUG test. BMI did not correlate significantly with the TUG test. TUG: Timed up and go, BMI: Body mass index, LTI: Lean tissue index

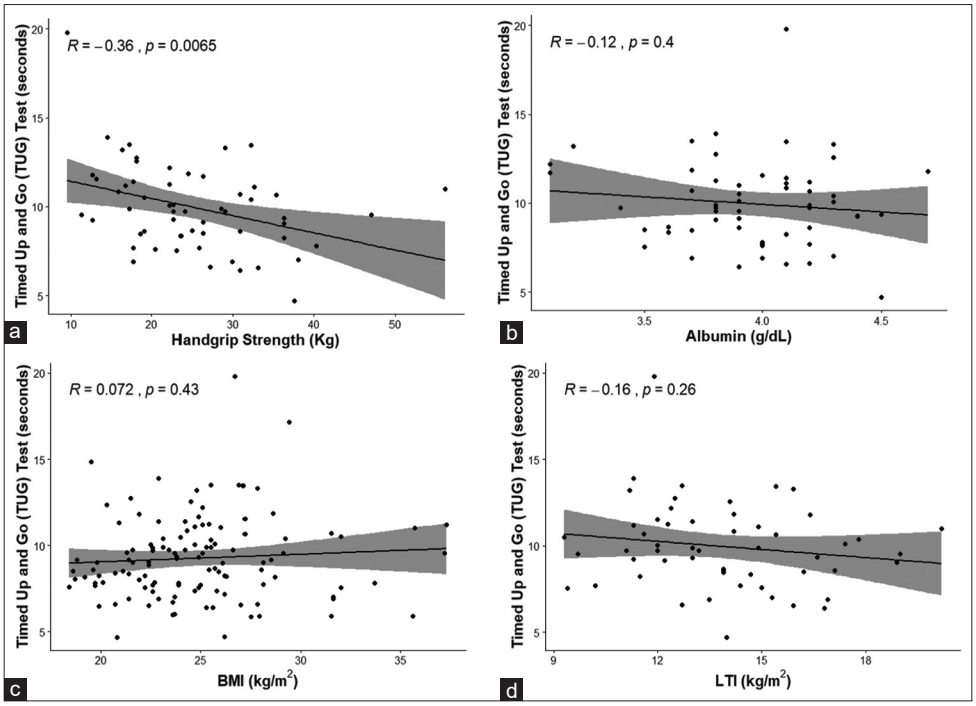

Figure 2: In 47 patients with DM, TUG test versus (a) handgrip strength test ($R = -0.36$, $P = 0.0065$), (b) albumin ($R = -0.12$, $P = 0.4$), (c) BMI ($R = 0.072$, $P = 0.43$), and (d) LTI ($R = -0.16$, $P = 0.26$). The only biomarker found to correlate with the TUG test was handgrip strength. DM: Diabetes mellitus, TUG: Timed up and go, BMI: Body mass index, LTI: Lean tissue index

than peripheral neuropathy,[22] there are metabolic factors, such as decrease in lean tissue body mass and muscle mass,[21,23] which should be considered when exploring fall etiologies in patients with DM, which are only further compounded by kidney failure.[24] Another plausible explanation is the limited diet options as a result of being restricted by both

Table 4: Variable coefficients for predicting handgrip strength

Variables	Groups (estimated coefficients)		
	All patients (n = 120)	DM (n = 56)	Non-DM (n = 64)
Gender (male)	18.989*	8.326*	26.794**
Dialysis vintage	−0.065	−0.167	−0.042
DM	−9.430	-	-
Kt/V	0.080*	−2.291**	0.075*
Hemoglobin	1.537	2.700	3.990
Albumin	4.106	−0.080	11.116
Cholesterol	0.012	0.029	0.031
Triglyceride	0.005	−0.016	0.017
HbA1c	0.332	−0.304	1.584
BMI	−1.705	6.274	−9.052
FTI	3.096	−4.353	10.753
LTI	5.554	−0.427	9.723

*P<0.05, **P<0.01. DM: Diabetes mellitus, HbA1c: Glycated hemoglobin A1c, Kt/V: Dialyzer clearance of urea × dialysis time/volume of distribution of urea, BMI: Body mass index, FTI: Fat tissue index, LTI: Lean tissue index

Table 5: The nutritional biomarkers of glycated hemoglobin A1c <7% or ≥7% in the 47 diabetic patients

Variable	Mean ± SD		P
	<7% (n = 29)	≥7% (n = 18)	
Hemoglobin (g/dL)	11.68 ± 1.81	11.01 ± 1.57	0.19
Albumin (g/dL)	3.99 ± 0.38	3.99 ± 0.27	0.99
Cholesterol (mg/dL)	161.24 ± 40.24	160.33 ± 40.28	0.94
Triglyceride (mg/dL)	188.31 ± 113.23	188.94 ± 128.7	0.99
BMI (kg/m^2)	25.62 ± 3.62	24.53 ± 3.96	0.35
FTI (kg/m^2)	13.38 ± 2.23	13.87 ± 2.7	0.52
LTI (kg/m^2)	11.42 ± 4.82	9.92 ± 3.71	0.24

BMI: Body mass index, FTI: Fat tissue index, LTI: Lean tissue index, SD: Standard deviation

limiting potassium and protein due to kidney disease and carbohydrates due to DM. However, there has been a recent change in perception toward protein restriction in patients on dialysis.[25] Even though albumin and LTI are surrogate markers for nutrition status and muscle mass, within our cohort, patients who developed ESRD due to DM showed no correlation between TUG and albumin or LTI. However, grip strength was the only significantly correlated factor associated with the TUG test. This key finding is especially important for physicians to be aware of because the commonly used biomarkers for nutritional status and muscle mass are not sufficient to assess the mobility status of patients with DM. Instead, evaluating a patient's muscle function status with grip strength will be a better-suited test to determine whether the patient can exert the needed physical effort for mobility testing.

In patients with DM on dialysis, glucose management remains a contentious topic among clinicians.[26] There are varying opinions on whether a tighter or looser control of glucose should be implemented for this particular group of patients.[27-29] More recently, there has been more evidence undermining tight glycemic control in patients on dialysis.[30,31] Studies showed that patients with DM with CKD or on dialysis can experience an increased frequency of hypoglycemic episodes,[32,33] which can lead to more syncopal episodes and falls.[34,35] Thus, clinicians are often tasked with maintaining a balance between preventing the progression of microvascular diseases associated with DM and not increasing the risk of falls due to hypoglycemia. In this study's cohort, the subset of patients with ESRD caused by DM was further divided based on whether they could keep their HbA1c below 7%, which was set by the dialysis unit's nephrologists as the goal for patients with DM. No significant differences in grip strength and TUG test were observed between these two groups: HbA1c ≥7% and <7% [Figure 3]. Furthermore, for both groups, no significant differences in BMI, LTI, albumin, and gender were observed. Thus, at least from the standpoint of preventing falls and maintaining mobility, keeping HbA1c below 7% in patients with DM on dialysis showed no benefit.

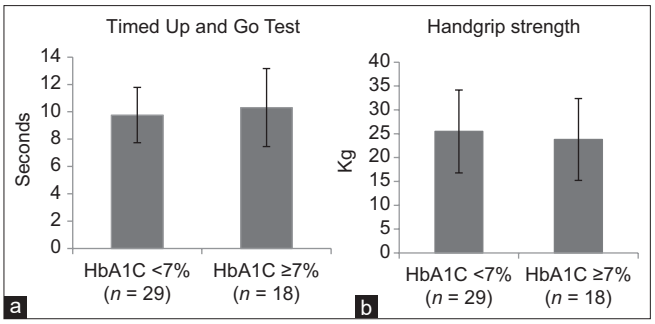

Figure 3: The 47 patients with DM were divided into two groups: HbA1c <7% and HbA1c ≥7%. (a) The mean duration of TUG completion was shown in both groups. (b) The mean force of the handgrip strength test was shown in both groups. As can be seen from both figures, no significant differences in the TUG test or handgrip strength were observed. DM: Diabetes mellitus, HbA1c: Hemoglobin A1c, TUG: Timed up and go

Conclusion

This study established that grip strength has a significant correlation with the TUG test. In patients on dialysis who are at risk of losing their mobility, measuring grip strength can be a reliable anthropometric measurement as an initial screen to determine whether patients can exert the necessary physical effort to perform the TUG test. This may prevent patients from unnecessary falls during the mobility assessment. Moreover, the utility of grip strength is further highlighted among patients on dialysis with ESRD due to DM because it was the only anthropometric measurement that was still significantly correlated with the TUG test. Additionally, we evaluated the possible role of strict glycemic control on the risk of falls in patients with DM on hemodialysis. Interestingly, we found that the goal of reducing and maintaining the HbA1c below 7% was found to provide no benefits in terms of muscle strength and mobility. Gait abnormality is inevitable morbidity for patients on dialysis. Thus, it is of the utmost importance for

healthcare providers to screen patients' mobility status and provide counseling and support as appropriate.

Financial support and sponsorship

Nil.

Conflicts of interest

Prof. Paik-Seong Lim, an editorial board member 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.

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Original Article

Clinical feature and outcome of spontaneous pneumomediastinum

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Abstract

Background: Spontaneous pneumomediastinum is an uncommon disorder. Spontaneous pneumomediastinum was first described by Laennec in the early 19th century, and the first case was reported by Hamman in 1939. Spontaneous pneumomediastinum is the presence of free air in the mediastinum that is not preceded by infection, trauma, hollow-organ perforation, surgery, or other iatrogenic injuries. **Objectives:** This study aimed to present our experience with spontaneous pneumomediastinum, clarify its clinical presentation and course, and determine effective diagnostic tests and what constitutes unnecessary medical intervention. **Methods:** All patients presenting with spontaneous pneumomediastinum between October 2000 and October 2012 were retrospectively analyzed. Data, including clinical findings, precipitating factors, diagnostic investigations, and treatment outcomes, were collected. **Results:** A total of 15 patients with spontaneous pneumomediastinum were identified (14 males and 1 female with a mean age of 24.1 years). Chest pain, dyspnea, and cough were the most common clinical presentations. Of the 15 patients, 6 had a previous history of pulmonary disease: four had a history of asthma and two had a history of bronchiectasis. Precipitating factors, including, in order, upper respiratory tract infection, asthma exacerbation, and violent cough, were identified in 14 patients. Subcutaneous emphysema was observed in 12 patients. Of the 15 patients, 10 were diagnosed by plain chest radiology and 5 by chest computed tomography. Conservative treatment was performed on 14 patients. Mediastinal exploration was performed in one patient, and the operation findings revealed minimal air surrounded by soft tissue in the right paratracheal area. All patients were discharged in excellent condition. **Conclusion:** Spontaneous pneumomediastinum is an uncommon disorder that primarily affects young adult males. Chest pain and dyspnea are the most common clinical presentations. The clinical course of spontaneous pneumomediastinum is very benign, and the disease is self-limiting. Unnecessary aggressive therapy and invasive diagnostic procedures should be limited.

Keywords: Mediastinum emphysema, spontaneous pneumomediastinum, subcutaneous emphysema

Introduction

Spontaneous pneumomediastinum was first described by Laennec in the early 19th century, and the first case was reported by Hamman in 1939.[1] Spontaneous pneumomediastinum is the presence of free air in the mediastinum that is not preceded by infection, trauma, hollow-organ perforation, surgery, or other iatrogenic injuries.[2-7] The pathogenesis occurs secondary to the rupture of a pulmonary alveolus bordering the bronchiole or pulmonary vessels. The air dissects from the hilum along the peribronchovascular sheath and spreads into the mediastinum.[8]

In this case series, 15 cases of spontaneous pneumomediastinum (including a patient with chronic spontaneous pneumomediastinum who underwent mediastinal exploratory surgery) were reviewed. This study aimed to investigate the clinical features of spontaneous pneumomediastinum and determine effective diagnostic tests and what constitutes unnecessary medical intervention.

Methods

Setting

This retrospective study was conducted at Buddhist Dalin Tzu

Received: 19-Feb-2021 **Revised:** 12-Apr-2021 **Accepted:** 16-Apr-2021
Published: 13-Dec-2022

Access this article online

Quick Response Code:

Website: https://journals.lww.com/TMJ

DOI: 10.4103/ETMJ.TMJ-110008

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How to cite this article: Huang C. Clinical feature and outcome of spontaneous pneumomediastinum. Tungs Med J 2022;16:61-5.

Chi Hospital, a tertiary-level teaching hospital. This hospital has 600 acute care beds, and the intensive care unit contains 59 beds.

Participants

All patients presenting with spontaneous pneumomediastinum who were admitted to the Buddhist Dalin Tzu Chi Hospital between October 2000 and October 2012 were enrolled. Cases of pneumomediastinum involving infection, trauma, hollow-organ perforation, surgery, and other iatrogenic injuries were excluded.

Data collection

Data on demographics, clinical symptoms and signs, precipitating factors, history of underlying lung diseases, imaging results, additional diagnostic test results, and clinical outcomes were obtained from the hospital's clinical information systems and medical charts.

Ethics approval and consent to participate

This study was a retrospective analysis of medical records. The study represented the lowest risk to the research subject, and all information was made anonymous before being made available for research. The study was conducted in accordance with the Declaration of Helsinki 1975 (revised Hong Kong 1989). The study protocol was approved by the Research Ethics Committee of the Buddhist Dalin Tzu Chi General Hospital (IRB Approval No. B1020410). Due to the retrospective nature of the study, the requirement for informed consent was exempted by the Research Ethics Committee.

Results

Demographics

A total of 15 patients were included in the study (14 males and 1 female). The mean age was 24.1 years (range 10-87 years). Of the 15 patients, 12 were <20 years, and 3 were more than 20 years (35, 51, and 87 years old).

The most commonly reported symptoms were chest pain (eight cases, 53.3%), dyspnea (eight cases, 53.3%), cough (eight cases, 53.3%), and neck pain (six cases, 40%). Of the 15 patients, 6 had a previous history of pulmonary disease: four had a history of asthma and two had a history of bronchiectasis. The precipitating factors were, in order, upper respiratory tract infection, asthma exacerbation, and violent cough [Table 1]. No cases of illegal drug inhalation were reported. Only one case had no reported specific trigger.

Table 1: Clinical characteristics of spontaneous pneumomediastinum patients (*n*=15)

	n (%)
Presenting symptoms	
Chest pain	8 (53.3)
Dyspnea	8 (53.3)
Cough	8 (53.3)
Neck pain	6 (40.0)
Dysphagia	0
Precipitating factors	
Respiratory tract infection	6 (40.0)
Asthma exacerbation	4 (26.7)
Violent cough	3 (20.0)
Athletic activity	1 (6.8)
Drug abuse	0
Vomiting	0

The patients underwent plain chest radiology, and spontaneous pneumomediastinum was identified in 10 patients (66.6%) based on the results. The remaining five patients were diagnosed based on chest computed tomography (CT) scans. Subcutaneous emphysema was noted in 12 patients (80%). The posteroanterior chest radiographs involved a case of asthma exacerbation with spontaneous pneumomediastinum and subcutaneous emphysema [Figure 1]. In two patients, pneumothorax was detected based on chest CT scans. Additional diagnostic procedures, including bronchoscopy, esophagogastroduodenoscopy, and esophagography, were performed in four patients, which did not yield any pathological findings.

Conservative treatment was performed on 14 patients, and they were discharged in excellent condition. Mediastinal exploratory surgery was performed on the remaining patient. The patient was a 52-year-old male who had a productive cough with hemosputum for several days. He underwent a chest CT scan in February 2010 [Figure 2], which revealed bronchiectasis affecting both lungs and free air in the right upper paratracheal area. Episodes of productive cough with hemosputum continued to occur on and off for several months. He underwent a chest CT scan in December 2010, which revealed unchanged bronchiectasis and mild progression of the right upper paratracheal free air [Figure 3]. He underwent bronchoscopy and esophagography before the mediastinal exploratory surgery, which revealed negative findings. The operation findings showed minimal air surrounded by soft tissue in the right paratracheal area and no fistula. The patient was discharged in excellent condition 2 days later.

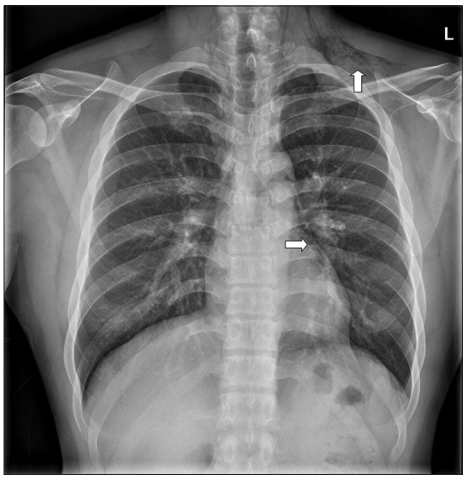

Figure 1: Posteroanterior chest radiology of spontaneous pneumomediastinum and subcutaneous emphysema. Subcutaneous emphysema (upper arrow) and pneumomediastinum (lower arrow)

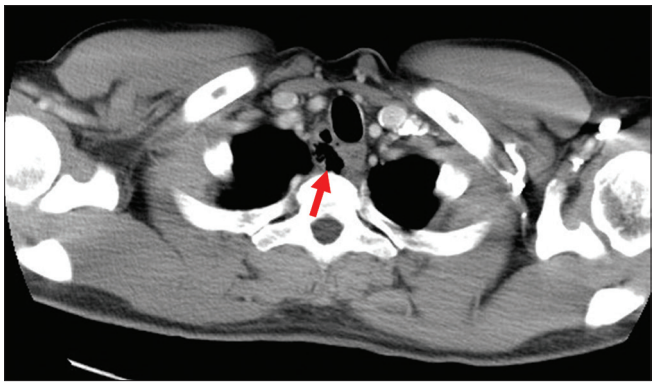

Figure 2: CT of the chest in February 2010 showed free air over the right upper paratracheal area. CT: Computed tomography

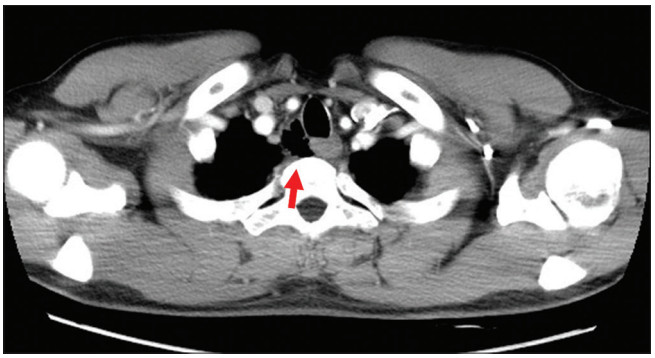

Figure 3: CT of the chest in December 2010 showed mild progression of the right upper paratracheal free air. CT: Computed tomography

Discussion

Spontaneous pneumomediastinum is uncommon and primarily affects young adult males. It has been reported that more than 80% of patients with spontaneous pneumomediastinum were with a mean age of <25 years.[5,6,9-22] The incidence of spontaneous pneumomediastinum in patients presenting at hospital emergency units has been reported to be 1 in 800-42,000.[2,9,23-25] Newcomb and Clarke reported that the incidence of spontaneous pneumomediastinum was 1 in 29,670.[17] Macia *et al*. reported that the incidence of spontaneous pneumomediastinum treated at the emergency department was 1 in 44,511.[5] However, the incidence is probably underestimated because the symptoms are not specific, some signs may go unnoticed, and some radiographic signs are difficult to identify.

Dajer-Fadel *et al*. reported in their review that pulmonary comorbidities were present in 22% of patients with spontaneous pneumomediastinum. The previous pulmonary diseases, in order of frequency, associated with spontaneous pneumomediastinum patients include asthma, interstitial lung disease, chronic obstructive pulmonary disease, and bronchiectasis.[26] In this case series, asthma was the most common pulmonary comorbidity, and bronchiectasis was the second most common.

The most common presenting symptoms of spontaneous pneumomediastinum reported in the literature include, in order, chest pain, dyspnea, neck pain, cough, and dysphagia. Patients in this case series had the same symptoms. Subcutaneous emphysema is the most common sign of spontaneous pneumomediastinum. The reported frequency varies among studies, with a range of 45%–70%.[4,5,9,27] In this case series, 80% of the cases had subcutaneous emphysema, which is more than the rates reported in the literature.

Pneumothorax involves disruption of the parietal pleura with gas in the pleural space. It is classified as primary spontaneous pneumothorax (with no apparent underlying lung disease), secondary spontaneous pneumothorax (due to a complication of underlying lung disease), and traumatic pneumothorax (due to physical trauma to the chest or a complication of a health-care intervention).[28] Some cases of spontaneous pneumomediastinum present with air leakage into the pleural space through the visceral pleura, with the parietal pleura remaining intact.[22] The pathogenesis and etiology of pneumothorax and spontaneous pneumomediastinum with pneumothorax differ. In this study, pneumothorax, which was not identified by plain chest radiology, was noted on chest CT scans in two patients. Furthermore, two cases of minimal pneumothorax were self-limiting. A few cases of spontaneous pneumomediastinum coexisting with pneumothorax have been reported in the literature.[9,14,17,18,29,30] However, in the literature on spontaneous pneumomediastinum, there are three cases with secondary pneumothorax that necessitated surgical intervention.[17,29,30]

Dajer-Fadel *et al*. reported in their review that the precipitating factors of spontaneous pneumomediastinum were identified in 66% of patients. These precipitating factors included athletic activity, drug abuse, violent cough, asthma exacerbation, vomiting, and respiratory tract infection, which are commonly found in spontaneous pneumomediastinum patients.[26] In this case series, the common precipitating factors were upper respiratory tract infection and asthma exacerbation. There were no cases involving illegal drug inhalation, which may be due to the fact that our hospital is located in a rural area.

Plain chest radiology remains the standard for diagnosing spontaneous pneumomediastinum. A lateral view is necessary because up to 50% of cases may remain undiagnosed if only posteroanterior radiography is used. In some cases of spontaneous pneumomediastinum, the diagnosis cannot be made based on plain chest radiology and requires chest CT scans. However, chest CT scans should not be routinely performed for spontaneous pneumomediastinum patients. Instead, they should be reserved for cases in which the diagnosis of spontaneous pneumomediastinum is unclear based on plain chest radiology.[16,31-32] In this case series, spontaneous pneumomediastinum was identified by plain chest radiology in only 10 patients (66.6%), which was less than in other case series in the literature. Additional invasive diagnostic procedures were performed in four of our patients, which did not yield any pathological

findings. These findings of additional invasive diagnostic procedures are consistent with those reported by other authors.[5,9,10,14,18] Invasive diagnostic procedures should be considered only for cases in which the diagnosis is unclear or the possibility of organ perforation cannot be ruled out, as the clinical course of spontaneous pneumomediastinum is very benign. It should be kept in mind that potentially life-threatening complications might arise. Furthermore, Boerhaave syndrome must be considered in any patient with a history of vomiting followed by chest pain with dyspnea.[33] Spontaneous tension pneumomediastinum requiring surgical intervention is very rare. Tension pneumomediastinum is most commonly associated with traumatic rupture of the tracheobronchial tree.[34-37] However, traumatic pneumomediastinum does not fit the definition of spontaneous pneumomediastinum. In this case series, one patient underwent mediastinal exploratory surgery for chronic spontaneous pneumomediastinum, and no fistula was observed. This surgical intervention was deemed an incident of excessive medical intervention.

The three main medical therapies for treating spontaneous pneumomediastinum include bed rest, analgesics, and oxygen therapy.[5,7,23] Most cases had excellent outcomes. Figure 4 shows an algorithm for the diagnosis and management of pneumomediastinum.

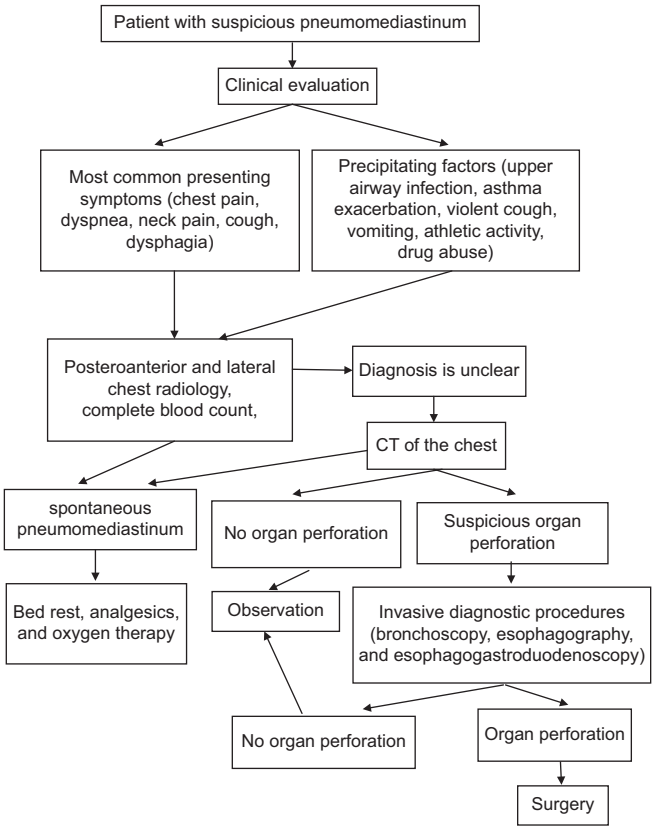

Figure 4: Algorithm for the diagnosis and management of pneumomediastinum

Conclusion

Spontaneous pneumomediastinum is an uncommon disorder that primarily affects young adult males. The most common clinical presentations are chest pain and dyspnea. Spontaneous pneumomediastinum was identified by posteroanterior and lateral chest radiology in most patients. Chest CT scans should be reserved for cases in which the diagnosis is unclear. The clinical course of spontaneous pneumomediastinum is very benign, and the disease is self-limiting. Unnecessary aggressive therapy and invasive diagnostic procedures should be limited. Surgical intervention does not play an important role in treating spontaneous pneumomediastinum.

Availability of data and materials

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

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Original Article

Exploring factors associated with uremic pruritus

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Abstract

Background: Uremic pruritus not only directly affects patients' health but also may reduce their quality of life. Few studies have examined the factors associated with pruritus disturbance among patients on hemodialysis. **Objectives:** This study aimed to compare the differences between patients on hemodialysis with and without uremic pruritus and explore the factors associated with uremic pruritus. **Methods:** A cross-sectional correlational design with convenience sampling was used in this study. Patients on hemodialysis in a regional hospital in southern Taiwan were recruited. A self-administered questionnaire was used, and some serum biochemistry data were collected from medical records. Research tools, including demographic characteristic form, pruritus visual analog scale (pruritus VAS), and the 5-D itch scale, were used. Multiple regression analysis was performed to explore the factors related to pruritus disturbance. **Results:** A total of 361 patients were included in this study. Most of the participants (n = 283, 78.4%) had pruritus. The two groups of patients with and without pruritus were different in diabetes status and creatinine and C-reactive protein (CRP) levels. The mean score of pruritus VAS was 5.0 in participants with pruritus, indicating that their pruritus was moderate. The level of pruritus disturbance was moderate to low (mean = 10.56), and "pruritus-affected sleep" possessed the highest score. Patients with higher CRP and pruritus gave higher scores for pruritus disturbance. Primary disease, heparin use, serum albumin, calcium, creatinine, blood urea nitrogen, CRP, and subjective pruritus severity could significantly predict disturbance from pruritus (R^2 = 28.5%, P < 0.05). Maintaining serum biochemistry such as CRP within the normal range may reduce pruritus feeling. **Conclusion:** Patients' serum biochemistry is related to uremic pruritus. Health-care professionals should regularly assess patients' CRP and patients' self-evaluation of itching so that disturbances from pruritus can be detected earlier and the possible factors can be found and treated. These strategies may provide appropriate care and maintain the patients' quality of life.

Keywords: Hemodialysis, pruritus, pruritus disturbance, uremia

Introduction

The prevalence of hemodialysis in Taiwan rose from 2285 to 2584 people per million between 2007 and 2010, according to the United States Renal Data System 2013 annual report, representing the world's highest prevalence rate.[1] The Taiwan Society of Nephrology reported in the Taiwan Renal Registry Data System that most patients (89.7%) with end-stage renal disease (ESRD) chose hemodialysis as their renal replacement therapy. Furthermore, 50%–90% of patients on hemodialysis have experienced pruritus. Pruritus is more common and severe among older patients on hemodialysis. Additionally, 20%–50% of patients expressed that pruritus affects their lives.[2,3] Severe pruritus can lead to sleep disorders, anxiety, depression, and social dysfunction. Patients with pruritus with ESRD had a higher mortality rate, 23% higher than those without pruritus.[2,4,5] The mechanism of pruritus is complex because the pathogenesis of pruritus involves various transmitters and receptors, and the neural pathway of pruritus remains unclear. The causes of pruritus include (1) skin diseases such as urticaria

Received: 09-Feb-2021 **Revised:** 13-Aug-2021 **Accepted:** 13-Aug-2021
Published: 13-Dec-2022

Access this article online

Quick Response Code:

Website: https://journals.lww.com/TMJ

DOI: 10.4103/ETMJ.TMJ-110005

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How to cite this article: Wu CF, Hsiao YC, Yeh TP, Hung PH, Chen HC, Tsai RY, *et al*. Exploring factors associated with uremic pruritus. Tungs Med J 2022;16:66-72.

and xerosis, (2) metabolic problems such as uremia and endocrine abnormalities, (3) neuropathy, (4) psychiatric or psychosomatic disease, and (5) multiple comorbidities.[6]

The mechanisms of pruritus in patients with uremia have not been confirmed in consensus. Some possible mechanisms have been found from clinical observation: (1) toxins accumulation on the skin, (2) peripheral neuropathy, and (3) the opioid-activated system inducing skin paresthesia and pruritus.[7,8] It happens more commonly in the elderly, males, and patients with diabetes.[9-11] Patients on hemodialysis with diabetes have more serious pruritus problems than those without diabetes,[7,9-12] and higher pruritus rates are accompanied by higher glycated hemoglobin (HbA1c).[13] Chiu *et al*. in 2008[14] reported that high-flux dialyzers were associated with less pruritus. Excessive serum phosphate, calcium, magnesium, C-reactive protein (CRP), and hyperparathyroidism levels and lower Kt/V levels are associated with higher pruritus levels.[7-11,15] However, several studies have suggested that pruritus is not associated with excessive serum calcium and phosphate or hyperparathyroidism levels.[7,11,16] Research results on the pruritus-related factors are inconsistent. Thus, further investigation is needed.

This study assumed that diabetes, older adults, males, dialyzers, HbA1c, CRP, hyperparathyroidism, and Kt/V are significantly related to pruritus problems in patients on dialysis. This study aimed to explore the important factors associated with pruritus in patients on hemodialysis.

Methods

Study design and participants

This study applied a cross-sectional correlational research design with convenience sampling to recruit patients on hemodialysis in a hospital in southern Taiwan. The data collection was from December 2014 to April 2015. The participants were asked to complete a questionnaire within 1 week before or after performing a monthly blood test. Inclusion criteria included (1) age ≥20 years, (2) voluntary participation, (3) having received regular hemodialysis for 3 months or longer, and (4) being conscious and able to communicate in Mandarin or Taiwanese. Exclusion criteria included (1) having a history of schizophrenia and (2) having skin diseases such as scabies, urticaria, and dermatophytosis. The whole study process was self-checked using the STROBE checklist; see Supplementary File 1.

Ethical consideration

This study was approved by the Institutional Review Board of the data collection hospital (IRB No. 103058). Informed consent was obtained voluntarily from the participants after information regarding this study was verbally explained in detail.

Measurements

Measurement tools, including visual analog scale of pruritus (VAS pruritus), 5-D itch scale, and demographic information, were used in this study. Serum biochemistry data, including serum calcium, phosphate, intact parathyroid hormone, hemoglobin, albumin, CRP, and HbA1c, and hemodialysis treatment types, including included each dialysis duration, total number of years on dialysis, whether the patient had received hemodiafiltration treatment, heparin used, and Kt/V, were collected from medical records.

Pruritus

The VAS has been adopted in many studies to assess individual subjective feelings, such as pain. This scale has been widely used to measure the subjective degree of pruritus in patients.[4,17,18] It possesses good reliability and validity as well as an intraclass coefficient correlation (ICC) >0.8. In this study, a horizontal scoring system supplemented with facial expressions was used to ensure that the participants could understand the implications of the scores. On the scale, 0 indicated no pruritus, and 10 represented the most severe pruritus.

Uremic pruritus disturbance

The 5-D itch scale (hereafter referred to as the 5-D scale) was used to understand the disturbance caused by pruritus among participants. The scale was developed by Elman,[19] and the content and scoring method for the questionnaire were described as follows: (1) duration of pruritus: less than 6 h/day (1 point), 6–12 h/day (2 points), 12–18 h/day (3 points), 18–23 h/day (4 points), and 24 h/day (5 points); (2) degree of pruritus in the past 2 weeks: no pruritus (1 point), a little pruritus (2 points), moderate degree of pruritus (3 points), severe pruritus (4 points), and unbearable pruritus (5 points); (3) direction of improvement in the past 2 weeks compared with 1 month ago: complete improvement (1 point); much better, but still feeling itchy (2 points); a little better, but still feeling itchy (3 points); no change (4 points); and itchier (5 points); (4) disability caused by pruritus, under which the subitems of sleep, leisure/social, housework/daily life, work, and school were assessed: not affected (1 point), a little affected (2 points), occasionally affected (3 points), frequently affected (4 points), and always affected (5 points); (5) distribution of pruritus: a total of 16 locations of the body could be selected: 0–2 parts (1 point), 3–5 parts (2 points), 6–10 parts (3 points), 11–13 parts (4 points), and 14–16 parts (5 points). The total scores of these 5 dimensions above would present a final score ranging from 5 points (no disturbance from pruritus) to 25 points (serious disturbance from pruritus). The ICC of the scale was 0.96, and Cronbach's α reached 0.734. Cronbach's α was 0.779 in this study.

Demographic characteristics

Demographic data included 8 items: gender, age, marital status, education level, residence, job, primary diseases, and any other chronic diseases.

Results

Demographic characteristics and hemodialysis types in patients with and without pruritus

Data of 361 patients on hemodialysis were collected. Of the patients, 283 were with pruritus, and 78 were without pruritus. The demographic data of the patients are shown in Table 1. About half of the participants (41.8%) had a primary cause of ESRD due to diabetes. The results showed that diabetes as the primary cause of ESRD was more common in the pruritus group than in the nonpruritus group (44.9% vs. 30.8%, $P < 0.05$). However, no significant difference was observed between both groups.

Serum biochemistry value differences between patients with and without pruritus

Table 2 shows the values of serum biochemistry. The results demonstrated that the creatinine level was significantly lower in the pruritus group than that in the nonpruritus group (median, 10.0 mg/dl vs. 10.7 mg/dl, $P < 0.01$). In contrast, the CRP levels were found to be greater in the pruritus group than in the nonpruritus group (median, 0.36 mg/dl vs. 0.27 mg/dl, $P < 0.05$). Regarding the remaining serum biochemistry data, no significant difference was observed between the two groups.

Pruritus locations, levels, and disturbances

A total of 283 participants (78.39%) had experienced pruritus. The results of pruritus degree and disturbance level are presented in Table 3. The pruritus VAS was used to measure patients' current degree of pruritus (0–10 points). The average degree of pruritus VAS was 5.0 (standard deviation [SD] = 2.51 points), which means that the participants had a medium level of pruritus. In the 5-D scale, the first item was the duration

Table 1: Demographic characteristics and hemodialysis types in the pruritus and no pruritus groups (n=361)

Variable	Total (n=361)	Pruritus (n=283)	No pruritus (n=78)	$P^{\dagger}$
Gender				
Female	174 (48.2)	133 (47.0)	41 (52.6)	0.443
Male	187 (51.8)	150 (53.0)	37 (47.4)	
Age (years)				
<65	194 (53.7)	151 (53.4)	43 (55.1)	0.799
≥65	167 (46.3)	132 (46.6)	35 (44.9)	
Marital status				
Single	63 (17.5)	48 (17.0)	15 (19.2)	0.617
Married	298 (82.5)	235 (83.0)	63 (80.8)	
Education				
Illiteracy	52 (14.4)	42 (14.8)	10 (12.8)	0.719
Literacy	309 (85.6)	241 (85.2)	68 (87.2)	
Residence				
Living alone	19 (5.3)	18 (6.4)	1 (1.3)	0.088
Live with family	342 (94.7)	265 (93.6)	77 (98.7)	
Job				
No	245 (67.9)	190 (67.1)	55 (70.5)	0.681
Yes	116 (32.1)	93 (32.9)	23 (29.5)	
Primary cause of ESRD				
Other cause	210 (58.2)	156 (55.1)	54 (69.2)	0.028
DM	151 (41.8)	127 (44.9)	24 (30.8)	
Number of comorbid diseases				
≤2	114 (31.6)	92 (32.5)	22 (28.2)	0.495
≥3	247 (68.4)	191 (67.5)	56 (71.8)	
Time of dialysis (h)				
≤3.5	34 (9.4)	25 (8.8)	9 (11.5)	0.511
≥4	327 (90.6)	258 (91.2)	69 (88.5)	
Years on dialysis (years)				
<3	139 (38.5)	115 (40.6)	24 (30.8)	0.117
≥3	222 (61.5)	168 (59.4)	54 (69.2)	
High-flux dialysis				
No	182 (50.4)	147 (51.9)	35 (44.9)	0.307
Yes	179 (49.6)	136 (48.1)	43 (55.1)	
Heparin				
Free or zero	116 (32.1)	89 (31.4)	27 (34.6)	0.587
Yes	245 (67.9)	194 (68.6)	51 (65.4)	

†Fisher's exact test. ESRD: End-stage renal disease, DM: Diabetes mellitus

Table 2: Blood biochemical in the pruritus and no pruritus groups (*n*=361)

Item	Population (*n*=361)	Pruritus group (*n*=283)	No pruritus group (*n*=78)	*P*[§]
Albumin (g/dL)	4.0 (3.8, 4.2)	4.0 (3.8, 4.2)	4.1 (3.9, 4.3)	0.103
Hemoglobin (g/dL)	10.2 (9.4, 10.8)	10.2 (9.4, 10.7)	10.1 (9.4, 11.0)	0.392
Calcium (meq/L)	9.3 (8.8, 9.7)	9.2 (8.8, 9.7)	9.3 (8.7, 9.7)	0.988
Phosphorus (me/dL)	4.8 (4.0, 5.9)	4.8 (3.9, 6.0)	4.8 (4.2, 5.6)	0.876
i-PTH (pg/mL)	275 (130, 535)	275 (133, 500)	274 (103, 616)	0.658
Creatine (mg/dL)	10.2 (8.5, 11.7)	10.0 (8.3, 11.6)	10.7 (9.4, 12.0)	0.005
BUN (mg/dL)	71.7 (59.6, 86.5)	71.7 (60.5, 86.0)	72.6 (56.2, 86.8)	0.952
CRP (mg/dL)	0.33 (0.13, 0.99)	0.36 (0.15, 1.04)	0.27 (0.09, 0.76)	0.033
HbA1c (%)	6.5 (5.8, 7.7)	6.5 (5.8, 7.5)	6.4 (5.7, 8.4)	0.906
Dialysis efficacy (Kt/v)				
Kt/v ≤1.5	92 (26.4)	75 (27.4)	17 (22.7)	0.462[†]
Kt/>1.5	257 (73.6)	199 (72.6)	58 (77.3)	

[†]Fisher's exact test, [§]Mann-Whitney *U*-test. CRP: C-reactive protein, BUN: Blood urea nitrogen, HbA1c: Glycated hemoglobin A1c, i-PTH: Intact parathyroid hormone

Table 3: Pruritus levels (degree of pruritus) and disturbances scores in 5-D itch scale (*n*=283)

Item	Mean	SD
Degree of pruritus (VAS-pruritus)	5.00	2.54
5-D total score	10.56	3.45
Duration of pruritus in the past 2 weeks[a]	1.40	1.03
Degree of pruritus in the past 2 weeks[b]	2.47	0.94
Improvement direction of pruritus compared with condition 1 month ago[c]	2.71	1.03
Effect of pruritus (on sleep)[d]	2.35	1.32
Distribution of pruritus[e]	1.63	0.91

[a]Between 6 h/day to 6-12 h/day. [b]Between a low and moderate level of pruritus. [c]Between much better, but still feel itchy, and a little better, but still feel itchy. [d]Between a little affected and occasionally affected. [e]Between 0-2 to 3-5 body parts. SD: Standard deviation, VAS: Visual analog scale

of pruritus in the past 2 weeks, and the mean score was 1.40, which means that the pruritus duration was between 6 h/day and 6–12 h/day. The second item of the 5-D scale was the degree of pruritus in the past 2 weeks, and the mean score represented a minor to moderate level of pruritus (mean = 2.47, SD = 0.94). The third item of the 5-D scale was the direction of improvement of pruritus in the past 2 weeks compared with 1 month ago. The average responses were between much better, but still feeling itchy, and no change (mean = 2.71, SD = 1.03). Regarding disability caused by pruritus, the most affected aspect of participants' daily lives was sleep, and the average score was 2.35 (SD = 1.32), which represents medium disturbance from pruritus. The distribution of pruritus mostly contained 0–2 or 3–5 body parts (mean = 1.63, SD = 0.91), and most participants had experienced pruritus on their backs (67.49%). The total score of the 5-D scale was 10.56 (SD = 3.45), indicating that the disturbance from pruritus was medium to low.

Comparison and correlation between demographic characteristics, hemodialysis types, serum biochemistry values, and 5-D scale in the pruritus group

Table 4 shows the *t*-test and Pearson's correlation results between major research variables and total score of the 5-D scale in the pruritus group. In the demographic data, only primary ESRD induced by diabetes showed significantly higher scores on the 5-D scale. In hemodialysis treatment types, only the heparin-using group had significantly lower 5-D scale scores. The levels of serum albumin, calcium, creatinine, and blood urea nitrogen (BUN) were negatively correlated with the 5-D scale scores, while levels of CRP were positively correlated with the 5-D scale scores. A moderately positive correlation was observed between pruritus VAS and 5-D scale scores ($r = 0.45$, $P < 0.001$).

Predictive factors of the 5-D scale

Table 5 shows the results of factors associated with total scores of the 5-D scale in the pruritus group. Variables that were significant ($P < 0.05$) in previous univariate correlation analysis were introduced into a multiple linear regression model. The multipredictor analysis identified that CRP and severity of pruritus VAS were independent explanatory variables of the 5-D scale scores. Higher levels of CRP and pruritus VAS were associated with higher 5-D scale scores ($\beta = 0.17$, $P < 0.01$; $\beta = 0.43$, $P < 0.001$). The total variance explained (R^2) was 28.5%.

Discussion

This study revealed the pruritus synptoms, disturbances, prevalence, locations, and predictors of hemodialysis patients. The demographic characteristics and serum biochemistry values were used to predict the pruritus levels and pruitus disturbance. The research results were compared with previous empirical studies.

Demographic characteristics between the pruritus and nonpruritus groups

A total of 361 patients on hemodialysis participated in this study. The number of men and women was approximately the same. The average age was 61.74 years (SD = 15.01). The primary cause of dialysis was mostly diabetes (41.8%). These results are similar to those published by USRD.[1] The type of

Table 4: Pearson's correlation between demographic characteristics, hemodialysis types, serum biochemistry values, and 5-D itch scale in the pruritus group (*n*=283)

5-D itch scale score	*t*/*r*
Demographic characteristics	*t*
Sex (male vs. female)	0.775
Age (years) (≥65 vs. <65)	0.324
Marital status (married vs. single)	0.704
Education (literacy vs. illiteracy)	0.071
Income (yes vs. no)	−0.348
Living arrangement (family vs. alone)	−0.288
Physical activity (yes vs. no)	−1.693
Job (yes vs. no)	−0.219
Eating-out frequency (often vs. seldom)	−0.957
Vegetarian (yes vs. no)	−0.291
Primary ESRD (other vs. DM)	−2.211*
Number of comorbid diseases (≥3 vs. ≤2)	−1.616
Hemodialysis treatment types	*t*
Time of dialysis (h) (≥4 vs. ≤3.5)	0.370
Years on dialysis (years) (≥3 vs. <3)	0.367
High flux dialyzer (yes vs. no)	−0.733
Heparin (free or zero vs. yes)	1.966*
Blood biochemistry value	*r*
Albumin	−0.170**
Hemoglobin	−0.050
Calcium	−0.140*
Phosphate	−0.02
i-PTH	0.050
Creatinine	−0.160
BUN	−0.173
CRP	0.200**
HbA1c	−0.010
Dialysis efficacy (Kt/v >1.5 vs. Kt/v ≤1.5)	−0.010
Severity of pruritus (VAS)	0.45***

*P<0.1, **P<0.01, ***P<0.001. SD: Standard deviation, VAS: Visual analog scale, CRP: C-reactive protein, BUN: Blood urea nitrogen, HbA1c: Glycated hemoglobin A1c, i-PTH: Intact parathyroid hormone, ESRD: End-stage renal disease, DM: Diabetes mellitus

Table 5: Predictive factors of 5-D itch scale in the pruritus group (*n*=283)

Explanatory variable	*B*	SE	β	*P*
Primary ESRD (DM vs. other)	0.44	0.39	0.06	0.256
Heparin (yes vs. free or zero)	−0.64	0.42	−0.09	0.130
Albumin	−0.98	0.57	−0.11	0.088
Calcium	−0.07	0.27	−0.02	0.785
Creatine	0.05	0.099	−0.00	0.961
BUN	−0.02	0.010	−0.11	0.085
CRP	0.39	0.13	0.17**	0.003
Severity of pruritus (VAS, 0-10 scores)	0.58	0.07	0.43***	<0.001

**P<0.01, ***P<0.001. R^2=28.5%. *B*: Regression coefficient, SE: Standard error, β: Standardized regression coefficient, ESRD: End-stage renal disease, DM: Diabetes mellitus, VAS: Visual analog scale, CRP: C-reactive protein, BUN: Blood urea nitrogen

hemodialysis treatment and serum biochemistry of the patients in this study were similar to those published by the Ministry of Health and Welfare in Taiwan.[20] The sample demographic characteristics were similar to the nationwide patients on hemodialysis in Taiwan. In this study, 78.4% (n = 283) of the participants had experienced pruritus, which was consistent with the result reported in previous research, revealing a 50%–90% prevalence rate.[2,3,12,20] Uremic pruritus had a higher prevalence rate in participants with diabetes than in those without diabetes, and this finding was consistent with Attia's research.[15]

No statistically significant differences were observed in hemodialysis treatment types between the pruritus and nonpruritus groups, which was consistent with several previous studies.[7,10,21,22] However, there are some diverse findings in other research, patients whose Kt/V >1.5 experienced lower level pruritus,[12] and patients who used high-flux dialyzers also experienced less pruritus.[12,14,23] However, Kt/V and dialyzers showed no statistically significant difference in this study. Among the serum biochemistry data of the pruritus and nonpruritus groups, only CRP and creatinine levels showed significant differences. The CRP of the pruritus group was significantly higher than that of the nonpruritus group, which was consistent with previous studies.[8,10,14,22] Lower levels of creatinine were associated with pruritus, and this finding was similar to that reported by Ko *et al*.[23] Some studies reported that abnormal serum calcium[8,16] and low albumin levels were associated with pruritus.[12,21] In this study, abnormal calcium and low albumin levels were not associated with higher pruritus.

This study confirmed that patients on hemodialysis with diabetes are more likely to have pruritus problems. In terms of other diverse results in a correlation between pruritus and gender, age, dialyzers, Kt/V, and the serum biochemistry data compared to other researches, it may due to the blood test results could be affected by a variety of factors such as malnutrition inflammation complex syndrome (MICS).[24]

Distribution of pruritus

Most of the participants (n = 283, 75.4%) had experienced pruritus. The mean score of the degree of pruritus according to the pruritus VAS was 5.00 (SD = 2.51), which was similar to the result reported by Rayner *et al*.[25] The mean score of the pruritus disturbance according to the 5-D scale was 10.56 (possible score = 5–25), indicating a moderate-to-low level of disturbance. Specifically, among the aspects of patients' daily lives affected by pruritus, sleep was the most affected aspect, and this result was consistent with previous research findings by Snit *et al*.[7] and Pisoni *et al*.[10] Additionally, pruritus most commonly occurred on the back (67.5%), consistent with previous studies.[4,22,26] This might be because most people lie down in a flat position to rest, which may cause rising body temperature in the back area, stimulating sensory receptors and causing pruritus.[4,26]

Correlations between specific variables and the 5-D scale

Patients who had experienced pruritus reported more severe disturbances if they possessed the following characteristics:

with diabetes, without anticoagulation (heparin) use, lower albumin, lower calcium, lower creatinine, lower BUN, higher CRP, and higher level of subjective pruritus. Patient's BUN, creatinine, and albumin may indicate the patient's recent protein intake, infection, nutrition, and dialysis status.[24] Therefore, when patients on hemodialysis have higher albumin (e.g., >3.5), urea nitrogen (e.g., >60), and creatinine (e.g., >10), they usually exhibit better nutrition status,[27] better dialysis effect, and less infection possibility.[24] Moreover, a study showed that patients with higher serum albumin and creatinine levels have better physical and psychological status.[28] These results were consistent with our study results, which showed that patients with good nutrition, e.g., higher serum albumin and creatinine levels, were less likely to have pruritus.[12,21] Therefore, future studies are needed to examine the correlation between nutrition, physical and mental health, and degree of pruritus.

This study revealed that the subjective degree of pruritus severity (VAS pruritus) was positively and significantly correlated with pruritus disturbance (5-D) ($r = 0.45$, $P < 0.001$). This result is consistent with that reported by Lai *et al*.[29] Additionally, our study's results of multiple regression analysis showed that demographic data, hemodialysis treatment types, serum biochemistry data, and degree of pruritus could predict patients' disturbance from pruritus ($R^2 = 28.5\%$, $P < 0.05$), particularly CRP levels; that is, high CRP may represent chronic inflammation. With inflammation, inflammatory factors stimulate the C nerve fibers in the skin, which are transmitters of itching, and make patients feel itchy.[30] Although patients reported more severe pruritus, they also felt a greater disturbance. Some serum biochemistry makers, like albumin, were not significantly related to pruritus disturbance (5-D). This may be due to the fact that the pruritus measurement (5-D scale) not only simply measures the degree of pruritus but also includes other variables such as itching parts of the body, lasting duration of pruritus, and disturbance caused by pruritus, including sleep, leisure/social, housework/daily life, work, and school. Additionally, the MICS of patients on hemodialysis may affect biochemistry markers, for instance, albumin. This might result in no statistical significance between biochemical markers and pruritus disturbance (5-D).

However, the results' interpretation may be limited because this study did not apply a randomized controlled trial design, and the serum biochemistry data and self-administrated questionnaires were collected within 1 week after hemodialysis instead of being synchronized with the hemodialysis.

Conclusion

This study collected data from 361 patients on hemodialysis; among them, 283 (78.4%) patients had experienced pruritus. This indicated that pruritus was a common discomfort. Only three factors showed significant differences between the pruritus and nonpruritus groups, including diabetes, lower creatinine, and higher CRP. Among the 283 pruritus patients, patients with diabetes, higher CRP, and higher VAS suffered more from severe pruritus disturbance (5-D). This study conducted multiple regression analyses and discovered that diabetes and CRP were the most important predictors of pruritus VAS and 5-D itch scale. Further research is needed to explore the relationship between pruritus and patients' nutrition status, chronic inflammation, and MICS.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Supplementary File 1:

STROBE Statement—Checklist of items that should be included in reports of cross-sectional studies			
	Item No	**Recommendation**	**Page No**
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	1
Objectives	3	State specific objectives, including any prespecified hypotheses	1
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	3
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3.4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4.5
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	NA
		(b) Describe any methods used to examine subgroups and interactions	NA
		(c) Explain how missing data were addressed	NA
		(d) If applicable, describe analytical methods taking account of sampling strategy	NA
		(e) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	Report numbers of outcome events or summary measures	5
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5.6
		(b) Report category boundaries when continuous variables were categorized	NA
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	6
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	6-9
Generalisability	21	Discuss the generalisability (external validity) of the study results	9.10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	10

*Give information separately for exposed and unexposed groups.

Cerebral venous sinus thrombosis as the initial presentation of occult adult leukemia

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Abstract

In this report, we present a rare case of cerebral venous thrombosis (CVT) as the initial presentation of hematological malignancy. A 49-year-old woman visited our hospital due to a progressive headache for 3 weeks. Brain imaging studies revealed edema in the right thalamus and bilateral caudate nuclei and acute thrombosis in the straight and right transverse sinuses. Initial laboratory investigations revealed only mild anemia and were negative for coagulopathy or autoimmune diseases. The patient had a complete recovery after anticoagulation therapy. Unfortunately, acute quadriparesis and coma occurred after warfarin was stopped for 3 months. Magnetic resonance imaging showed acute thrombosis of the basilar artery with brainstem infarction. At 11 months after the first presentation, acute leukemia was diagnosed due to marked leukocytosis and immature myeloblast cells in the peripheral blood. Bone marrow examination should be performed in patients with CVT with unexplained anemia. A continuous search for CVT causes after the acute phase is essential for patients with CVT.

Keywords: Anemia, cerebral venous thrombosis, leukemia

Introduction

Cerebral venous thrombosis (CVT) is an uncommon but potentially serious disease. The CVT causes include infection, pregnancy, severe dehydration, anemia, malignancy, congenital or acquired prothrombotic conditions, mechanical precipitants, and drugs.[1,2] Malignancy-related CVT could result from direct tumor invasion, emboli of tumor cells, hypercoagulation state, surgical ligation or injury of venous structures, and complications of chemotherapy. CVT has been described as a complication of acute lymphocytic leukemia and its treatment with L-asparaginase, prednisone, intrathecal methotrexate, and vincristine.[3,4] To our knowledge, CVT as the initial presentation of occult leukemia has not been reported. We report the case of an adult woman who sequentially presented with CVT, basilar artery occlusion, and pulmonary embolism and was eventually diagnosed with acute leukemia. The underlying causes and treatment of CVT were reviewed and discussed.

Received: 15-Sep-2021 **Revised:** 28-Mar-2022 **Accepted:** 01-Apr-2022
Published: 13-Dec-2022

Access this article online

Quick Response Code:

Website: https://journals.lww.com/TMJ

DOI: 10.4103/ETMJ.TMJ-110020

Case Report

A 49-year-old woman was admitted with a chief complaint of progressive headaches for 3 weeks. The headache was intermittent, diffuse, moderate to severe with deep-seated dull pain, not related to head position or straining, accompanied by nausea and vomiting, and usually lasting for 1–3 h. Neurological examination at admission revealed mild left central-type facial palsy and left hemiparesis (the Medical Research Council scale for muscle power assessment, Grade 4+). The patient had no remarkable past medical history, traveling history, drug history, or family history. Cranial computed tomography (CT) without contrast showed high-signal intensity at the straight sinus and bilateral internal cerebral veins [Figure 1a and b], suggesting acute thrombosis. Brain magnetic resonance imaging (MRI) on the 2nd day

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How to cite this article: Chen SY, Yang TC, Chen CW, Hsu HY. Cerebral venous sinus thrombosis as the initial presentation of occult adult leukemia. Tungs Med J 2022;16:73-6.

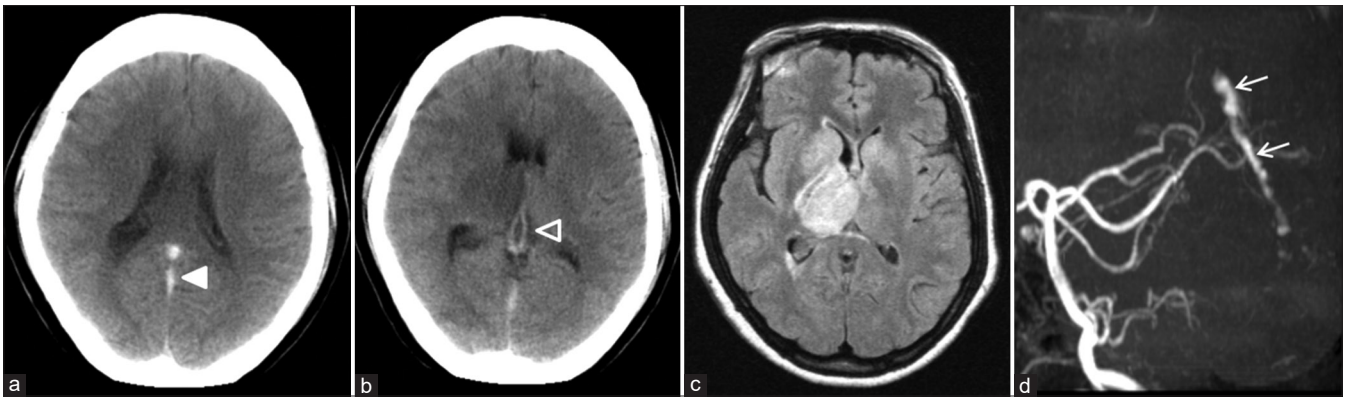

Figure 1: Initial CT without contrast showed acute thrombosis in the straight sinus (a: arrowhead) and internal cerebral veins (b: open arrowhead). Brain MRI showed (a) high-signal intensity in bilateral caudate nuclei and right thalamus on fast FLAIR images (c) and high-signal intensity in the straight sinus on TOF MRA (d: arrow) indicating acute thrombosis in the straight sinus. CT: Computed tomography, MRI: Magnetic resonance imaging, FLAIR: Fluid-attenuated inversion recovery, TOF: time-of-flight, MRA: Magnetic resonance angiography

showed increased signal intensity in the right thalamus and bilateral caudate nuclei on fluid-attenuated inversion recovery (FLAIR) images [Figure 1c]. Time-of-flight magnetic resonance angiography (MRA) showed acute thrombus in the straight sinus and no significant arterial stenosis in the intracranial arteries [Figure 1d]. CVT was impressed. Blood tests showed mild normocytic anemia (hemoglobin: 9.0 g/dL), normal white blood cell count and morphology, normal platelet count, normal serum iron level, normal prothrombin time, and activated partial thromboplastin time. The fecal occult blood test, Coombs test, and sugar-water test were negative. A survey of CVT causes were negative for antinuclear antibody, antineutrophil cytoplasmic antibody, lupus anticoagulant, anticardiolipin antibody, anti-β2-glycoprotein I antibody, rheumatoid factor, C3, C4, protein C, protein S, antithrombin III, and tumor markers, including Alpha-fetoprotein (αFP), Carcinoembryonic antigen (CEA), Squamous cell carcinoma antigen (SCC), CA-199, and CA-153. Intravenous heparin was started on the 2nd day. After heparin use for 3 days, the patient's headache and left facial and left limb weakness improved. On the 11th day, she was discharged and continued treatment with regular dose-adjusted warfarin to keep the international normalized ratio between 2 and 3 at the outpatient clinic. After 3 months, she clinically had no residual neurological deficit. Follow-up of MRI showed complete resolution of the brain lesion with some hemosiderin deposition in the right thalamus [Figure 2a and b]. However, magnetic resonance venography (MRV) showed no recanalization of the right transverse and right sigmoid sinus [Figure 2c]. Hemoglobin levels were 8.7 g/dL and 8.6 g/dL on discharge and 2 weeks after discharge, respectively. The patient quit all medications against advice and did not receive a follow-up for 5 months after the first admission.

The patient was sent to the emergency room due to a sudden loss of consciousness while watching TV 8 months after the first admission. Neurological examination revealed comatose consciousness, isochoric small pupils with normal pupillary light reflexes, ocular bobbing, disconjugate eye position, and Babinski sign of extensor type bilaterally. Emergent brain CT showed no acute parenchymal lesion. Blood tests showed marked anemia (hemoglobin: 5.9 g/dL), normal white blood cell count, and platelet count. Thrombolytic therapy was not administered because the patient arrived at the emergency room more than 3 h after the onset of the symptoms. On the following day, a brain MRI showed high-intensity lesions in the bilateral brainstem on FLAIR and diffusion-weighted imaging images [Figure 3a-c]. MRA showed occlusion of the rostral half of the basilar artery [Figure 3d]. Repeated blood tests for vasculitis and hypercoagulation state showed negative findings. She received anticoagulants and a blood transfusion but remained comatose and had quadriparesis. On the 50th day of the second admission, acute dyspnea developed. Arterial blood gas showed hypoxemia, and chest CT showed acute pulmonary embolism in the right pulmonary artery and its superior and inferior branches. On the 162nd day of the second admission, marked leukocytosis (white blood cell count: 104,500/cum) with numerous immature blast cells (82% of all white blood cells) was observed in the peripheral blood. On the 189th day of the second admission, the white blood cell count eventually rose to 25,200/cum. Acute leukemia was impressed. The patient's family asked for palliative care and refused further investigation due to severe neurological deficits and poor prognosis. She was transferred to the respiratory care ward and expired 13 months after the first presentation.

Discussion

The malignancy-related prothrombotic state is one of the common causes of CVT. However, CVT followed by pulmonary embolism and basilar artery occlusion as clinical presentations of occult leukemia have not been reported. This report suggests that hematological malignancy should be considered a cause of CVT, although very rare because delayed diagnosis and treatment could lead to poor outcomes. In a recent national-wide study, systemic malignancy and hematologic disorders were the most common causes of

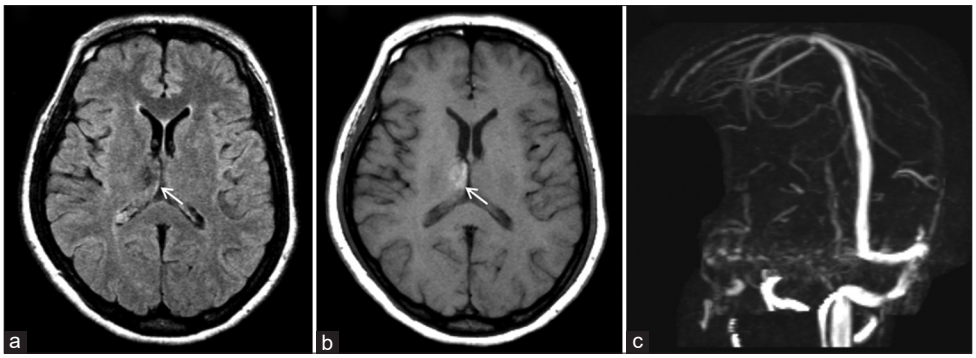

Figure 2: Brain MRI 4 months after the first MRI examination showed residual petechial hemorrhage without edema on FLAIR (a) and T1-weighted (b) images and no recanalization of the straight sinus, right transverse sinus, and right sigmoid sinus on MRV (c). MRI: Magnetic resonance imaging, FLAIR: Fluid-attenuated inversion recovery, MRV: Magnetic resonance venography

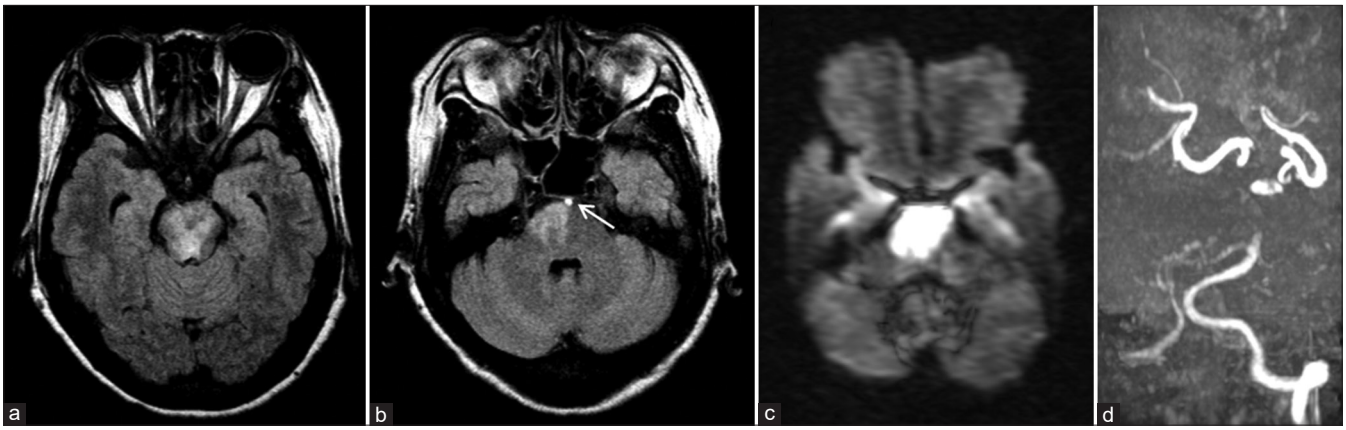

Figure 3: Brain MRI during the second admission showed a high-intensity lesion in the bilateral midbrain (a) and left pons (b) on FLAIR images, high intensity on diffusion-weighted imaging images (c) consistent with acute infarction, high-signal intensity in the basilar artery (b: arrow), and nonopacification of the rostral part of the basilar artery on TOF MRA (d) indicating thrombosis of the basilar artery. MRI: Magnetic resonance imaging, FLAIR: Fluid-attenuated inversion recovery, TOF: time-of-flight, MRA: Magnetic resonance angiography

nonpyogenic CVT.[5] In addition, multiple risk factors may be found in about half of adult patients with CVT.[2] This case highlights the importance of a complete evaluation of risk factors, including hematological malignancy, in patients with CVT. Although a randomized controlled trial showed that an extensive screening strategy for occult cancer in unprovoked venous thromboembolism did not significantly increase the detection of cancer,[6] novel blood biomarkers, such as platelet mRNA, circulating tumor DNA, and plasma proteomics analysis, might help detect occult cancer.

CVT recurrence occurred in 2%–7% of patients,[2] and the incidence of other venous thromboses doubled.[2,7] CVT usually presents with no apparent focal neurological deficit in examination and is easily overlooked in the early phase.[1,2] With rising clinical awareness and the widespread use of MRI, CVT is more frequently recognized. MRI and MRV have good sensitivity for CVT detection. However, conventional cerebral angiography remains the diagnostic gold standard. CVT should be suspected when the infarct boundaries are inconsistent with arterial territories. Different from that observed in arterial infarction, brain lesions resulting from CVT have high-signal intensity on the apparent diffusion coefficient map, indicating vasogenic edema predominant over cytotoxic edema.

Mild anemia was the only clue that might lead to the correct early diagnosis in this patient during the first admission. Although the pathogenetic mechanism is unclear, anemia is a documented cause of CVT. We failed to find the cause of anemia by searching for possible causes of blood loss and performing tests for autoimmune diseases, serum iron level test, Coombs test, and sugar water test during the first admission. Although mild anemia is not an unusual finding in middle-aged women, unexplained anemia could be a very early sign of a disastrous hematological problem. The negative Coombs tests, normal lactate dehydrogenase level, and stable hemoglobin level during the first admission and after the first discharge suggested that anemia was not due to hemolysis or consumption due to acute illness. A thorough evaluation of persistent anemia, including bone marrow examination, must be carried out in patients with CVT and anemia.

Arterial thromboses following CVT, as in our patient, are rare. Although the pathological type of the patient's leukemia was unknown because we could not get the bone marrow

specimen, the hypercoagulation state due to leukemia probably contributed to CVT, brainstem infarction, and pulmonary embolism. The normal white blood cell count on admission and the morphology in the peripheral blood made tumor emboli or leukostasis unlikely to be the cause of CVT.

Although patients with underlying malignancy have less favorable results, CVT in patients with hematological malignancy could be effectively prevented using anticoagulants.[8] Our case had excellent clinical recovery after anticoagulation treatment during the first few months. Dose-adjusted warfarin could be used for 3 to 12 months in adults after the acute phase of CVT. However, no clinical trial has assessed the effectiveness of oral anticoagulation for preventing recurrent CVT.[9,10] Long-term oral anticoagulation could be reserved for patients with recurrent CVT, severe thrombophilia, or combined prothrombotic conditions.[9] However, some conditions, such as autoimmune diseases, polycythemia, thrombocythemia, or malignancy, could be discovered weeks or months after the acute phase of CVT. A continuous search for a cause after the acute phase could be helpful for some patients. A thorough search for additional causes should be carried out before the termination of oral anticoagulants.

In conclusion, occult leukemia with subtle clues, such as mild anemia, was a catastrophic cause of CVT. A complete survey of CVT causes, including malignancy, is crucial for treating CVT. Bone marrow examination could be performed in patients with CVT with unexplained anemia.

Declaration of patient consent

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

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Guillain–Barré syndrome associated with *Helicobacter pylori* infection in a male adolescent: A case report and literature review

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Abstract

Guillain–Barré syndrome (GBS) is a potentially life-threatening acute immune-mediated demyelinating peripheral neuropathy. It could be triggered by many pathogens, including *Campylobacter jejuni*, *cytomegalovirus*, *Epstein–Barr virus*, *Helicobacter pylori*, and influenza. A 14-year-old boy presented with GBS caused by *H. pylori*. Upper gastrointestinal endoscopy showed chronic gastritis and a shallow gastric ulcer. He had right lower limb weakness and sensory loss, which were relieved after intravenous immunoglobulin (Ig) treatment. He was also prescribed triple therapy with lansoprazole, amoxicillin, and clarithromycin and achieved complete eradication of *H. pylori*. No recurrent neurological or gastrointestinal symptoms were observed. *H. pylori* secrete a protein called "vacuolating cytotoxin A (VacA)," and the cerebrospinal fluid level of a specific IgG antibody against VacA was found to be increased in patients with GBS. GBS should be included in the differential diagnosis list in patients presenting with neurological signs with concurrent *H. pylori* infection.

Keywords: Adolescent, Guillain–Barré syndrome, *Helicobacter pylori*

Introduction

Guillain–Barré syndrome (GBS) is an acute immune-mediated demyelinating peripheral neuropathy. Its main characteristic is progressive ascending weakness from distal-to-proximal muscles. Sensory symptoms, such as paresthesia, may occur.[1,2] GBS incidence is about one person per 100,000, and the men-to-women ratio appears to be 1: 1 in the epidemiologic database.[1] It is preceded by either upper respiratory tract or gastrointestinal tract infection in about two-thirds of cases. The precipitating pathogens include *Mycoplasma pneumonia*, *Campylobacter jejuni*, *cytomegalovirus*, *Epstein–Barr virus*, *Helicobacter pylori*, and influenza.[3-5] This disease may affect and impair respiratory muscles or muscles innervated by cranial nerves, leading to respiratory failure and death. Therefore, it is important to timely and properly initiates the treatment for GBS.

Received: 18-Jan-2022 **Revised:** 21-Mar-2022 **Accepted:** 22-Mar-2022
Published: 13-Dec-2022

Access this article online

Quick Response Code:

Website: https://journals.lww.com/TMJ

DOI: 10.4103/ETMJ.TMJ-111002

This report presents a case of a 14-year-old boy who presented with a sudden onset of right leg numbness and weakness, which is compatible with GBS associated with *H. pylori* infection. His problems were remarkably relieved after intravenous immunoglobulin (Ig) and triple eradication therapy.

Case

A 14-year-old boy presented with complaints of sudden onset of sensory loss and muscle weakness in his right lower limb for 3 weeks. Before the occurrence of numbness and weakness, he had been vaccinated with the first dose of BNT162b2 at school. He began to suffer from the progressive right lower limb weakness and sensory loss 2 days after receiving the

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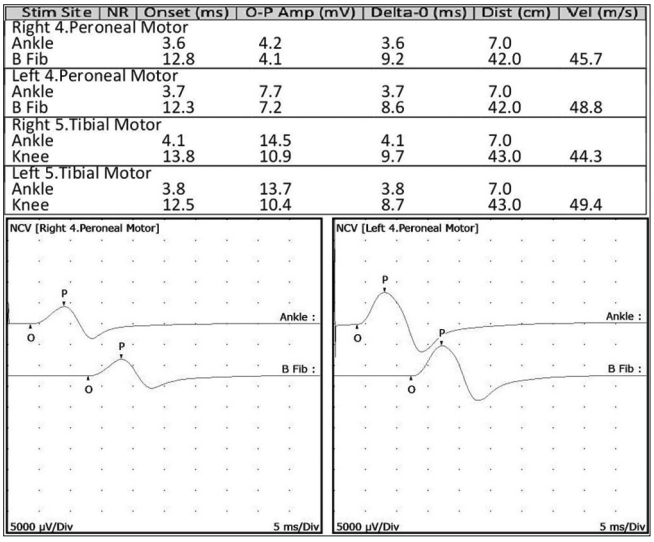
How to cite this article: Hu SW, Fan HC. Guillain–Barré syndrome associated with *Helicobacter pylori* infection in a male adolescent: A case report and literature review. Tungs Med J 2022;16:77-9.

vaccine. The muscle power was 1/5 in the right lower limb and 5/5 in the other limbs. The deep tendon reflex of the right lower limb decreased compared with that of the left lower limb. He had been admitted to a teaching hospital for these problems, where his brain computed tomography scan and spinal cord magnetic resonance imaging showed no abnormalities. He also mentioned that he had a productive cough for a couple of weeks, and the serum *Mycoplasma* Ig M was positive. A 7-day course of doxycycline was prescribed. Although the cough improved to some extent, weakness and numbness in his right leg persisted even after a rehabilitation program. He matched the level 4 disability by the GBS disability scale. Therefore, he was transferred to our hospital.

The laboratory studies included a complete blood cell count with differential counting: white blood cells – 10,100/μL, hemoglobin – 15.4 g/dL, platelets – 320,000/μL, neutrophils – 53.3%, lymphocytes – 38.9%, monocytes – 4.6%, eosinophils – 2.8%, and basophils – 0.4%. Alanine aminotransferase and serum creatinine levels were 60 IU/L and 0.34 mg/dL, respectively. The lactic acid level was 1.170 mmol/L. Sodium, potassium, chloride, calcium, and phosphorus levels were 133 mEq/L, 4.1 mEq/L, 101 mEq/L, 9.1 mg/dL, and 3.7 mg/dL, respectively. The creatine phosphokinase level was 52 U/L. The above laboratory workup was essentially negative. Substance intoxication screening also showed negative findings. His cerebrospinal fluid (CSF) analysis revealed white blood cells – 6/μL, red blood cells – 89/μL, glucose – 59 mg/dL, and protein – 24 mg/dL, which were all within the normal range. Autoimmune encephalitis markers, including anti–N-methyl-D-aspartate receptor antibody, glutamic acid decarboxylase antibody, and anti-aquaporin-4 antibody, were all negative.

The nerve conduction study of his legs showed a significant decrease in conduction velocity of the right peroneal motor nerve (velocity 45.7 m/s) and right tibia motor nerve (velocity 44.3 m/s) compared with his left leg [Figure 1], which were compatible with GBS based on the Brighton key diagnostic criteria. However, the conduction velocity of the right sural sensory nerve was not less than that of the left leg although he had right leg numbness. After intravenous Ig (1 g/kg/day) administration for 2 consecutive days, his muscle weakness and sensory loss dramatically improved. His family reported that he had intermittent abdominal pain and vomiting for several weeks preceding the episode. Therefore, an upper gastrointestinal endoscopic examination was performed, which identified hemorrhagic gastritis, chronic gastritis, and shallow gastric ulcers [Figure 2]. In addition, the *H. pylori* stool antigen rapid test was positive. His gastrointestinal and neuromuscular symptoms were synchronically relieved after initiating a triple therapy with lansoprazole, amoxicillin, and clarithromycin. Consistently, a follow-up nerve conduction study of the legs revealed improved results 2 weeks later compared with the previous study [Figure 3]. *H. pylori* was eradicated after a 14-day course of triple therapy. So far, he completely recovered, and no residual gastrointestinal and neurological sequelae were observed during the clinical follow-up.



Stim Site	NR	Onset (ms)	O-P Amp (mV)	Delta-0 (ms)	Dist (cm)	Vel (m/s)
Right 4.Peroneal Motor						
Ankle		3.6	4.2	3.6	7.0	
B Fib		12.8	4.1	9.2	42.0	45.7
Left 4.Peroneal Motor						
Ankle		3.7	7.7	3.7	7.0	
B Fib		12.3	7.2	8.6	42.0	48.8
Right 5.Tibial Motor						
Ankle		4.1	14.5	4.1	7.0	
Knee		13.8	10.9	9.7	43.0	44.3
Left 5.Tibial Motor						
Ankle		3.8	13.7	3.8	7.0	
Knee		12.5	10.4	8.7	43.0	49.4

Figure 1: Nerve conduction velocity test before treatment. The right velocity and amplitude of the right peroneal motor nerve were lower than those of the left peroneal motor nerve

Discussion

H. pylori is a Gram-negative, spiral-shaped, and flagellated bacterium and affects about one in two people in Asia.[4] *H. pylori* is associated with chronic gastritis, peptic ulcer, gastric carcinoma, and mucosa-associated lymphoid tissue lymphoma. Besides, *H. pylori* is also associated with GBS and Miller Fisher syndrome.[4,6,7] A previous meta-analysis study reported that anti-*H. pylori* IgG was significantly more prevalent in patients with GBS than in controls in both CSF and serum.[4]

Vacuolating cytotoxin A (VacA) is an *H. pylori*-secreted protein, which binds to host cells and causes vacuolation. This is an important step for initial colonization and

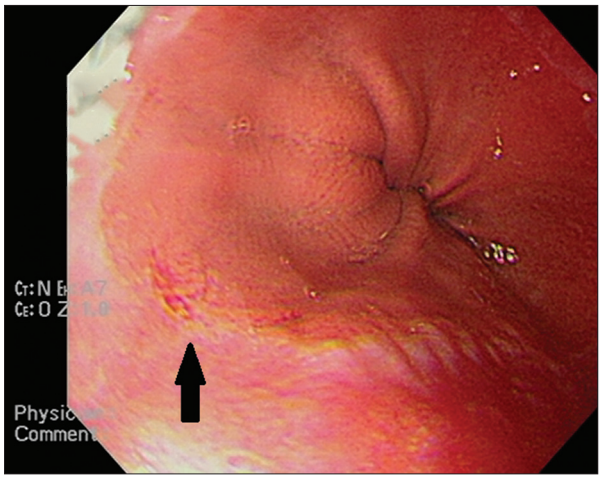


Figure 2: Upper gastrointestinal endoscopy showed a diffuse erythematous change of the gastric mucosa. A shallow ulcer in the antral area was also observed (black arrow)

Stim Site	NR	Onset (ms)	O-P Amp (mV)	Delta-0 (ms)	Dist (cm)	Vel (m/s)
Right 4.Peroneal Motor						
Ankle		3.7	5.4	3.7	7.0	
B Fib		12.6	5.4	8.9	43.0	48.3
Left 4.Peroneal Motor						
Ankle		3.4	7.5	3.4	7.0	
B Fib		11.7	6.2	8.3	43.0	51.8
Right 5.Tibial Motor						
Ankle		3.6	11.2	3.6	7.0	
Knee		12.2	6.9	8.6	44.0	51.2
Left 5.Tibial Motor						
Ankle		3.0	14.5	3.0	7.0	
Knee		12.2	11.5	9.2	44.0	47.8

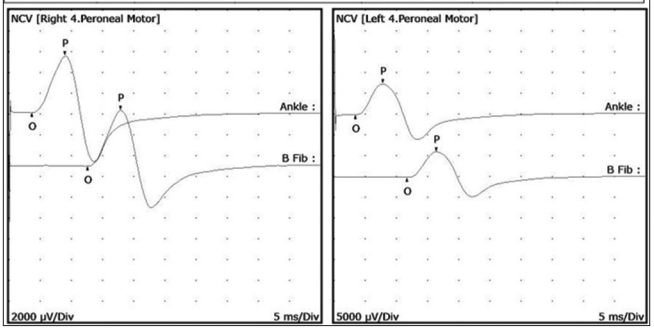


Figure 3: Nerve conduction velocity test after treatment. The right velocity and amplitude of the right peroneal motor nerve were improved

subsequent persistence in the host stomach.[8] Chiba *et al*. found in their study that six of the 13 patients with GBS had a specific IgG antibody to VacA of *H pylori*, and every patient with positive CSF anti-recombinant-VacA IgG had acute inflammatory demyelinating polyradiculoneuropathy.[7] The effects of *H. pylori* on the gut–brain axis can derive from the direct activation of inflammatory processes in the nervous system.[9] Gut microbiota creates a natural protective barrier and is responsible for the secretion of numerous neurotransmitters and neuromodulators, and microbiota is disturbed by the colonization of *H. pylori*.[9] In addition, epidemiological studies reported a significantly increased number of *H. pylori* infections in patients with GBS compared to individuals without the disease.[9]

This case had been exposed to a single dose of the BNT162b2 vaccine before the onset of GBS. GBS was infrequent among individuals receiving BNT162b2. The incidence of GBS occurring in any individual vaccinated with the first dose of BNT162b2 was approximately 0.18/100,000.[10] Consequently, we postulate that the possibility of GBS occurrence due to the BNT162b2 vaccine is less likely in this case.

In this case, GBS was diagnosed with preceding gastrointestinal symptoms and concurrently active *H. pylori* infection. The lower serum titer of the antimycoplasma antibody did not support *M. pneumoniae* infection as the disease-causing pathogen in GBS. There are some limitations regarding the diagnosis of this case. The anti-VacA IgG level was not checked in CSF. Electromyography was not conducted, so the differential diagnoses of muscle-related disorders, including myasthenia gravis, mitochondrial disease, and drug-induced toxic myopathy, were not ideally excluded from the study. GBS is a potentially life-threatening disorder and progresses quickly during the clinical course. Therefore, early diagnosis and proper treatment are necessary for saving patients' lives.

Declaration of patient consent

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

Financial support and sponsorship

Nil.

Conflicts of interest

Dr. Hueng-Chuen Fan, an executive editor at *Tungs' Medical Journal*, had no role in the peer review process of or decision to publish this article. Dr. Shu-Wei Hu declared no conflicts of interest in writing this article.

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Pneumobilia in one 6-month-old female infant with choledochal cyst type I status post Roux-en-Y hepaticojejunostomy

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[#]Both authors contributed equally to this study

A 6-month-old female infant with a history of choledochal cyst type I was admitted to our medical center with intermittent bilious vomiting for 3 days. Roux-en-Y hepaticojejunostomy was performed 2 months ago. The initial plain abdominal radiography revealed typical hepatic pneumobilia and marked dilated bowel loops with gas content in the abdomen [Figure 1]. Empiric antibiotic therapy with ceftriaxone and metronidazole was administered at admission, and nasogastric decompression was performed. The follow-up plain abdominal radiography [Figure 2] 5 days later revealed a complete resolution of the hepatic pneumobilia, but the ileus was still present. On the 12th day of admission, the patient was discharged in stable condition.

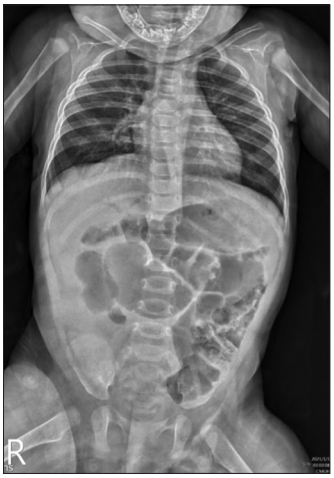

Figure 1: Initial abdominal radiography on admission showed bowel loop pneumobilia with gas content in the abdomen. Hepatic pneumobilia can be seen, showing the presence of gas in the biliary tree

Received: 22-Dec-2021 **Revised:** 06-Apr-2022 **Accepted:** 08-Apr-2022
Published: 13-Dec-2022

Access this article online

Quick Response Code:

Website: https://journals.lww.com/TMJ

DOI: 10.4103/ETMJ.TMJ-110030

Pneumobilia is the presence of gas in the biliary tree, which suggests an abnormal communication between the biliary tract and the gastrointestinal tract. It is usually benign. However, a life-threatening disease may occasionally occur when it is associated with a gas-forming bacterial infection.[1] It is usually caused by biliary interventions, including biliary-enteric anastomosis, endoscopic biliary manipulations, and percutaneous transhepatic cholangiography, incompetent sphincter of Oddi, and spontaneous biliary-enteric fistula. Although pneumobilia may appear on plain abdominal radiography, it more commonly presents on computed tomography (CT) scans and ultrasounds. Hepatic portal venous

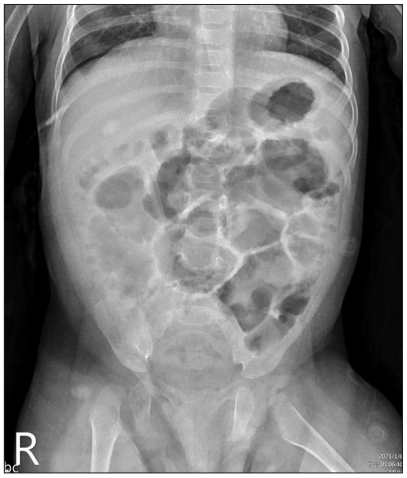

Figure 2: Plain abdomen radiography 5 days after admission showed no significant findings

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How to cite this article: Wu LY, Yeh CY, Hu SW, Wu SF, Chen AC. Pneumobilia in one 6-month-old female infant with choledochal cyst type I status post Roux-en-Y hepaticojejunostomy. Tungs Med J 2022;16:80-1.

gas (HPVG) and pneumobilia may appear similarly on plain abdominal radiography and CT. Plain abdominal radiography may demonstrate the "saber sign," a sword-shaped lucency, in up to 50% of patients with pneumobilia, which describes the air accumulation in the left intrahepatic and the common bile duct. HPVG, in comparison, is with more branching, extending to within 2 cm beneath the liver capsule.[2]

In this case, we inspected that the hepatic pneumobilia on the X-ray might be associated with her previous Roux-en-Y hepaticojejunostomy with anastomosis of the biliary tract and small bowel that was potentially connected to ascending cholangitis, leading to such findings on the X-ray.[1]

Plain abdominal radiography is the first diagnostic choice for patients with intermittent bile vomiting. Physicians should focus not only on the bowel pattern but also on the liver contour. In conclusion, prudent history taking, meticulous physical examination, laboratory tests and imaging, and in particular, a high level of suspicion may provide important clues for the early diagnosis of pneumobilia.

Declaration of patient consent

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

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Type A Wellens' syndrome - A critical electrocardiographic sign

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Wellens' syndrome was first described in 1982[1] and classified into type A and type B. Type A Wellens' syndrome is characterized by biphasic T-waves in leads V2 and V3, and type B is characterized by deep symmetrical T-wave inversions in the same leads. The study reported that Wellens' syndrome electrocardiographic (ECG) finding related to left anterior descending (LAD) total or near-total occlusion, which is also described as one of the ST-segment elevation myocardial infarction (STEMI) equivalent signs.[2] Cardiology consultation for possible coronary angiography is necessary for evaluating patients.[3]

A 29-year-old male without underlying medical diseases was admitted to our emergency department due to intermittent retrosternal chest tightness for 1 week. His chest pain usually occurs after exertion, accompanied by nausea and dizziness, and subsides 10–15 min after rest. He did not notice other exacerbating or relieving factors. Thus, he visited our emergency department for a consultation. The patient is a nonsmoker with no family history of acute coronary syndrome.

In the emergency department, his chest pain had already subsided. He was vitally stable. On physical examination, his cardiac auscultation revealed a regular heartbeat with no murmurs. His ECG performed in the emergency department showed sinus rhythm with biphasic T-waves in leads V2 and V3 without precordial Q waves [Figure 1], which is compatible with type A Wellens' syndrome. As for his blood examination, his troponin I level is 3.2 ng/mL (normal range < 0.02 ng/mL) and creatine kinase-myocardial band mass is 8.5 ng/mL (normal range <5 ng/mL). He also had thrombocytosis with a platelet count of 993,000/μL.

The patient received aspirin, ticagrelor, and heparin for the myocardial infarction.

He received urgent coronary angiography and the examination showed an 85% stenosis of the proximal LAD artery [Figure 2] that was successfully opened through angioplasty. Two drug-eluted stents were placed. After angioplasty, his ECG showed sinus rhythm with no Wellens' pattern. In addition, he did not experience any chest pain attack after angioplasty. On admission, the patient was diagnosed with essential thrombocythemia through positive JAK-2 V617F mutation test and bone marrow biopsy.

Wellens' syndrome is one of the STEMI equivalent ECG signs that need to be treated as acute myocardial infraction in the emergency department.[2] A previous study[1] showed that 75% of the patients with Wellens' syndrome developed extensive anterior wall myocardial infarction a few weeks after admission. T-wave findings of Wellens' syndrome are classified into two patterns. In type B, which comprises approximately 75% of cases, the T-wave is deeply inverted and the inverted T-wave is symmetric in contour. In type A, which comprises 25% of cases, the T-wave is biphasic in leads V2 and V3. Other ECG criteria included no loss of R rave or precordial Q waves. Considering noncoronary causes of T-wave inversions, the left ventricular hypertrophy and bundle branch block patterns should be readily recognized by their significant coexistent findings.[3] The characteristic ECG pattern often develops when the patient is not experiencing angina.[3]

Patients with ET may present with vasomotor symptoms such as myocardial infarction or stroke. However, in this case, the patient was young and without any risk factors for myocardial infarction before diagnosis. Prompt recognition of the ECG pattern and early cardiology consultation are essential to prevent missing the diagnosis of myocardial infarction.

Declaration of patient consent

The authors certify that they have obtained appropriate patient

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Received: 07-Jan-2022 **Revised:** 23-Feb-2022 **Accepted:** 23-Feb-2022
Published: 13-Dec-2022

Access this article online

Quick Response Code:

Website: https://journals.lww.com/TMJ

DOI: 10.4103/ETMJ.TMJ-111001

How to cite this article: Hsu YT, Chen KH. Type A Wellens' syndrome - A critical electrocardiographic sign. Tungs Med J 2022;16:82-3.

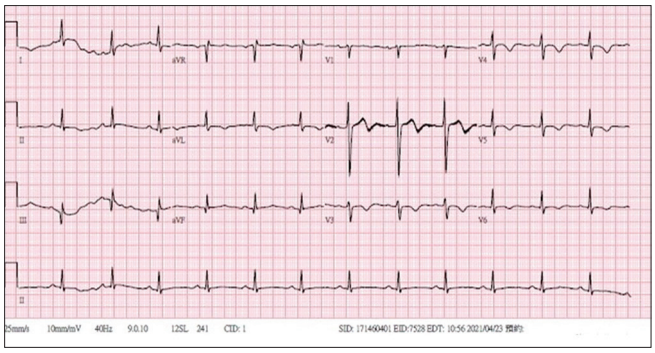

Figure 1: Patient's initial ECG. ECG: Electrocardiographic

consent form. In the form, the patient has given his consent for the images and other clinical information to be reported in the journal. The patient understands that name and initial will not be published and due efforts will be made to conceal the identity, but anonymity cannot be guaranteed.

Acknowledgments

We would like to thank the patient for allowing us to share his details.

Financial support and sponsorship

Nil.

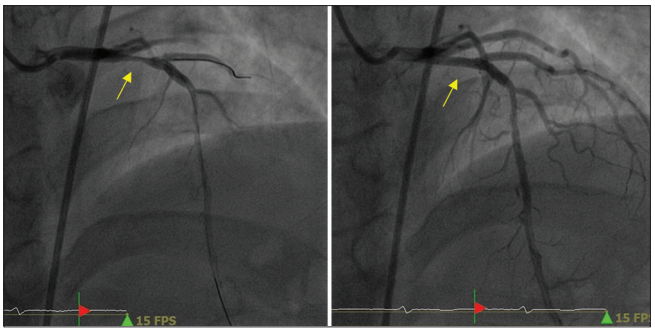

Figure 2: Patient's coronary angiography showed LAD stenosis. (Left) Before the intervention. (Right) After the intervention. LAD: Left anterior descending

Conflicts of interest

There are no conflicts of interest.

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