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## IMAGE

Editorial

# Safety Concerns for Metformin use in Type 2 Diabetic Patients with Chronic Kidney Disease

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**Abstract**

Over the past 30 years, diabetes mellitus (DM) has become one of the 10 leading causes of death in Taiwan. Its serious complications have caused a great economic burden. DM is also the most important underlying disease contributing to the high incidence of end-stage renal disease in Taiwan. The majority (>90%) of patients with diabetes have type 2 DM (T2DM). Metformin is the first-line treatment for T2DM due to its safety, low cost, anti-inflammatory properties, and potential cardiovascular benefits. Metformin is predominantly (90%) excreted via the kidney and may impair lactate excretion. Thus, T2DM patients with chronic kidney disease (CKD) are at high risk of metformin-associated lactic acidosis. Due to a lack of data from studies into metformin-associated lactic acidosis, there are no consistent recommendations across the international guidelines about the safe dosage of metformin for patients at different stages of CKD. The recommended dose of metformin only considers T2DM patients with mild CKD [estimated glomerular filtration rate (eGFR) 45–60 mL/min/1.73 $m^2$), although this should be reduced for those with moderate CKD (eGFR 30–45 mL/min/1.73 $m^2$). There are few empirical studies on use of metformin in T2DM patients with severe CKD (eGFR < 30 mL/min/1.73 $m^2$) due to difficulties conducting randomized controlled trials. Metformin use in T2DM patients with advanced CKD was previously shown to be associated with increased risk of all-cause mortality compared with non-users, based on a nationwide population database. A recent population-based study in the United States also showed that patients with mild and moderate CKD were not at risk of lactic acidosis, whereas those with severe CKD showed a significant risk. Therefore, the safety of metformin usage must be considered in T2DM patients at different CKD stages. Based on the safe use and therapeutic effect of metformin, the Taiwan Food and Drug Administration recently modified the contraindications for metformin to state that use should be discontinued for T2DM patients with severe CKD.

**Key words:** chronic kidney disease, type 2 diabetes mellitus, metformin

A previous study that analyzed data from 138 countries and territories reported that, in 2019, the global prevalence of DM in adults aged 20–79 years was 9.3% (463 million people), and is expected to increase to 10.2% and 10.9% in 2030 and 2045, respectively[1]. Over the past 30 years, diabetes mellitus (DM) has been among the 10 leading causes of death in Taiwan. Its serious complications have caused great economic burden, affecting 2.3 million people, with an estimated prevalence of 11% until the end of 2019 in Taiwan.

DM is a major cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD). In 2016, the prevalence of DM among patients with ESRD was 50.4%, with the incidence of ESRD increasing from 352 per million in 2003 to 493 per million in 2016, based on the 2018 Annual Report on Kidney Disease in Taiwan.

Type 2 DM (T2DM) is the most common type of diabetes, accounting for around 90% of all cases.

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Metformin is the recommended first-line antihyperglycemic pharmacotherapy for patients with T2DM. While adverse side effects including gastrointestinal irritation, such as abnormal pain, diarrhea, and nausea, are common, metformin is still widely used due to the benefits of its low cost, potential cardiac function protection, inflammation inhibition, and enhancement of antioxidant defenses. Metformin is a biguanide antihyperglycemic drug that reduces gluconeogenesis. Its mechanism of action is thought to be via activation of AMP-activated protein kinase (AMPK) in the cell. The AMPK cascade activates catabolic pathways to produce ATP and reduces visceral fat and cholesterol synthesis [2, 3]. Metformin may act via inhibition of mitochondrial respiratory chain complex I in the liver to further activate AMPK. Metformin also reduces intestinal glucose levels and decreases insulin sensitivity in peripheral muscle mass and liver. Single use of metformin has a low risk of hypoglycemia as it does not act directly on the β-cells in the pancreas.

Metformin has distinct pharmacokinetics and is eliminated unchanged via the urine, liver, or bile. Around 90% of metformin is eliminated rapidly and actively via renal extraction after drug absorption during the first 24 h[4]. Common side effects of metformin include gastrointestinal symptoms, such as diarrhea, nausea, vomiting, and indigestion, as well as vitamin B12 deficiency, headache, and excessive fatigue. Lactic acidosis is a rare but dangerous side effect, with a high risk (around 50%) of mortality[5]. A large-scale retrospective study to evaluate the risk of lactic acidosis in T2DM patients with different levels of kidney function showed incidence rates of 10.4, 4.6, 17, and 39 per 100,000 person-years for all patients and patients with mild, moderate, and severe kidney dysfunction, respectively[6]. Another cohort study also found that metformin use was associated with a significantly increased risk of lactic acidosis [adjusted hazard ratio (aHR), 6.37; 95% confidence interval (CI), 1.48–27.5] among patients with estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 $m^2$ despite some study limitations, such as incomplete eGFR data (27.4% missing among metformin users) and not accounting for changes in eGFR over time.[7] A recent community-based cohort study (n = 75,413) in the United States examined the association between metformin use and risk of lactic acidosis in patients with different levels of kidney function and concluded that metformin use was not associated with overall incident lactic acidosis among DM patients with eGFR of 45–59 mL/min/1.73 $m^2$ (aHR, 1.16; 95% CI, 0.95–1.41) or eGFR of 30–44 mL/min/1.73 $m^2$ (aHR, 1.09; 95% CI, 0.83–1.44) compared with metformin non-users. However, among DM patients with eGFR < 30 mL/min/1.73 $m^2$, metformin users were associated with an increased risk of lactic acidosis compared with metformin non-users (aHR, 2.07; 95% CI, 1.33–3.22). Further analysis using propensity score-matching showed no significant association between metformin use and increased risk of lactic acidosis across in patients with eGFR < 30 (aHR, 0.82; 95% CI, 0.55–1.23), 30–44 (aHR, 0.71; 95% CI, 0.45–1.12), and 45–59 (aHR, 1.46; 95% CI, 0.86–2.48) mL/min/1.73 $m^2$.[8] A recent Taiwan population-based, observational, retrospective, propensity score-matched cohort study reported that the all-cause mortality rates for metformin users and non-users with advanced CKD (approximately stage 5) were 53% (434/813) and 41% (1012/2439), respectively, with 2.1 years median follow-up. These study also revealed that metformin users had a significantly higher risk of all-cause mortality and serum creatinine levels >530 μmol/L (equivalent to ESRD) after adjustment for potential risk factors (aHR: 1.35, 95% CI: 1.20–1.51) compared with non-users with T2DM. There was a dose-response effect between metformin and increased all-cause mortality risk. In the subgroup analysis, consistent results were found across all subgroups. However, compared with metformin non-users, metformin users had a higher but non-significant risk of lactic acidosis (aHR, 1.30; 95% CI, 0.88–1.93), with the highest risk found among T2DM patients taking >1000 mg metformin per day[9].

According to the international prescribing guidelines for metformin in kidney impairment, the United States Food and Drug Administration[10], American Diabetes Association[11], and the European Association[11] recommend that a dose reduction should be considered for T2DM patients with eGFR < 45 mL/min/1.73 $m^2$, and use of metformin is not recommended for patients with eGFR 30–45 mL/min/1.73 $m^2$. The National Institute for Health and Care Excellence[12] recommend that metformin should be prescribed with caution in patients with eGFR < 45 mL/min/1.73 $m^2$, as well as for those at risk of a sudden deterioration of kidney function and those at risk of eGFR < 45 mL/min/1.73 $m^2$. Similarly, metformin

use should be discontinued if eGFR reaches <30 mL/min/1.73 $m^2$. The New Zealand Medicines and Medical Device Safety Authority, Medsafe [13], recommends adjustment of metformin dosage for patients with creatinine clearance (CrCl) of 30–60 and 15–30 mL/min to 1000 and 500 mg/day, respectively. Use of metformin in patients with CrCl < 15 mL/min should be discontinued. The Australian Medicines Handbook[14] states similar recommendations to that of Medsafe, but differs in that metformin is not recommended for patients with CrCl <30 mL/min, but it can be considered for patients with stable kidney function and CrCl > 15 mL/min with careful monitoring.

In conclusion, metformin is a first-line oral hypoglycemic agent with a similar curative effect to that of insulin. There are some benefits of metformin for patients with T2DM, such as lower risk of hypoglycemia and cardiovascular disease, low cost, anti-inflammatory, and weight loss. Despite its benefits, metformin use among patients with CKD is associated with increased risk of lactic acidosis and all-cause mortality, particularly in patients with late-stage CKD. The findings from a previous Taiwanese population-based study support the increased risk of all-cause mortality among metformin users with T2DM and advanced CKD. Therefore, the Taiwan Food and Drug Administration has modified the contraindications for metformin to recommend that it must be discontinued in T2DM patients with eGFR < 30 mL/min/1.73 $m^2$.

## Reference


1. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9(th) edition. Diabetes Res Clin Pract 2019; 157:107843.
2. Hawley SA, Gadalla AE, Olsen GS, Hardie DG. The antidiabetic drug metformin activates the AMP-activated protein kinase cascade via an adenine nucleotide-independent mechanism. Diabetes 2002;51:2420-5.
3. Zhou G, Myers R, Li Y, Chen Y, Shen X, Fenyk-Melody J, et al. Role of AMP-activated protein kinase in mechanism of metformin action. J Clin Invest 2001;108:1167-74.
4. Lipska KJ, Bailey CJ, Inzucchi SE. Use of metformin in the setting of mild-to-moderate renal insufficiency. Diabetes Care 2011;34:1431-7.
5. Misbin RI, Green L, Stadel BV, Gueriguian JL, Gubbi A, Fleming GA. Lactic acidosis in patients with diabetes treated with metformin. N Engl J Med 1998;338:265-6.
6. Richy FF, Sabido-Espin M, Guedes S, Corvino FA, Gottwald-Hostalek U. Incidence of lactic acidosis in patients with type 2 diabetes with and without renal impairment treated with metformin: a retrospective cohort study. Diabetes Care 2014;37:2291-5.
7. Eppenga WL, Lalmohamed A, Geerts AF, Derijks HJ, Wensing M, Egberts A, et al. Risk of lactic acidosis or elevated lactate concentrations in metformin users with renal impairment: a population-based cohort study. Diabetes Care 2014;37:2218-24.
8. Lazarus B, Wu A, Shin JI, Sang Y, Alexander GC, Secora A, et al. Association of Metformin Use With Risk of Lactic Acidosis Across the Range of Kidney Function: A Community-Based Cohort Study. JAMA Intern Med 2018;178: 903-910.
9. Hung SC, Chang YK, Liu JS, Kuo KL, Chen YH, Hsu CC, et al. Metformin use and mortality in patients with advanced chronic kidney disease: national, retrospective, observational, cohort study. Lancet Diabetes Endocrinol 2015;3: 605-14.
10. US Food and Drug Administration. FDA drug safety communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function. Silver Spring: FDA, 2016.
11. Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, et al. Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2018;41: 2669-2701.
12. National Institute for Health and Care Excellence. Type 2 diabetes in adults: management. [NICE guideline NG28] Manchester: NICE, 2015.
13. Medsafe. Metformin — renal impairment and risk of lactic acidosis. Prescriber update [website]. Wellington: New Zealand Medicines and Medical Devices Safety Authority, 2015.
14. Australian Medicines Handbook 2018 [online]. Adelaide: Australian Medicines Handbook, 2018.

# 有慢性腎臟病之第二型糖尿病患使用 metformin 的安全性考量

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**摘要**

在過去 30 年，糖尿病皆高居台灣地區十大死因前五位，糖尿病所引起的嚴重的併發症，已造成國家社會經濟沉重的負擔，糖尿病也是導致台灣民眾發生末期腎臟病的主要原因。在糖尿病患中，超過 9 成罹患第二型糖尿病。而 metformin 是目前主要被用來治療第二型糖尿病的第一線降血糖藥物，因為其安全、較便宜、抗發炎且具有保護心血管的好處。由於 90% 是經由腎臟代謝，所以對於有慢性腎臟病的第二型糖尿病患而言，會有因為乳酸代謝不足而引起乳酸中毒風險，所以有慢性腎臟病的第二型糖尿病患具有因服用 metformin 引起乳酸中毒的高風險。礙於相關研究缺乏完整資料及不同的研究限制，因此不同臨床指引在慢性腎臟病不同階段的安全處方及用量並不一致，雖然一般建議中度慢性腎臟病（eGFR 30-45 ml/min/1.73 $m^2$）需減量使用，但在輕度（estimated glomerular filtration rate (eGFR) 45-60 ml/min/1.73 $m^2$）建議仍可以正常使用，唯重度（eGFR<30 ml/min/1.73 $m^2$）在使用 metformin 上因為臨床試驗研究較難進行而較少實證依據，一個利用全國性資料庫研究結果顯示，晚期慢性腎臟病患使用 metformin 會增加死亡的風險，近期美國全國性研究亦顯示，輕度及中度慢性腎臟病患使用 metformin 不會造成乳酸中毒的風險，但是重度則有顯著風險，因此在 metformin 使用的安全性考量上，仍然要依照病患慢性腎臟病不同嚴重度採取不同考量，基於藥物的安全性及療效，台灣食品藥物管理署已於近年修正此藥品仿單禁忌症，將有重度慢性腎臟病的第二型糖尿病患列為禁用。

**關鍵詞**：慢性腎臟病、第二型糖尿病、metformin

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Review Article

# Unusual Causes of Paraplegia: Literature Review

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**Abstract**

Paraplegia refers to damage to the neurons in the thoracic, lumbar, or sacral segments of the spinal cord, resulting in an injury that is often associated with the loss of motor or sensory functions. In general, the function of the upper limbs is not affected, and the extent of damage to the lower body is determined by the location and level of the injury. Due to advancements in medical technology, a considerable proportion of paraplegic patients can resume independent functions of daily life and return to work or school, following proper treatment and rehabilitation. However, paraplegia is only a symptom, not a cause; therefore, the early diagnosis of paraplegia is of great importance. The causes associated with paraplegia are numerous, ranging from common trauma to rare infections, and the symptoms can vary. We discussed five uncommon paraplegia causes that have been cited in the literature, including spinal dural arteriovenous fistula, spontaneous spinal epidural hematoma, aortic dissection, decompression sickness, and spinal tuberculosis, and review the pathophysiology and clinical symptoms associated with each cause, as well as their treatment and prognosis. We hope to expand the range of possibilities for the differential diagnosis of paraplegia, to increase the likelihood of proper diagnoses and treatment at early stages.

**Key words:** paraplegia, arteriovenous fistula, spontaneous hematoma, decompression, aortic dissection, spinal tuberculosis

## Introduction

Paraplegia refers to the impairment or loss of motor or sensory function in the thoracic, lumbar, or sacral regions of the spinal cord, secondary to the damage of neural elements within the spinal canal. Arm functioning is generally spared, but the trunk, legs, and pelvic organs may be involved, depending on the level of injury [1]. Symptoms can include the loss of sensation or mobility below the level of injury, the loss of bladder and bowel function, and unexplained pain. Paraplegia can be further categorized into complete and incomplete paraplegia. Complete paraplegia is defined as the complete lack of motor or sensory function at the lowest sacral segment, whereas incomplete paraplegia indicates that some amount of function, either motor or sensory, is preserved below the neurological level. Paraplegia is predominantly caused by spinal cord injuries that result from accident or trauma; however, other causes include iatrogenic injuries, genetic disorders, autoimmune diseases, infections, tumors, and stroke. Treatment varies, depending on the severity, the level of injury, and the etiology. In this article, we briefly discuss some uncommon etiologies, to expand the possibilities available to readers when performing differential diagnosis for paraplegic patients.

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## Relevant Case Presentation

**Case 1: Spinal dural arteriovenous fistula (SDAVF)**

A 79-year-old female patient, with a history

of chronic atrial fibrillation under anticoagulation therapy, was admitted to the hospital with persistent coma after a first episode of seizure. Lumbar puncture was performed, and prophylactic enoxaparin was instituted 24 hours later. Abrupt lower limb anesthesia and paraplegia developed 5 days after the lumbar puncture. Magnetic resonance imaging (MRI) revealed a subarachnoid hematoma from T12-L5, and arteriography showed a spinal dural arteriovenous fistula at T12 to L1. Embolization and spinal laminectomy were performed, for subarachnoid hematoma evacuation [2].

**Case 2: Spontaneous Spinal Epidural Hematoma (SSEH)**

A 31-year-old female patient, without a recent history of infection, trauma, surgery, or anticoagulant use, presented at the emergency department with weakness in the bilateral lower extremities, after waking up in the morning. The patient then deteriorated to the acute onset of flaccid quadriplegia [American Spinal Injury Association (ASIA) score A]. The initial laboratory tests and blood pressure were within normal limits. Neurological exam disclosed the loss of bilateral lower extremity muscle power (0/5), the loss of skin sensation below the T4 vertebral level, with saddle anesthesia, a positive Babinski sign of the bilateral lower extremities, and reduced bilateral tendon reflex. MRI revealed a posterior epidural hematoma, from the T2 to T3 levels, with spinal cord compression. Spontaneous spinal epidural hematoma was diagnosed. An urgent, posterior-approach, decompression laminectomy with hematoma evacuation was performed, and early rehabilitation was initiated [6].

**Case 3: Acute Aortic Dissection**

A 56-year-old female patient, with a medical history of chronic obstructive pulmonary disease, presented to the emergency department with the chief complaints of lumbar back pain and paresthesia and paralysis in both lower extremities. She was in her usual state of health, without walking difficulties, 90 minutes before the presentation of symptoms. She denied any previous surgeries, intravenous drug abuse, fever, or recent trauma. Her vital signs were remarkable for hypertension and tachypnea. The initial laboratory findings disclosed hypokalemia, elevated glucose levels, and elevated white blood cell counts. Computed tomography (CT) scan revealed disc herniation, which resulted in L5/S1 spinal stenosis. After the administration of pain control and antibiotics, she was referred for MRI scanning. Upon arrival, she was noted for a blood pressure of 176/84 mmHg and sustained low back pain. Physical examination revealed flaccid paralysis and both lower extremities were cold and pulseless to palpation. Neurologic examination disclosed anesthesia below the level of T10, with absent patella tendon reflexes. Doppler ultrasound failed to detect bilateral dorsalis pedis and femoral pulses. CT angiography (CTA) showed Stanford type A aortic dissection (AD), extending to the celiac trunk, with an abdominal aortic thrombus proximal to the iliac bifurcation. Anti-hypertensive agents were administered, and urgent surgical repair was performed [9].

**Case 4: Decompression Illness (DCI)**

A 46-year-old, experienced, female diver dived to 110 feet for 27 minutes and conservatively decompressed for 13 minutes, at 10 feet. Within 10 minutes after she surfaced, her right foot felt hot and tingly while climbing onto the boat. Then, it became progressively numb, with radiation to the thigh. Her left limb suffered from the same symptoms, and low back pain developed. She could not walk after reaching the shore for 30 minutes. Immediately, pure oxygen was delivered for 60 minutes, and her sensation and strength gradually recovered. She was fully recovered and felt normal one week later [14].

**Case 5: Spinal Tuberculosis**

A 33-year-old female presented to the hospital with low back pain that radiated to her lower extremities and the inability to walk. She began experiencing these symptoms approximately four months previously and was incapable of performing her usual activities. One month prior to her presentation, she noticed the progressive inability to move her lower limbs and eventually became bed-bound. Occasional fever, decreased appetite, and weight loss were mentioned, beginning six months prior to presentation. No cough, chest pain, or shortness of breath was noted. On examination, she appeared malnourished, with tachypnea and raised body temperature. Chest auscultation revealed bilateral crackles. Lower limb examination disclosed bilaterally decreased muscle power (3/5), with diminished plantar reflexes and

tenderness at the L1-L2 area. X-ray of the lumbosacral spine region showed L2 compression, with the involvement of the L1-L2 paradiscal area. MRI of the spine revealed spondylodiscitis at the L1-L2 level, with a soft tissue component compromising the spinal canal and a bilateral psoas muscle abscess. Chest X-ray revealed a bilateral heterogeneous opacity, with right upper lobe (RUL) cavitation. Sputum acid-fast staining was positive. She was diagnosed with pulmonary tuberculosis, with vertebral involvement. Spinal decompression was performed, and anti-tubercular therapy was administered [17].

## Discussion

### A. Spinal dural arteriovenous fistula

SDAVF is the most common vascular malformation of the spine. SDAVF has a male predilection and many cases become symptomatic during middle age, suggesting that it is likely to be an acquired disease. Most lesions are solitary and are frequently found in the thoracolumbar region (T6-L2). The exact etiology remains unclear [2,3].

Typically, a radiculomeningeal artery enters a radicular vein and forms an SDAVF on the dorsal surface of the dural root sleeve in the intervertebral foramen. Consequently, the increased pressure within the perimedullary venous plexus results in decreased spinal vein drainage, leading to venous congestion, with intramedullary edema and dilated and torturous veins, which subsequently cause spinal cord hypoxia and myelopathy [4].

Symptoms progress slowly and are nonspecific, including tingling pain, lower back pain, paresthesia, sensory loss, lower extremity weakness, and unsteady gait. Symptoms become worse during physical activity. Bowel and bladder incontinence and erectile dysfunction often present late during the course of the disease. However, spinal hemorrhage is very rare [3,4].

SDAVF diagnosis is generally confirmed by MRI and spinal angiography. On a T1-weighted scan, after contrast administration, the dilated perimedullary vessels are enhanced. Meanwhile, cord edema appears as hyper-intensity, with peripheral sparing, on a T2-weighted scan. A prominent, serpiginous, and engorged perimedullary venous plexus can be observed on the dorsal aspect of the cord. Digital subtraction angiography (DSA) is the gold standard for diagnosis because it can help identify the location of the fistula. After injection, the delayed return of contrast material in the radiculomedullary arteries, with the early venous filling of the radiculomedullary veins, can be observed [4,5].

Treatment with endovascular embolization is performed using liquid embolic agents, to occlude the distal part of the feeding artery and the proximal part of the draining vein. Other options include surgical therapy to ligate the draining vein, which should be considered if endovascular treatment is contraindicated or fails [2-4].

Prognosis is associated with the duration of the symptoms and disability before treatment. Although motor and sensory impairment benefit the most from treatment, sphincter and erectile dysfunction often respond less effectively [3,4].

### B. Spontaneous spinal epidural hematoma

SSEH is defined as the accumulation of blood within the epidural space, without known traumatic or iatrogenic causes, and constitutes less than 1% of all spinal epidural lesions, with an annual incidence of approximately 1 per million individuals. SSEH typically occurs in individuals in their forties and fifties, and the exact etiology remains unknown. Predisposing factors include underlying coagulopathy, anticoagulant use, arteriovenous malformation, increased intra-thoracic or intra- abdominal pressure, and hypertension [6,7].

The origin of hemorrhages remains under debate. However, most evidence supports the hypothesis of venous bleeding. The low pressure, valveless, epidural venous plexus is vulnerable to any changes in pressure from the thoracic and abdominal cavities, such as those that occur during coughing and sneezing, which can result in a venous rupture. According to the arterial bleeding hypothesis, a hematoma forms quickly, resulting in the abrupt onset of SSEH. However, the origin of bleeding is not a major prognostic factor [6,7].

Compared with the ventral epidural side, SSEH is more often observed on the dorsal aspect, due to the larger dorsal epidural plexus and a region called the locus minor resistentiae, which is more susceptible to rupture following minor variations in intravenous pressure. Moreover, the ventral epidural veins receive more support from the posterior longitudinal ligament. SSEH occurs predominantly

at the cervicothoracic and thoracolumbar segments because the increased mobility of these segments applies more tension to the epidural veins [7].

Symptoms vary, depending on the location and severity of spinal cord compression. Typically, patients present with the acute onset of severe neck or back pain, with occasional radiation to the extremities, followed by the rapid progression to nerve root or spinal cord compression symptoms. Hyporeflexia and flaccid paralysis may also present [6-8].

MRI is the diagnostic standard because it can determine both the location of the hematoma and the severity of spinal cord compression. Within the first 24 h of symptom onset, hematoma typically appears hyperintense on T2-weighted images and often becomes hyperintense on both T1- and T2-weighted scans 24 h later. Chronic hematomas may emerge as hypointensities on both T1- and T2-weighted images [7].

Surgical decompression, along with hematoma evacuation, is the standard treatment for SSEH. Based on a small number of case reports, many have suggested urgent surgical decompression within 12–48 h of symptom onset, to achieve optimal neurologic improvements. Only those who are not fit for surgery and those who are asymptomatic, with spontaneous hematoma resorption, can be managed conservatively [7,8].

The time interval to surgery and, more importantly, the degree of preoperative neurological deficits are two major prognostic indicators. Other poor prognostic factors include the involvement of four or more spinal segments, sensory impairment, and the involvement of areas that have narrow spinal canals [6-8].

**C. Acute Aortic Dissection**

AD is a life-threatening condition that describes a tear in the intimal layer of the aortic wall, leading to blood extravasation into the media of the aorta and the creation of a false lumen. AD may affect other arteries, by blocking blood flow in the true lumen, resulting in decreased blood flow to the vital organs. Dissection weakens the aortic wall, causing aneurysm formation or vessel rupture. The mortality rate increases by approximately 1% per hour during the first 48 hours if the diagnosis is delayed [9,10].

AD can be classified into two types, DeBakey or Stanford, depending on the site of the dissection. DeBakey ADs can be further subdivided into type I, which involves both the ascending and descending aorta, type II, which involves only the ascending aorta, and type III, which involves the descending aorta, distal to the left subclavian artery. Stanford Ads can be subdivided into type A, which involves the ascending aorta, and type B, which involves the descending aorta. Dissection is more commonly observed at proximal sites [9,10].

Risk factors for AD development include hypertension, age, being male, smoking, connective tissue disease, and congenital anomalies [9,10].

Typically, the patient presents with abrupt, severe, tearing, sharp chest pains that may radiate to the back. Other symptoms include syncope, heart failure, cerebral vascular accidents, shock, pulse deficits, limb ischemia, and a murmur of aortic insufficiency [10].

However, paraplegia as an initial presentation observed in fewer than 2%–5% of all AD cases, most likely caused by anterior spinal artery syndrome, due to direct compression from the dissection or dissection of branch vessels. For instance, the artery of Adamkiewciz, between T10-L2, can cause spinal cord ischemia. AD often starts with the loss of pain and temperature sensation while maintaining intact vibration and proprioception sensations. Depending on the duration of ischemia, paraplegia may then develop [9,11-12].

Diagnosis includes history taking, physical examination, and imaging evaluations, such as chest X-rays, trans-esophageal echocardiogram, CT, or CTA [10].

However, if paraplegia is the initial manifestation, doctors may be misled by the lack of spinal cord compression on MRI. Therefore, the prompt suspicion of acute AD should be considered when symptoms and signs of distal vascular abnormalities, asymmetric radial pulses, uncontrolled blood pressure, or persistent chest pain occur [9,11-12].

Treatment plans depend on the type of acute AD. In general, intravenous beta-blockers are administered first, followed by intravenous vasodilators, to reduce the heart rate below 60 bpm and blood pressure to the lowest level that preserves perfusion. If the ascending aorta is involved, urgent intervention, with surgical management, is usually required. If only the descending aorta is involved, conservative treatment with medical therapy is generally sufficient [9,11-12].

Moreover, if spinal cord ischemia develops, a lumbar drain can be placed, to lower intraspinal pressure, optimize cord perfusion, and improve neurologic outcomes [9,12].

The prognosis of paraplegia due to acute AD is often considered poor [11].

**D. Decompression illness**

Decompression illness (DCI) is a dysbaric disease that includes decompression sickness (DCS) and arterial gas embolism (AGE). Factors, such as depth-time exposure, breathing gas, diver exertion, and water temperature can affect the probability of DCI. The estimated incidence of DCI is approximately 0.03%, with increased risks among patients with persistent patent foramen ovale, and the mean age of DCI patients is 39 years [13,14].

Decompression sickness occurs due to Henry's Law, when nitrogen gas comes out of solution and supersaturation occurs during ascent, forming bubbles in the tissue and venous blood. The level of bubble formation depends on the depth and duration of the dive and the rate of ascent. Once bubbles develop, they result in vascular injuries, such as intravascular coagulation and plasma leakage, and central nervous system (CNS) injuries, caused by secondary oxidative stress and inflammation. DCS presentations differ in severity, with pain in the joints or muscles and paresthesia being the most common symptoms. The classification depends on the manifestations of DCS. Type I includes joint pain, skin rash or marbling, swelling or pain in the lymph nodes, and focal edema. Type II includes cardiorespiratory failure, inner ear presentations, such as vertigo, and neurologic symptoms involving the brain or spinal cord, including weakness or paralysis, visual disturbances, bowel or bladder dysfunction, lethargy, and confusion. Most patients become symptomatic within the first 24 hours [13-15].

An arterial gas embolism occurs when a diver breathes compressed gas at depth and rapidly ascends, without exhaling the air from the lungs. According to Boyles's Law, this series of events may result in alveolar rupture and subsequent air leakage into the surrounding spaces, leading to barotrauma, such as pneumothorax, and pneumomediastinum. Moreover, air can enter the pulmonary arterial circulation, causing embolisms that occlude the terminal arteries, such as those in the brain, resulting in the development of stroke-like events. Manifestations vary depending on the sites that are involved. Pain, respiratory distress, headache, unconsciousness, seizure, blindness, or paresis may be presented [13-15].

The diagnosis of both DCS and AGE is based on clinical evaluations, including diving history, depth-time profile, onset of the symptoms, and physical examination. Laboratory and imaging studies generally provide little benefit to the diagnosis. Although chest X-ray and CT can help to detect complications associated with pulmonary barotrauma, they are often only used to exclude other etiologies. MRI may aid the diagnosis of neurologic DCS; however, MRI results are often normal [13,14].

The severity of the injury and the time to effective treatment greatly affect neurologic outcomes. DCS and AGE are associated with similar presentations, often occur together, and management strategies are essentially the same for both syndromes. The immediate administration of 100% oxygen can promote the oxygenation of hypoxic tissues and accelerate the rate of nitrogen removal. The timely transport the patient to a recompression chamber for hyperbaric therapy with oxygen as the primary treatment, as this treatment can reduce bubble volumes and inflammation and improve tissue ischemia and edema. Additional management strategies, such as the use of non-steroidal anti-inflammatory drugs (NSAIDs) can decrease the number of recompression therapy but do not alter clinical outcomes. Fluid resuscitation is necessary for potential hypovolemia and hemoconcentration. Anticoagulants are administered prophylactically in the event of paraplegia. The avoidance of hyperglycemia and hyperthermia is also recommended [13,15,16].

The risks of DCI can be reduced by adopting decompression procedures, which allow divers to ascend at a rate that is compatible with the slowest tissue that accepts and releases gas for the depth and duration of the dive. The avoidance of vigorous exercise, the use of alcohol, and cold conditions during decompression after diving is also recommended [13,15,16].

In general, the long-term neurologic prognosis is good, and patients achieve complete recovery, likely because most injured divers are young and have better health conditions[13,15,16].

**E. Spinal tuberculosis**

Spinal tuberculosis (TB), often referred to as Pott's disease, accounts for 1%–2% of total tuberculosis cases and is the most common manifestation of musculoskeletal tuberculosis. Spinal TB is most often observed in poorly developed countries and is more common among HIV-infected patients. Spinal TB generally occurs secondary to an extra-spinal source of infection, such as the lungs. Mycobacterium tuberculosis spreads through hematogenous routes to the vertebral bodies, where thoracic and lumbar segments are most commonly involved. The anterior aspect of the vertebral body, adjacent to the subchondral plate, is usually affected. As bone destruction progresses, collapsing vertebral bodies and kyphotic deformities may present, forming an internal gibbus. Associated abscesses, granulation tissues, and tubercular debris may result in spinal cord compression and neurologic deficits. Inflammation edema, cord atrophy, or even myelomalacia may develop [18,19].

The presentation is insidious, and constitutional symptoms, such as fever, night sweats, and weight loss are often reported. Non-specific, chronic back pain may also be noted. If the cervical spine is affected, the disease may manifest as neck pain and stiffness, dysphagia, stridor, and hoarseness. Cutaneous sinuses, paraspinal abscesses, muscle rigidity, and spasm may be detected. Neurologic abnormalities present as early spasticity, with exaggerated deep tendon reflexes. The loss of motor power, including weakness and paraplegia, develops prior to the reductions in pain and temperature sensations. As compression increases, flaccidity and flexor spasm, complete sensory loss, and the disturbance of bowel and bladder sphincters may occur [18,19].

To describe the severity of paraplegia, some experts have proposed a 4-grade classification, based on motor weakness, walking ability, and neurological deficits, as detected on neurological exam. This classification system can help plan and manage spinal TB and paraplegia symptoms [18,20].

Grade 1: Negligible weakness, ability to walk without help, clinician detects plantar extensor, muscle power grade 4-5.

Grade 2: Mild weakness, ability to walk with help, brisk tendon jerks, muscle power grade 3, paresthesia.

Grade 3: Moderate weakness, confined to a bed but able to move the limbs, brisk tendon jerks, sustained muscle clonus, muscle power grade 1-2, hypoesthesia, or anesthesia.

Grade 4: Severe weakness, inability to move the limbs, paraplegia to extension or flexion, muscle power grade 0, total sensory loss, bowel and bladder incontinence.

History taking and examination are important for diagnosis. With a high index of suspicion, percutaneous CT-guided biopsy can be performed, to obtain bone tissue and abscess samples for acid-fast bacilli staining and culture. A biopsy can also allow the therapeutic drainage of paraspinal abscesses. Nucleic acid amplification tests, which have higher specificity and sensitivity and faster results, can also be performed. Histological findings showing features of caseating granuloma and giant cells can also assist the diagnosis. Hematological lab data can present with elevated erythrocyte sedimentation rates (ESRs) and usually display normal white blood cell counts [18-21].

The evaluation of spinal images can also provide an adequate diagnosis. Plain radiographs may show lytic lesions, the wedging of the anterior part of the vertebral body, the destruction of the intervertebral disc, and paravertebral shadow, with or without calcification, suggesting abscess formation. CT scans provide better bony details and allow the earlier detection of disease. The maintenance of disc height until late in the disease and abscess with calcification favor tuberculous lesion over pyogenic diseases. MRI is the gold standard for evaluating disk-space infections and osteomyelitis of the spine, allowing the visualization of cord compression [18-21].

Conservative anti-tubercular therapy, consisting of a 4-drug regimen (isoniazid, rifampicin, ethambutol, and pyrazinamide), is the usual course of spinal TB management. Many experts have suggested treatment for 9 to 12 months, using the directly observed treatment short-course (DOTS) method. Most patients can achieve pain relief and neurological improvements within 3 months of treatment onset. The rate of lesion recrudescence is approximately 2%–5%. Drug resistance has been noted to occur in 5%–10% of cases, requiring the use of second-line drugs, such as quinolone and aminoglycoside [18-21].

Although surgical intervention remains controversial, it is generally advised in patients with neurological deficits, including paraplegia with

acute deterioration, established or predicted spinal deformity with instability or pain, large paraspinal abscesses, non-diagnostic percutaneous biopsies, and poor response to medical therapy. Surgery can decompress the spinal cord, correct kyphosis, and result in more rapid pain relief. Some surgical interventions include anterior decompression, with debridement and posterior instrumentation for stabilization. However, laminectomy is contraindicated during typical anterior spinal tuberculosis because it makes the spine unstable [18-21].

Other management strategies include bed rest and the use of braces. However, the efficacy of these strategies remains questionable [18-21].

Overall, the prognosis is good, with almost all patients achieving improvements in neurological deficits and pain [18-21].

## Conclusions

Paraplegia is a variable condition, and the extent of functional loss is correlated with the degree of spinal cord injury and the area that is affected. Immediate and proper treatment may result in the best chances of recovery. Therefore, the early diagnosis of the underlying cause is important. Though not commonly observed, these etiologies should be considered whenever unusual paraplegic situations are encountered.

## References


1. Kirshblum SC, Burns SP, Biering-Sorensen F, Donovan W, Graves DE, et al. International standards for neurological classification of spinal cord injury (Revised 2011). J Spinal Cord Med 2011 Nov; 34(6): 535-546.
2. Andériz FO, Malpica AB, Sorribas EM, Clotet NC, Chasín JA. Paraplegia after lumber puncture. Am J Med Sci 2014 Feb; 347(2): 170-171.
3. Babichev KN, Orolov KP, Stanishevskiy AV, Savello AV, Svistov DV. Spinal Dural Arteriovenous Fistulas: A Series of Clinical Cases and an Analysis of the Literature Data. Burdenko's J Neurosurg 2017 Apr; 81(4): 33-44.
4. T. Krings, S. Geibprasert. Spinal Dural Arteriovenous Fistula. Am J Neuroradiol 2009 Apr; 30(4): 639-648.
5. Ying J, Chen DY, Hsu HL, Huang YL, Chen CJ, Tseng YC. Spinal Dural Arteriovenous Fistula: Imaging Features and Its Mimics. Korean J Radiol 2015 Sep-Oct; 16(5): 1119-1131.
6. Zuo B, Zhang Y, Zhang J, Song J, Jiang S, Zhang X. Spontaneous Spinal Epidural Hematoma: A Case Report. Case Rep Ortho Res 2018; 1: 26-33.
7. Figueroa J, DeVine JG. Spontaneous spinal epidural hematoma: literature review. J Spine Surg 2017 Mar; 3(1): 58-63.
8. Xian H, Xu LW, Li CH, Hao JM, Wan WX, Feng GD, et al. Spontaneous spinal epidural hematomas: One case report and rehabilitation outcome. Medicine (Baltimore) 2017 Nov; 96(44): e8473.
9. Hughes KE, Seguin C, Felton B, Hughes MJ, Castle D. Acute Aortic Dissection Presenting as Bilateral Lower Extremity Paralysis: A Case Report. J Emerg Med 2016 Oct; 51 (4): 450-453.
10. Elsayed RS, Cohen RG, Fleischman F, Bowdish ME. Acute Type A Aortic Dissection. Cardiol Clin 2017 Aug; 35(3): 331-345.
11. Nazari P, Tan LA, Kasliwal MK, Traynelis VC. Aortic dissection: An Unusual Extraspinal Cause of Acute Paraplegia in the Emergency Department. J Emerg Med 2017 Jan; 52 (1): e19-e21.
12. Hdiji O, Bouzidi N, Damak M, Mhiri C. Acute aortic dissection presenting as painless paraplegia: a case report. J Med Case Rep 2016 Apr 5; 10: 99.
13. Massey EW, Moon RE. Neurology and Diving. Handb Clin Neurol 2014; 120: 959-969.
14. Yoshiyama M, Asamoto S, Kobayashi N, Sugiyama H, Doi H, Sakagawa H, et al. Spinal cord decompression sickness associated with scuba diving: correlation of immediate and delayed magnetic resonance imaging findings with severity of neurologic impairment—a report on 3 cases. Surg Neurol 2007 March; 67(3): 283-287.
15. Eichhorn L, Leyk D. Diving Medicine in Clinical Practice. Dtsch Arztebl Int 2015 Feb; 112 (9): 147-158.
16. Bove AA. Diving Medicine. Am J Respir Crit Care Med 2014 Jun 15; 189 (12): 1479-1486.
17. Adhikari S, Basnyat B. Extrapulmonary tuberculosis: a debilitating and often neglected public health problem. BMJ Case Rep 2018 Dec 19; 11(1). pii:e226098.
18. Kumar K. Spinal tuberculosis, natural history of disease, classifications and principles of management with historical perspective. Eur J Orthop Surg Traumatol 2016 Aug; 26(6): 551-558.
19. Dunn RN, Ben Husien M. Spinal tuberculosis. Bone Joint J 2018 April 1; 100-B (4): 425-431.
20. Agrawal V, Patgaonkar P R, Nagariya S P. Tuberculosis of spine. J Craniovertebr Junction Spine 2010 Jul; 1 (2): 74-85.
21. Jain AK, Kumar J. Tuberculosis of spine: neurological deficit. Eur Spine J 2013 Jun; 22 (Supp 4): 624-633.

# 非尋常病因之截癱：文獻回顧

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**摘要**

截癱是指脊髓的胸、腰或薦段中神經元的傷害，導致運動或感覺功能的損傷或喪失。一般而言，上肢的功能不受到影響，而其下半身受損的程度則依據受傷的位置和範圍決定。以現今的醫療水平，截癱的病人在經過適當的治療與復健之後，仍有相當比例的患者能恢復生活獨立自主的功能，甚至重返工作崗位或學校進修。然而，截癱只是種表象而非病因，因此，早期的診斷顯得更重要。其造成的原因族繁不及備載，症狀也是各式各樣，從常見的創傷到少見的感染都有可能。本篇文章列舉了五個不常見的原因，包括脊髓硬脊膜動靜脈瘻管、自發性脊椎硬腦膜外血腫、主動脈剝離、潛水減壓症與脊椎結核病，並且從病例的呈現到簡單討論個別病因的病生理機轉、症狀和治療等，希望藉此使各位讀者在遇到截癱的病人時可以有更多的鑑別診斷，從而提早進行治療。

**關鍵詞**：截癱、動脈廔管、硬脊膜外血腫、主動脈剝離、潛水減壓症、脊椎結核病

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Original Article

# Factors Affecting Quality of Life Among Patients with Advanced Prostate Cancer Undergoing Hormonal Therapy

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**Abstract**

This study aimed to analyze quality of life (QOL) in advanced prostate cancer patients who are undergoing hormonal therapy (H/T) to assess major influencing factors and to develop a strategy to improve their QOL. This study enrolled 108 men with advanced prostate cancer aged 43 to 98 years old (median = 74) who had been receiving androgen deprivation therapy for six months to seven years; this therapy consisted of luteinizing hormone-releasing hormone (LHRH) agonists, anti-androgen agents alone, or a combination administered at a single medical center. We used the 47-item Functional Assessment of Cancer Therapy-Prostate (FACT-P, version 3) questionnaire, which was translated into Chinese. The completion rate was 100% using one-on-one and face-to-face interviewing methods. We analyzed the relationship between QOL and the diagnostic age, therapeutic duration, modality of H/T, tumor stage, and therapeutic result. The results concluded that changes in the serum prostate-specific antigen (PSA) level significantly influenced QOL. A better therapeutic result promotes higher FACT-P scores. Although PSA elevation during H/T usually indicates disease progression, it seldom affects the physical condition initially. Nevertheless, increased PSA levels did reduce the total QOL scores according to our study results. Therefore, adequately informing our patients about the relationship between the PSA level and the clinical course of disease progression including salvage strategy for biochemical failure was suggested to minimize their significant fears of an uncertain future and thus improve their QOL during standard H/T for prostate cancer.

**Key words:** androgen deprivation therapy, prostate cancer, quality of life

## Introduction

Prostate cancer is the leading type of cancer in the recent prostate-specific antigen (PSA) era. Patients have at least five choices for most localized prostate cancer treatments, including radical prostatectomy, external beam radiation therapy, brachytherapy, cryotherapy, or watchful waiting. However, for distant metastatic, locally advanced, or localized prostate cancer with a high risk for invasive management[1], hormonal therapy (H/T), or so called androgen deprivation therapy (ADT), has been the best strategy since first reported by Huggins and Hodges in 1941[2]. H/T is currently applied as a first-line, neoadjuvant, adjuvant, or salvage therapy for different statuses of prostate cancer.

The incidence of prostate cancer has increased from 9.94 cases per 100,000 in 1996 to 26.51 per 100,000 in 2006 and 30.1 per 100,000 in 2016, when it was ranked as the fifth leading cause of cancer[3]. Furthermore, 48.72% of the total newly diagnosed cases were advanced stage cases (stages II and IV), and 59.62% of patients were receiving H/T.[3] H/T plays an important role in prostate cancer patients, particularly in those with advanced or metastatic cancer, in

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whom ADT is usually the first choice. Therefore, the importance of identifying the key factors affecting QOL among prostate cancer patients undergoing H/T cannot be overemphasized.

Although H/T alone and combined radiotherapy or surgery have been proven to improve the survival rate of prostate cancer[4,5], there is a lack of large studies addressing the QOL of Oriental patients who have different backgrounds, lifestyles, and cultures compared to Western men. There are many side effects of ADT, such as hot flashes[6], loss of libido, osteoporosis, gynecomastia and/or breast tenderness[7], muscle weakness, diarrhea, etc[8]. However, the true QOL of prostate cancer patients may be influenced by numerous psychosocial factors separate from the direct physical response to ADT. We aimed to analyze the major factors that affect QOL among this group by cancer stage, duration of H/T, modality of H/T, therapeutic results, and age at disease diagnosis.

Cella et al. first developed a 34-item Functional Assessment of Cancer Therapy-General (FACT-G) measurement tool in 1989 to evaluate QOL for all cancer patients. They added 12 prostate items to the FACT-G and designed the FACT-P questionnaire in 1992[9]. Subsequently, the QOL for prostate cancer was investigated by Peg Esper and colleagues in 1997 with the modified 47-item questionnaire (FACT-P, version 3), which includes six domains consisting of the traditional 34 items/5 domains adopted from FACT-G instrument; the last 13 items address symptoms and problems specific to prostate cancer[10]. We used the translated 47-item questionnaire to analyze the QOL of 108 advanced prostate cancer patients at a single medical center and compared the results with previous Western studies.

## Material and Methods

H/T was applied to locally advanced or distant metastatic prostate cancer patients with three different conditions (or combinations): (1) biochemical (PSA) failure following radical prostatectomy or radiation therapy; (2) pelvic lymph node metastases diagnosed by bilateral pelvic lymph node dissection or imaging studies; and (3) prostate cancer with bone metastasis according to scintigraphy or radiologic studies.

This cross-sectional study of QOL was performed in 108 men with prostate cancer aged 43 to 98 years old (median = 74 years) who were treated with H/T at a medical center (Veterans General Hospital Tai-Chung, VGHTC) in central Taiwan. All patients had been undergoing H/T, including luteinizing hormone-releasing hormone (LHRH) analogues and steroidal or non-steroidal anti-androgen treatment, for six months to seven years while enrolled in this study. All patients (100%) were interviewed and answered the 47-item questionnaire cooperatively during the regular follow-up at our outpatient department over the same period. Our single interviewer administered the instruments to each consenting patient by reading the items to him face-to-face and recording his responses in a private space.

The 47-item questionnaire was composed of two parts. The first portion is the traditional FACT-G, which is a 34-item general QOL measurement tool consisting of four cornerstone dimensions of QOL: physical well-being (eight items), social/family well-being (eight items), emotional well-being (seven items), functional well-being (eight items), and a brief assessment of the relationship with the doctor (three items). The second portion is the prostate cancer subscale, which includes 13 items specific to prostate cancer related to sexuality, bowel/bladder function, and pain. Due to the last item in each domain, questions 8, 16, 19, 26, 34, and 47, got 10-leveled score; these six questions were excluded in this study according to Esper's study[10]. The other 41 questions were scored from 0 to 4, which indicated "not at all" to "very much", respectively.

Some of the patients who were verified as having adenocarcinoma of the prostate at a clinically advanced stage via a digital rectal examination (DRE) with transrectal ultrasonographic (TRUS) biopsy and imaging studies received H/T alone. Others accepted salvage H/T following tumor recurrence or increasing PSA levels after undergoing local treatment such as radical prostatectomy or external beam radiation therapy. All patients had a clear sensorium without evidence of brain metastasis or any confirmed major psychological disorders. Twenty-four randomized patients were interviewed twice by the same interviewer with the same questionnaire with a one-month interval between assessments.

The patient characteristics are summarized in Table 1, including diagnostic age, performance status, duration of H/T, tumor stage, therapeutic modality,

**Table 1.** Patient demographics

| Variable | No of Pt |
|---|---|
| Diagnostic age (year) | |
| ≤ 64 | 20 (18.5%) |
| 65 ~ 74 | 65 (60.2%) |
| ≥ 75 | 23 (21.3%) |
| Performance status | |
| Grade 0 | 76 (70.4%) |
| Grade 1 | 24 (22.2%) |
| Grade ≧ 2 | 8 (7.4%) |
| Durations of H/T (year) | |
| 0-1 | 24 (22.2%) |
| 1-3 | 43 (39.8%) |
| > 3 | 41 (38.0%) |
| Tumor stage | |
| Locally advanced | 63 (58.3%) |
| Distant metastasis | 45 (41.7%) |
| Therapeutic modality | |
| H/T only | 61 (56.5%) |
| H/T with OP or R/T | 47 (43.5%) |
| Therapeutic result | |
| Effectiveness | 92 (85.2%) |
| Progression | 16 (14.8%) |

KEY: No = number; Pt = patient; H/T = hormonal therapy; OP = operation; R/T = radiotherapy

and therapeutic result. The performance status ratings were determined by the investigators using a standard Zubrod scoring method. Grade 0 indicates asymptomatic with normal activity; grade 1 indicates symptomatic: fully ambulatory; grade 2 indicates symptomatic: in bed less than 50% of the time; grade 3 indicates symptomatic: in bed more than 50% of the time; and grade 4 indicates bedridden: in bed 100% of the time.

An increasing PSA level after androgen deprivation reliably predicts the development of prostate cancer progression.[11] Therefore, the therapeutic results were categorized into "effectiveness" and "progression". The latter indicates biochemical failure according to the definition established by the American Society for Therapeutic Radiology and Oncology (ASTRO) in 1997, which is defined as three consecutive increases in PSA levels separated by three to four months each.[12]

Taking the tumor stage into consideration, localized tumors including seminal vesicle invasion or prostate capsule penetration were defined as "locally advanced" whereas pelvic lymph node or other distant organ metastases represented "distant metastasis".

We divided the patients into two groups based on therapeutic modality; each group underwent some type of ADT. One group received only H/T whereas the other group received either radiation therapy or a major operation, such as bilateral pelvic lymph node dissection (BPLND) with or without radical retropubic prostatectomy (RRP). Patients underwent BPLND first, and then the lymph node sample was sent to pathology to be frozen. RRP was performed if the nodes were negative; RRP was not performed if the lymph nodes showed malignancy.

The internal consistency (Cronbach's alpha) of the FACT-P, FACT-G, and each domain was calculated. Then, the FACT-P and each subscale score were summarized and analyzed according to the diagnostic age, duration of H/T, tumor stage, modality of therapy, and therapeutic result. Finally, we compared the FACT-P scores of 24 patients who each underwent two separate interviews conducted one month apart to evaluate the test-retest reliability of the Chinese questionnaire using the Wilcoxon signed-rank test.

## Results

Table 1 shows that 81.5% of the prostate cancer victims receiving H/T were elderly (age ≥ 65 years). One hundred patients (92.6%) presented with good performance status (between grade 0 and grade 1) using the standard Zubrod scoring method, whereas the other 8 (7.4%) patients were evaluated as grade 2.

Of the 108 patients assessed, 41 (38.0%) patients had been undergoing ADT for more than three years, and 45 (41.7%) suffered distant metastatic prostate cancer. Although all patients were receiving oral antiandrogenic agent treatment or combined androgen blockage therapy, 47 (43.5%) patients had also undergone major operations (BPLND with RRP or BPLND only) or radiotherapy before the study. Regarding therapeutic results, 92 (85.2%) patients had good efficacy with current H/T whereas the other 16 (14.8%) patients presented with consecutive increases of serum PSA levels.

The Cronbach's alpha values of FACT-P, FACT-G, and the other domains, which were evaluated using the SPSS RELIABILITY procedure, were almost all good (0.70 to 0.79) or high (0.80 to 1.0), except for the subscales of "social/family well-being" (Cronbach's alpha = 0.48).

Table 2 shows that the FAC-P (score = 121.4; range: 0–164) and all other subscales had high scores. When we divided the participants into two groups

**Table 2.** Comparison of FACT-P scores by the therapeutic result

| | Effectiveness (n = 92) | Progression (n = 16) | | Total (n = 108) |
|---|---|---|---|---|
| Subscale | Mean ± SEM | Mean ± SEM | *P* value* | Mean ± SEM |
| A+B+C+D+E+F (0-164 / 41 items) | 123.1 ± 1.6 | 111.4 ± 5.6 | 0.042† | 121.4 ± 1.6 |
| A+B+C+D+E (0-116 / 29 items) | 89.5 ± 1.1 | 80.9 ± 3.7 | 0.013† | 88.2 ± 1.1 |
| A (0-28 / 7 items) | 25.3 ± 0.3 | 23.3 ± 1.4 | 0.126 | 25.0 ± 0.4 |
| B (0-28 / 7 items) | 20.3 ± 0.4 | 18.3 ± 1.0 | 0.038† | 20.0 ± 0.3 |
| C (0-8 / 2 items) | 7.9 ± 0.1 | 7.6 ± 0.3 | 0.099 | 7.9 ± 0.1 |
| D (0-24 / 6 items) | 19.2 ± 0.3 | 17.9 ± 1.3 | 0.401 | 19.0 ± 0.3 |
| E (0-28 / 7 items) | 16.7 ± 0.6 | 13.9 ± 1.3 | 0.074 | 16.3 ± 0.5 |
| F (0-48 / 12 items) | 33.6 ± 0.6 | 30.4 ± 2.4 | 0.33 | 33.2 ± 0.7 |

KEY: A = physical well-being; B = social/family well-being; C = relationship with physician; D = emotional well-being; E = functional well-being; F = prostate cancer scale; S EM = standard error of the mean.
*Mann-Whitney U Test.
† $P < 0.05$.

according to the therapeutic result, disease progression significantly reduced the FACT-P, FACT-G, and social/family well-being subscale scores using the Mann-Whitney U test ($P < 0.05$) although there were no significant differences in the physical well-being, relationship with physician, emotion well-being, functional well-being, and prostate-specific subscales.

The same statistical analysis method was performed to determine the relationship between the FACT-P subscales and other variables including diagnostic age of advanced prostate cancer, duration of H/T, tumor stage, and therapeutic modality. However, all the analysis results showed that QOL was not significantly affected by these factors except for the therapeutic result.

Because Table 2 indicated that the therapeutic result played a significant role in the QOL of advanced prostate cancer patients undergoing ADT, we compared the patients' demographics of the two groups (effectiveness and progression) using Pearson's Chi-square test and Yate's correction of contingency in Table 3. We found that the two groups with different therapeutic results had similar patient characteristics.

Finally, there were no significant differences in the QOL scores of the FACT-P between baseline and the re-test conducted one month later ($P > 0.05$) among the 24 randomized patients who performed this assessment twice. This finding reveals good reliability of the FACT-P questionnaire in Chinese.

**Table 3.** Comparision of patient's characteristics between two groups with different therapeutic result

| | Eff. (n = 92) | Pro. (n = 16) | *P* value |
|---|---|---|---|
| Diagnostic age (year) | | | 0.329* |
| ≤ 64 | 18 | 2 | |
| 65 ~ 74 | 56 | 9 | |
| ≥ 75 | 18 | 5 | |
| Performance status | | | 0.641* |
| Grade 0 | 66 | 10 | |
| Grade 1 | 20 | 4 | |
| Grade ≧ 2 | 6 | 2 | |
| Durations of H/T | | | 0.559* |
| 0-1 year | 21 | 3 | |
| 1-3 years | 38 | 5 | |
| > 3 years | 33 | 8 | |
| Tumor stage | | | 0.035† |
| Locally advanced | 58 | 5 | |
| Distant metastasis | 34 | 11 | |
| Therapeutic modality | | | 0.800† |
| H/T only | 51 | 10 | |
| H/T + OP or R/T | 41 | 6 | |

KEY: Abbreviations as in Table 1; Eff. = effectiveness; Pro. = progression.
*Pearson Chi-spuare test.
† Yate's correction of contigency.

## Discussion

The PSA level has been widely used as an important monitoring tool for prostate cancer follow-up in recent decades, although it may be influenced by prostatitis[13], prostate massage, or laboratory errors. Given the easy detection of tumor recurrence or out of control tumors via an increasing PSA level, the low

incidence of vital organ metastases, and several well-developed cancer therapies, the survival rate of prostate cancer is better than that of other malignancies. According to Nima Sharifi's recent study, the median overall survival from the onset of H/T was 89.0 and 63.0 months for biochemical failure with no radiographic evidence of disease and radiographic metastatic disease, respectively[14]. This indicates that patients with advanced prostate cancer must face and cope with the disease physically and psychologically for a long time since the natural history of prostate cancer results in a protracted course[15].

Based on this cross-sectional analysis, we can infer that the PSA level is an important factor affecting the QOL of prostate cancer patients in Taiwan. Patients in the disease progression subgroup had a significantly lower mean QOL score (FACT-P and FACT-G) than the effective subgroup. However, most of the subscales except for the social/family well-being subscale showed no significant differences between the two subgroups. This finding suggests that disease progression under the definition of consecutive increases in PSA levels did not alter the patients' physical and functional conditions but did reduce generalized QOL. Thus, increasing PSA levels may place stress and anxiety on the victim before the progressed prostate cancer produces or increases cancer-related physical pain or other discomforts. During the treatment period, most patients and their families profoundly considered the PSA level to reflect disease control, which may be their primary concern at the end of life. The latest study from Andri Konski and colleagues also showed the same phenomenon that although survival was similar in the long-term androgen deprivation and short-term androgen deprivation groups, the patients who received long-term androgen deprivation gained quality-adjusted life years because it prevented biochemical failure[16].

We adopted a 47-item valid and reliable Chinese questionnaire that was translated from the English FACT-P (version 3) tool developed and revised by Cella et al. in 1990. All data were collected by the same well-trained technician through a face-to-face interview after obtaining informed consent from each patient. This minimizes bias due to misunderstanding the questions. Additionally, the 100% completion rate supports the fact that we did not lose any information from any patients undergoing H/T at our out-patient department during the same period. According to the study by Crosby and colleagues in 1991, face-to-face contact is the most effective strategy for data collection, yielding a 95% acceptance rate, compared to 50% and 0% for telephone and mail contact at a medical center, respectively[17].

The high internal consistency (Cronbach's alpha = 0.86) of the FACT-P in our study was similar to that in Esper's study, in which the original FACT-P (version 3) was used[10]. This suggests that there was no change in the validity of the Chinese version of this 47-item questionnaire.

The previous study conducted by Esper et al. in 1997 collected data from three samples to analyze the QOL of patients with prostate cancer. No group was similar to our study in that patients all had advanced disease and were undergoing H/T. Therefore, the scores could not be compared. Their results showed that patients at different disease stages had significantly different QOL scores[10]. In our study, however, there were no significant differences between the FACT-P subscales when we divided the 108 patients with advanced prostate cancer into distant metastatic and locally advanced groups.

Wesley and colleagues reported significant decreases in QOL, most profoundly in urinary and sexual function, among locally advanced prostate cancer patients in a cohort study with a minimum of two years of follow-up. The deteriorated urinary and sexual function may be secondary to invasive treatment (46%) including radical prostatectomy, brachytherapy, and cryotherapy[18]. In our study, however, there were no major complications from surgery or external beam radiation therapy such as total urinary incontinence, radiation cystitis or colitis, etc. Thus, the duration of H/T and therapeutic modality did not significantly affect the QOL of advanced prostate cancer patients in this study.

In summary, according to the statistical analysis, we can conclude that therapeutic duration, therapeutic modality, age at diagnosis, and even tumor stage do not significantly differ in terms of QOL, but the therapeutic efficacy affects QOL significantly. Specifically, effective therapy results in a better QOL than therapeutic failure, which presented with as consecutive PSA level increases. This finding is compatible with Frohmuller's study, which found that local progression is the main parameter influencing QOL among stage D1 prostate cancer patients.[19] Although patients' physical conditions did not worsen

in association with increasing PSA initially, they may have felt anxiety, depression, and disappointment once the biochemical failure occurred.

## Conclusions

Therapeutic result according to the biochemical level is a key factor affecting the QOL of advanced prostate cancer patients undergoing H/T. Thus, PSA levels profoundly affect QOL in patients with advanced prostate cancer. Therefore, physicians should carefully and adequately inform patients about the relationship between the PSA level and the clinical course of disease progression including salvage strategy for biochemical failure to minimize their significant fears and anxiety of an uncertain future and thereby improve their QOL during prostate cancer therapy and surveillance.

## References


1. N. Mottet (Chair), J. Bellmunt, E. Briers (Patient Representative), M. Bolla, L. Bourke, P. Cornford (Vice-chair), M. De Santis, A.M. Henry, S. Joniau, T.B. Lam, M.D. Mason, H.G. van der Poel, T.H. van der Kwast, O. Rouvière,T. Wiegel Guidelines Associates: N. Arfi, R.C.N. van den Bergh, T. van den Broeck, M. Cumberbatch, N. Fossati, T. Gross, M. Lardas, M. Liew, P. Moldovan, I.G. Schoots, P.M. Willemse. EAU - ESTRO - ESUR - SIOG Guidelines on Prostate Cancer. https://uroweb.org/wp-content/uploads/09-Prostate-Cancer_2017_web.pdf.
2. Huggins C, Hodges CV. Studies on prostate cancer: I. The effects of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. Cancer Res, 1941. 1: p. 293-7.
3. Cancer registration on Health Promotion Administration (HPA) of Ministry of Health and Welfare (Taiwan), https://www.hpa.gov.tw/Pages/List.aspx?nodeid=269
4. Whittington R, Malkowicz B, Barnes MM, et al. Combined hormonal and radiation therapy for lymph node-positive prostate cancer. Urology, 1995. 46: p. 213-9.
5. Hillner BE, McLeod DG, Crawford ED, et al. Estimating the cost effectiveness of total androgen blockade with flutamide in M1 prostate cancer. Urology, 1995. 45: p. 633-40.
6. Joyce R, Fenton MA, Rode P, et al. High dose bicalutamide for androgen independent prostate cancer: effect of prior hormonal therapy. J Urol, 1998. 159: p. 149-53.
7. Verhelst J, Denis L, Van VP, et al. Endocrine profiles during administration of the new non-steroidal anti-androgen Casodex in prostate cancer. Clin Endocrinol-(Oxf), 1994. 41: p 525-30.
8. Schellhammer P, Sharifi R, Block N, et al. Maximal androgen blockade for patients with metastatic prostate cancer: Outcome of a controlled trial of bicalutamide versus flutamide, each in combination with luteinizing hormone-releasing hormone analogue therapy. Casodex Combination Study Group. Urology, 1996. 47: p54-60.
9. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therepy (FACT) scale: development and validation of the general measure. J Clin Oncol, 1993. 11: p 570-9.
10. Esper P, Mo F, Chodak G, et al. Measuring quality of life in men with prostate cancer using the functional assessment of cancer therapy-prostate instrument. Urology, 1997. 50: p 920-8.
11. Eisenberger M, McLeod D, Hussain M, et al. Bilateral orchiectomy with or without flutamide for metastatic prostate cancer. N Engl J Med, 1998. 339: p 1036-42.
12. American Society for Therapeutic Radiology and Oncology Consensus: Consensus statement: Guidelines for PSA following radiation therapy. Int J Radiat Oncol Biol Phys, 1997. 37: p 1035.
13. Palou J, Morote J: Elevated serum PSA and acute bacterial prostatitis. Urology, 1990. 35:p 373.
14. Sharifi N, Dahut WL, Steinberg SM, et al. A retrospective study of the time to clinical endpoints for advanced prostate cancer. BJU Int, 2005. 96: p985-9.
15. Adolfsson J. Health-related quality-of-life assessments in patients with advanced cancer of the prostate. Pharmacoeconomics, 2005. 21: p 241-7.
16. Andre Konski, Deborah Watkins-Bruner, Harmar Brereton, et al. Cancer, 2006. 106: p 51-7.
17. Crosby N, Ventura M, Finnick M, et al. Enhancing subject recruitment for nursing research. Clinical nurse Specialist, 1991. 5(1): p 25-30.
18. Wesley MW, Natalia SW, Bedford W. Quality of life in men with locally advanced adenocarcinoma of the prostate: an exploratory analysis using data from the CaPSURE database. J Urol, 2008. 180: p 2409-14.
19. Frohmuller HG, Theiss M, Manseck A, et al. Survival and quality of life of patients with stage D1 (T1-3 pN1-2 M0) prostate cancer. Radical prostatectomy plus androgen deprivation versus androgen deprivation alone. Eur Urol, 1995. 27: p 202-6.

# 影響接受荷爾蒙治療的晚期前列腺癌患者生活品質的因素

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**摘要**

本研究分析正在接受荷爾蒙治療（又稱為雄激素剝奪治療）的晚期前列腺癌患者的生活品質，以評估主要影響因素並制定改善其生活品質的策略。這項研究納入了 108 名患有晚期前列腺癌的男性，年齡為 43 至 98 歲（中位數 = 74 歲），他們接受了 6 個月至 7 年的荷爾蒙治療治療，其中包括促黃體激素釋放激素激動劑，抗雄激素單獨的藥劑或合併促黃體激素釋放激素激動劑及抗雄激素。我們使用了 47 項問卷的癌症治療功能評估 - 前列腺（第 3 版）中文版。完成率為 100％，採用研究護理師對病患逐個面對面的問卷方法。我們分析了生活品質與診斷年齡，治療時間，激素治療方式，腫瘤分期和治療結果之間的關係。結論是血清前列腺特異性抗原值的變化顯著影響生活品質。較好的治療效果可提高癌症治療功能評估評分。雖然荷爾蒙治療治療期間的前列腺特定抗原升高通常代表疾病進展，但它最初很少影響身體狀況。然而，根據我們的研究，它確實惡化了整體生活品質分數。因此，建議我們的患者了解前列腺特定抗原數值與疾病進展的臨床過程之間的關係，包括生化指數復發的挽救策略，以盡量減少他們對不確定未來的巨大恐懼，從而對於前列腺癌標準激素治療期間提高他們的生活品質。

**關鍵詞**：荷爾蒙治療、雄激素剝奪療法、前列腺癌、生活品質

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Original Article

# Uric Acid and Atrial Fibrillation: A systematic review and meta-analysis

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**Abstract**

***Background :*** Hyperuricemia is undoubtedly associated with the development of cardiovascular disease (CVD). Herein, we describe the results of a systematic review and meta-analysis of observational studies conducted to explore the relationship between serum uric acid (sUA) and atrial fibrillation (AF).
***Methods :*** PubMed, Cochrane, and Web of Science databases were comprehensively and electronically searched using EndNote X9 for articles published up to March 31, 2019. The search terms used were "uric acid," "urate," "hyperuricemia," or "gout" AND "atrial fibrillation." This method was repeated with the Chinese Electronic Periodicals Service (CEPS) in Taiwan. Review Manager (ver. 5.3) was used to derive standardized mean differences (SMDs) with 95% CI (confidence intervals), heterogeneity ($I^2$), weights, and Funnel plots. Forest plots were drawn using MS-Excel and VBA wherein significant difference is indicated by error bars that do not cross the no effect line at X = 0.0.
***Results :*** A total of 29 studies with 372,638 patients were included for quantitative analyses differences in sUA levels between the patients with and without AF. The sUA level in patients with AF was found to be significantly higher than those without AF (SMD 0.63; 95% CI 0.49-0.78; P < 0.00001).
***Conclusions :*** As sUA levels are significantly higher in AF patients, it may be used as a potential biomarker of AF risk.

**Key words:** atrial fibrillation, hyperuricemia, standardized mean difference, Visual Basic for Application

## Introduction

Serum uric acid (sUA) levels are the result of an interplay among dietary purine intake, xanthine oxidase activity, and renal UA excretion[1], and hyperuricemia is defined as sUA levels greater than 6.8-7.0 mg/dL. sUA is associated with the precipitation of monosodium urate crystals in the joints and development of gout[2]. Moreover hyperuricemia is also definitively associated with risk of several cardiovascular diseases (CVD), such as coronary heart disease (CHD) and stroke[3], and the Taiwan I-Lan Longitudinal Aging Study suggests that patients with hyperuricemia could have increased CVD, irrespective of the presence of other risk factors such as hypertension or diabetes[4]. Therefore, treating hyperuricemia is pivotal for cardiovascular risk management[5].

Hyperuricemia has been recently speculated to be associated with the development of atrial fibrillation (AF)[6], which is highly associated with greater risk of CHD and stroke[7, 8]. However, the exact pathogenesis of AF is still not well-established and a better understanding of its pathogenesis can help develop novel prevention and treatment strategies. Numerous studies have proposed several potential causes for AF,

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which include inflammation[9], oxidative stress (OS)-induced atrial structural abnormalities, autonomic nervous system dysfunction, and deficits in vascular supply[10]. Among these, the potential mechanism by which hyperuricemia induces AF through an inflammatory pathway has been gaining increased attention and it has been postulated that uric acid activates the Nod-like receptor family protein 3 inflammasome pathway, leading to a massive release of cytokines and chemokines[11].

Rare researches were noted in this field at Taiwan, thus, we performed a systematic review and a meta-analysis to evaluate the evidence of an association between sUA levels and AF.

## Material and methods

We comprehensively and electronically searched PubMed, Cochrane, and Web of Science databases using EndNote X9 for articles published up to March 31, 2019. The search terms used were "uric acid," "urate," "hyperuricemia," or "gout" AND "atrial fibrillation." An identical strategy was used with the Chinese Electronic Periodicals Service (CEPS) in Taiwan. The inclusion criteria were (1) prospective or retrospective observational studies, and (2) reported means and standard deviations (SDs) of sUA in patients with and without AF. Unpublished studies were excluded due to difficulties in assessing the internal validity and reliability.

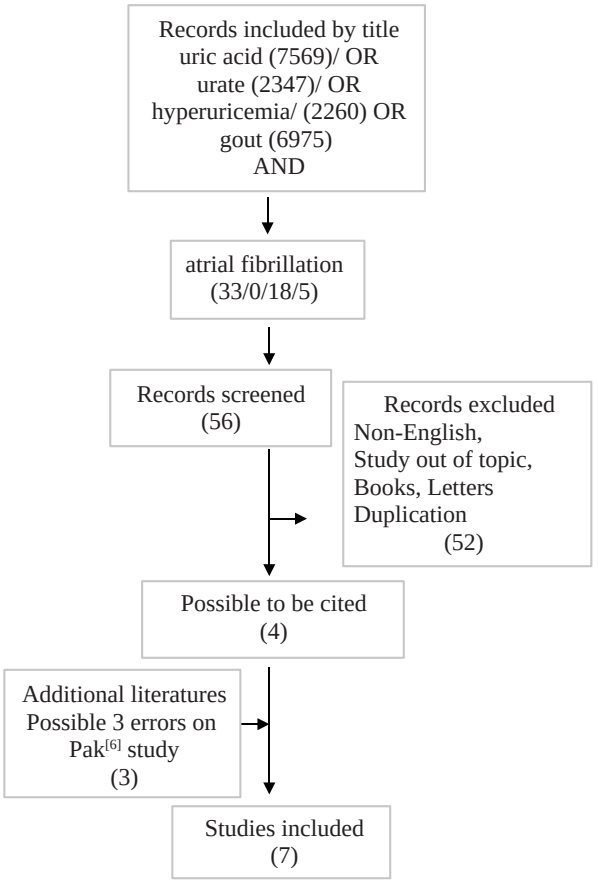


**Fig. 1** Flow diagram of search process and study selection.

### Statistical Analysis

Standardized mean difference (SMD) with 95% CI (confidence interval) and weights were calculated and a random-effects model was used for this meta-analysis. The $I^2$ value was used to assess heterogeneity between the studies and an $I^2$ value greater than 50% was considered representative of significant heterogeneity. The funnel plot was used to detect and adjust for possible publication bias. All statistical tests were two-sided and all statistical analyses were performed using RevMan 5.3. Forest plots were drawn with MS-Excel and its VBA, wherein differences are considered significant if the error bars do not cross the no effect line at X = 0.0. All units in μmol/L were converted to mg /dL by 59.48.

## Results

### Study characteristics

A total of 29 studies with 372,638 patients (3,811 cases and 368,827 controls) were included for quantitative analyses of potential differences in sUA levels between the patients with and without AF. As illustrated in Fig. 1, only four studies were selected from database search records for possible citation. Table 1 provides a summary of cited literature. We found 3 inconsistencies between Table 1 and Fig. 3 of Letsas, Mantovani and Shi's data and Pak's meta-analysis[6], and these 3 publications were re-confirmed as additional literature. Thus, the total citations used in this meta-analysis increased to seven.

As illustrated in Fig. 2, our analysis identified significant differences in sUA level between patients with and without AF. The sUA level of patients with AF was higher than those without AF (SMD = 0.63, 95% CI 0.49-0.78; P < 0.00001). A funnel plot (Fig. 3) did not reveal significant publication bias; however, heterogeneity among studies was determined to be significant ($I^2$= 93%; P < 0.00001). Subgroup analysis

was performed based on cardiac intervention. The $I^2$ values for patients who did not undergo either catheter ablation or coronary artery bypass graft (CABG) and those who underwent ablation or CABG were 86% and 98%, respectively. As there was only one study on patients who underwent CABG, a fixed-effects model was used in this subgroup, which yielded a SMD of 2.96 (95% CI 2.47-3.44). The SMD values for no CABG nor ablation and ablation were 0.55 (95% CI 0.44-0.66), 0.65 (95% CI -0.35-1.64), respectively.

## Discussion

This meta-analysis shows that mean sUA levels were significantly higher in patients with AF than those without AF and lend support to a possible link between sUA and prevalence of AF. Additionally, subgroup analyses revealed that this relationship varied largely on the type of therapeutic intervention. These findings can be used to guide study designs that can further advance our understanding of the role of sUA in the development of AF.

Zhang performed a meta-analysis of six cohort studies to evaluate the evidence for an association between sUA and AF and they report that hyperuricemia was significantly associated with an increased risk of AF (RR 1.49, 95%CI 1.24-1.79, $P < 0.001$)[12] (Fig. 4). Another meta-analysis using pooled SMD data of sUA values for those with and without AF, undertaken by Tamariz et al[13] in 2011. Pak's meta-analysis[6] then developed on these previous meta-analyses by including data from 24 observational studies, and they further strengthend the analyses by incorporating patient groups based on whether they underwent invasive intervention, including CABG and catheter ablation. We have further expanded on these results by inlcuding data from 5 other studies, and the results show the same trend.

Hyperuricemia has been shown to be associated with risk of several cardiovascular morbidities, such as CHD and stroke[3], and AF is a common and important risk factor for these as well. Moreover, the results of previous meta-analyses also serve to explain the association between hyperuricemia and CHD or stroke[7, 8]. In humans, sUA is the end product of purine degradation with peroxide production, and sUA has been clearly associated with inflammation and OS in several pathological conditions. sUA can also promote inflammation via the activation of pro-inflammatory cytokines, such as interleukin-1β and tumor necrosis factor-α (TNF-α)[14, 15]. Inflammation and OS have been demonstrated to play a role in the pathophysiology of atrial fibrillation [9, 16], and thus, uric acid may also have a certain role in the development of AF. Inflammation and/or OS may cause the accumulation of uric acid inside atrial cardiomyocytes which might lead to atrial remodeling, including ionic and structural remodeling of the

**Table 1.** Summary of the cited publications

| First author, year journal | Summary |
|---|---|
| Pak[6] 2018<br>Crit Pathw Cardiol | Inclusion criteria were as follows: (1) prospective or retrospective observational studies; and (2) reported means and standard deviations (SDs) of serum uric acid (sUA) for patients with and without atrial fibrillation (AF) in all published articles. Unpublished studies were excluded due to difficulties in assessing the internal validity and reliability.<br>There were three mismatches/inconsistencies between Table 1 and Figure 3 of Letsas, Mantovani and Shi's data. |
| Kwon[29] 2018<br>Circ J | AF was identified in 365 subjects vs. 282,108 normal sinus rhythm with sUA values of 6.2±1.4 vs. 5.3±1.5 mg/dL |
| Huang[30] 2018<br>Sci Rep | 55 patients with permanent AF (382.3 ± 94.0μmol/L, 6.43 ± 1.58 mg/dL), and 983 control subjects (348.9 ± 89.6 μmol/L, 5.87 ± 1.51 mg/dL)<br>*1 mg /dL = 59.48 μmol/L |
| Mantovani[31] 2016<br>J Endocrinol Invest | 91 patients with permanent AF (6.6 ± 2.5 mg/dL), and 751 control subjects (5.3 ± 1.8 mg/dL) |
| Letsas[32] 2010<br>Hellenic J Cardiol | 41 patients with permanent AF (6.7 ± 1.4 mg/dL), and 48 control subjects (5.1 ± 1.3 mg/dL) |
| Shi[33] 2016<br>Aging Clin Exp Res | 84 patients with permanent AF (6.71 ± 2.13 mg/dL), and 136 control subjects (4.73 ± 1.19 mg/dL) |
| Chen[34] 2017<br>BMJ Open | 53 patients with permanent AF (5.5 ± 1.4 mg/dL), and 8884 control subjects (5.0 ± 1.5 mg/dL) |

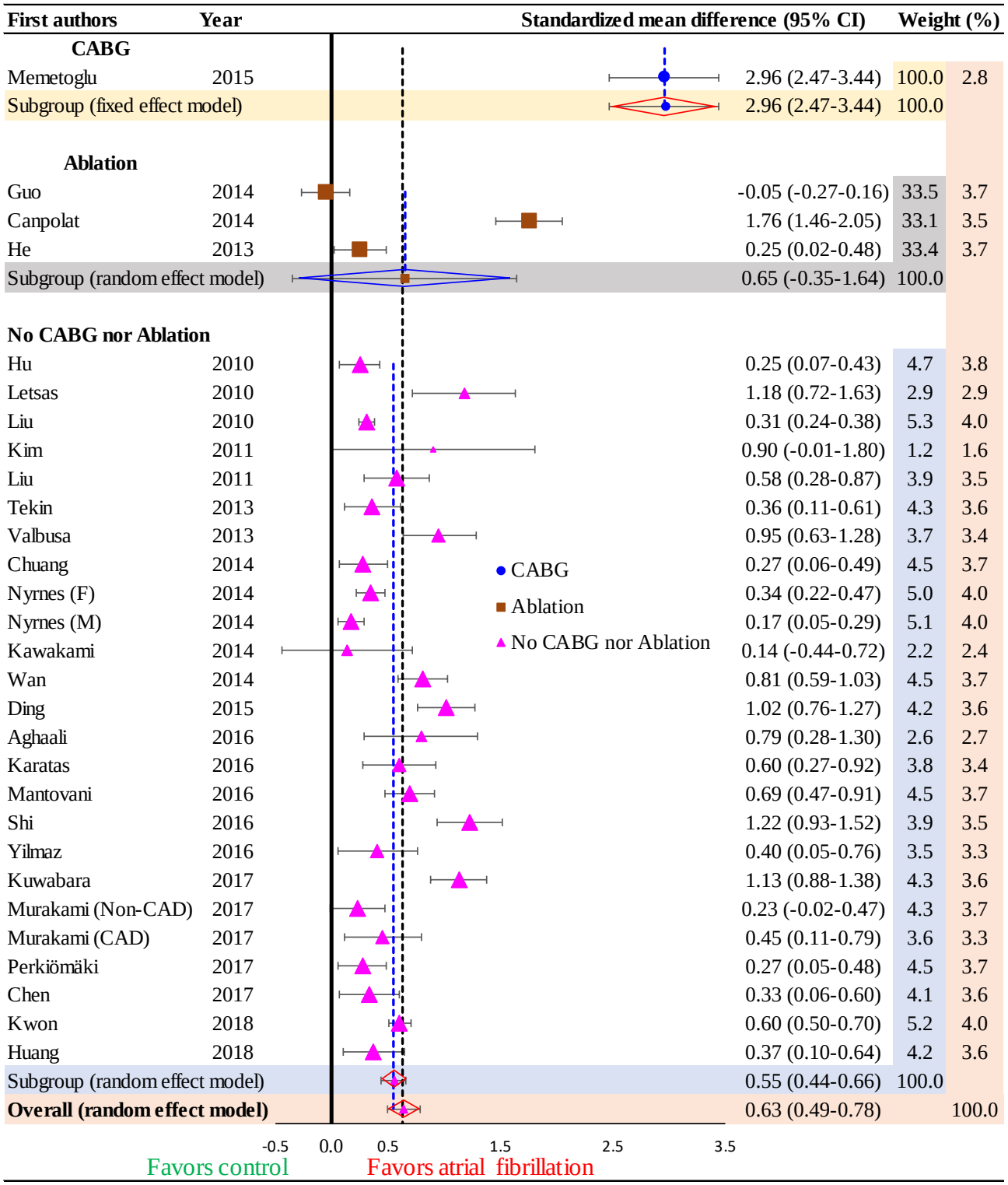


**Fig. 2** Summary of standardized mean difference (SMD) calculated using the random-effects model for sUA levels between individuals with and without atrial fibrillation.
CAD indicates coronary artery disease.

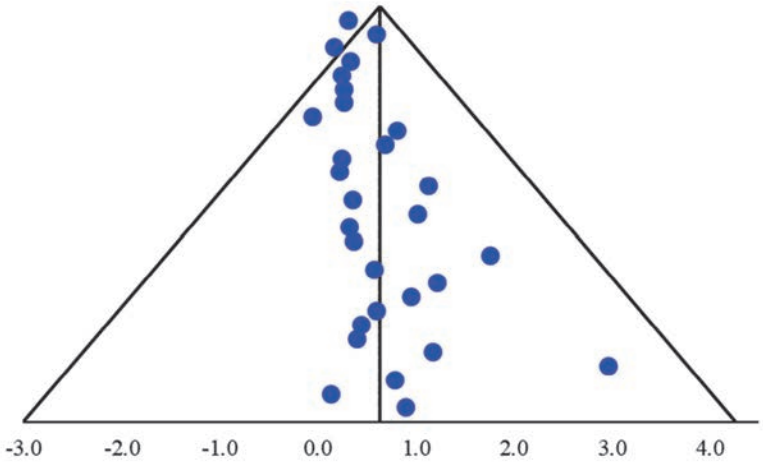


**Fig. 3** Funnel plot of the studies including serum uric acid value of individuals with and without atrial fibrillation.

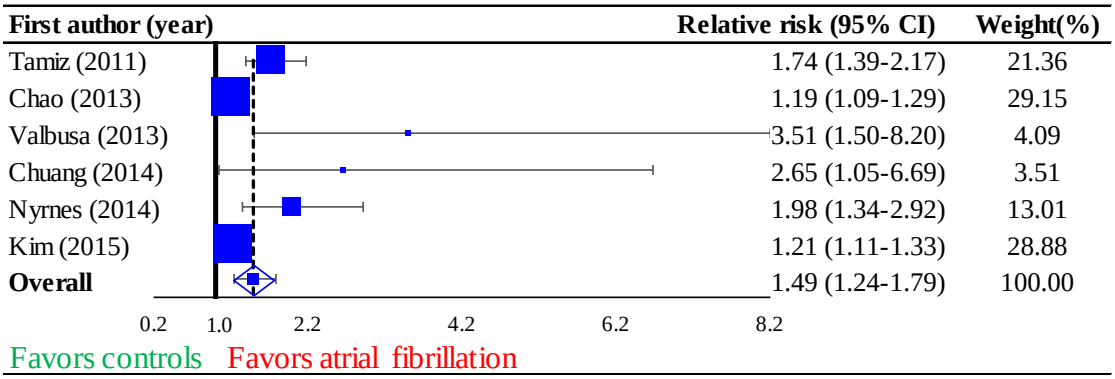


**Fig. 4** Hyperuricemia was significantly associated with atrial fibrillation risk. Adapted from Zhang et al.2 016[12]

atria. Therefore, reduction of OS through inhibition of xanthine oxidase using allopurinol or other similar drugs, NADPH-oxidase using apocynin, or the use of N-acetylcysteine, might be beneficial[17]. On the other hand, prevention of structural and ionic remodeling through inhibition of atrial inflammation might also provide benefits. Uric acid transporters (UATs) are the regulators of intracellular uric acid concentration and mediate hyperuricemia-induced atrial remodeling. Targeting UATs might also be another option for comprehensive hyperuricemia management to reduce the risk of AF[17].

One study showed that intracellular urate taken up by UATs could enhance Kv1.5 protein expression and function in atrial myocytes, which may be due to OS derived from NADPH-oxidase activity[18]. Thus, findings from previous studies and our meta-analysis have provided strong evidence for hyperuricemia as an important risk factor for several common CVDs, and it is possible that the risk of CVD in individuals with hyperuricemia may be reduced through allopurinol treatment. In support of this, another meta-analysis suggests that treatment of hyperuricemia with allopurinol is associated with an improvement in endothelial function[19]. However, results from other studies do not provide a definite conclusion on the preventive effects of allopurinol against cardiovascular diseases [20, 21] and further studies are needed to assess the effect of uric acid-lowering therapy on AF risk or cardiac events and death in individuals with AF.

Recognition of AF risk factors is essential for its prevention and to reduce the risk of death from AF. Our study shows that hyperuricemia is associated with AF, as well as with risk of AF in post-cardiovascular surgery patients. However, other studies have shown that sUA may exert neuroprotective effects in Parkinson's disease (PD) and Alzheimer's disease[22] due to its antioxidant effects and several studies

have indeed reported antioxidant effects of sUA in humans[23-25]. Gao et al. have observed that men, but not women, with higher sUA concentrations had a lower future risk of developing PD, suggesting that sUA could be protective against PD risk[26]. Kuo found that sUA levels of 5.0-6.9 mg/dL (0.30-0.41 mmol/L) were associated with the lowest mortality rate; specifically, crude all-cause mortality rates across the six sUA strata of ≤2.9, 3.0-4.9, 5.0-6.9, 7.0-8.9, 9.0-10.9, ≥11.0 mg/dL were 52.5, 19.7, 17.4, 20.0, 28.0 and 41.1 deaths per 1000 person-years, which showed a U-shaped association[27]. Considering the above, the treatment of hyperuricemia may also need to avoid too low sUA levels, i.e., below 3.0 mg/dL.

### Limitations

The present study has several limitations; most importantly, there was substantial heterogeneity among the studies selected. Multiple confounding factors, such as the presence of additional cardiovascular diseases, renal impairment, and socioeconomic variation, could have also contributed to this heterogeneity. Nevertheless, the vast majority of included studies indicate a positive association between hyperuricemia and AF[6].

## Conclusion

Our results support a positive association between sUA level and AF; thus, sUA might be a potential biomarker of AF risk. As the American College of Cardiology Foundation and the American Heart Association do not recommend either for or against primary prevention of AF due to insufficient evidence[28], the outcomes of this study may be used to guide future studies on risk stratification and preventative strategies for AF.

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## Conflict of interest

No potential conflict of interest was reported by the authors.

## References

1. Tana C, Busetto L, Di Vincenzo A, et al: Management of hyperuricemia and gout in obese patients undergoing bariatric surgery. Postgrad Med 2018;130:523-35.
2. Dalbeth N, Merriman TR, Stamp LK: Gout. Lancet 2016; 388:2039-52.
3. Abeles AM: Hyperuricemia, gout, and cardiovascular disease: an update. Curr Rheumatol Rep 2015;17:13.
4. Chang CC, Wu CH, Liu LK, et al: Association between serum uric acid and cardiovascular risk in nonhypertensive and nondiabetic individuals: The Taiwan I-Lan Longitudinal Aging Study. Sci Rep 2018;8:5234.
5. Borghi C, Verardi FM, Pareo I, Bentivenga C, Cicero AF: Hyperuricemia and cardiovascular disease risk. Expert Rev Cardiovasc Ther 2014;12:1219-25.
6. Pak S, Yatsynovich Y, Valencia D, Chen T: Serum Uric Acid and Atrial Fibrillation: Meta-analysis. Crit Pathw Cardiol 2018;17:161-6.
7. Verheugt FW, Granger CB: Oral anticoagulants for stroke prevention in atrial fibrillation: current status, special situations, and unmet needs. Lancet 2015;386:303-10.
8. Faerch K, Witte DR, Tabak AG, et al: Trajectories of cardiometabolic risk factors before diagnosis of three subtypes of type 2 diabetes: a post-hoc analysis of the longitudinal Whitehall II cohort study. Lancet Diabetes Endocrinol 2013;1:43-51.
9. Lip GY, Tse HF, Lane DA: Atrial fibrillation. Lancet 2012; 379:648-61.
10. Pellman J, Sheikh F: Atrial fibrillation: mechanisms, therapeutics, and future directions. Compr Physiol 2015;5:649-65.
11. Gicquel T, Robert S, Loyer P, et al: IL-1beta production is dependent on the activation of purinergic receptors and NLRP3 pathway in human macrophages. Faseb J 2015;29: 4162-73.
12. Zhang CH, Huang DS, Shen D, et al: Association Between Serum Uric Acid Levels and Atrial Fibrillation Risk. Cell Physiol Biochem 2016;38:1589-95.
13. Tamariz L, Agarwal S, Soliman EZ, et al: Association of serum uric acid with incident atrial fibrillation (from the Atherosclerosis Risk in Communities [ARIC] study). Am J Cardiol 2011;108:1272-6.
14. Rock KL, Kataoka H, Lai JJ: Uric acid as a danger signal in gout and its comorbidities. Nat Rev Rheumatol 2013;9:13-23.
15. Zhang Y, Hong Q, Huang Z, et al: ALDR enhanced endothelial injury in hyperuricemia screened using SILAC. Cell Physiol Biochem 2014;33:479-90.
16. Korantzopoulos P, Letsas KP, Liu T: Xanthine oxidase and uric Acid in atrial fibrillation. Front Physiol 2012;3:150.
17. Maharani N, Kuwabara M, Hisatome I: Hyperuricemia and Atrial Fibrillation. Int Heart J 2016;57:395-9.
18. Maharani N, Ting YK, Cheng J, et al: Molecular Mechanisms Underlying Urate-Induced Enhancement of Kv1.5 Channel Expression in HL-1 Atrial Myocytes. Circ J 2015;79:2659-68.
19. Kanbay M, Siriopol D, Nistor I, et al: Effects of allopurinol on endothelial dysfunction: a meta-analysis. Am J Nephrol 2014;39:348-56.
20. Kim SC, Schneeweiss S, Choudhry N, Liu J, Glynn RJ, Solomon DH: Effects of xanthine oxidase inhibitors on cardiovascular disease in patients with gout: a cohort study.

Am J Med 2015;128:653 e7- e16.
21. Guedes M, Esperanca A, Pereira AC, Rego C: What is the effect on cardiovascular events of reducing hyperuricemia with allopurinol? An evidence-based review. Rev Port Cardiol 2014;33:727-32.
22. Tana C, Ticinesi A, Prati B, Nouvenne A, Meschi T: Uric Acid and Cognitive Function in Older Individuals. Nutrients 2018;10.
23. Bowman GL, Shannon J, Frei B, Kaye JA, Quinn JF: Uric acid as a CNS antioxidant. J Alzheimers Dis 2010;19:1331-6.
24. Davies KJ, Sevanian A, Muakkassah-Kelly SF, Hochstein P: Uric acid-iron ion complexes. A new aspect of the antioxidant functions of uric acid. Biochem J 1986;235:747-54.
25. Kim TH, Lee JH: Serum uric acid and nigral iron deposition in Parkinson's disease: a pilot study. PLoS One 2014;9: e112512.
26. Gao X, O'Reilly EJ, Schwarzschild MA, Ascherio A: Prospective study of plasma urate and risk of Parkinson disease in men and women. Neurology 2016;86:520-6.
27. Kuo CF, See LC, Yu KH, Chou IJ, Chiou MJ, Luo SF: Significance of serum uric acid levels on the risk of all-cause and cardiovascular mortality. Rheumatology (Oxford) 2013; 52:127-34.
28. Fuster V, Ryden LE, Cannom DS, et al: 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in partnership with the European Society of Cardiology and in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. J Am Coll Cardiol 2011;57:e101-98.
29. Kwon CH, Lee SH, Lee JY, Ryu S, Sung KC: Uric Acid and Risk of Atrial Fibrillation in the Korean General Population. Circ J 2018;82:2728-35.
30. Huang G, Xu RH, Xu JB, et al: Hyperuricemia is associated with atrial fibrillation prevalence in very elderly - a community based study in Chengdu, China. Sci Rep 2018; 8:12403.
31. Mantovani A, Rigolon R, Pichiri I, et al: Hyperuricemia is associated with an increased prevalence of atrial fibrillation in hospitalized patients with type 2 diabetes. J Endocrinol Invest 2016;39:159-67.
32. Letsas KP, Korantzopoulos P, Filippatos GS, et al: Uric acid elevation in atrial fibrillation. Hellenic J Cardiol 2010;51: 209-13.
33. Shi D, Meng Q, Zhou X, et al: Factors influencing the relationship between atrial fibrillation and artery stiffness in elderly Chinese patients with hypertension. Aging Clin Exp Res 2016;28:653-8.
34. Chen Y, Xia Y, Han X, et al: Association between serum uric acid and atrial fibrillation: a cross-sectional community-based study in China. BMJ Open 2017;7:e019037.

# 尿酸與心房顫動：系統回顧與統合分析

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**摘要**

**背景**：高尿酸血症與心血管疾病（CVD）有關，在此，我們以系統回顧和統合分析觀察性的研究，以探討血清尿酸（sUA）與心房顫動（AF）間的關係。
**方法**：以 PubMed，Cochrane 和 Web of Science 搜索 2019 年 3 月 31 日前的文章，使用以下搜索策略：（"uric acid" 或 "urate" 或 "hyperuricemia" 或 "gout"）且 "atrial fibrillation"，同時使用相同的中文關鍵詞搜索台灣 CEPS（Chinese Electronic Periodicals Service）。以 Review Manager 5.3 計算標準化平均差異（SMD）、95%CI 、異質性（heterogeneity, $I^2$）、權重及漏斗圖。結果再使用 MS-Excel 和 VBA 繪製森林圖，如果誤差線沒有交叉到無效線 X = 0.0，則表示達統計學上顯著的差異。
**結果**：共納入 29 項研究之 372,638 名患者，結果發現 AF 患者的 sUA 顯著高於無 AF 患者（SMD 0.63; 95%CI 0.49-0.78; P <0.00001）。
**結論**：研究發現 AF 患者的 sUA 水平顯著升高，因此，它可能是 AF 風險的潛在生物標誌。

**關鍵詞**：心房顫動、高尿酸血症、標準化平均差異、VBA

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Case Report

# A Case of Unprovoked Venous Thromboembolism and Occult Colon Cancer

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**Abstract**

Unprovoked venous thromboembolism (uVTE) can be an early manifestation of occult cancer. Regarding the relationship between uVTE and occult cancer, it is beneficial for clinicians to screen for potential occult malignancies when acute event occurs at the first time. However, currently, physicians evaluate uVTE patients by taking a detailed medical history, performing physical examinations and basic blood investigations; occult cancer screening is restricted for patients with relevant risk factors. Routine extensive cancer screening strategies, including routine computed tomography and positron emission tomography, are still debated in patients with uVTE. Most representative studies show that routine extensive cancer screening for patients with uVTE does not effectively detect occult cancers or reduce overall mortality. However, targeted advanced treatment should be conducted on the basis of age, sex, and ethnicity of the colon, breast, cervix, and prostate; or advanced treatment by individual situation. Cancer-associated complications such as uVTE can be prevented by detecting and treating occult cancer at an early, curable stage. Here we report the case of uVTE with a review of current related literature.

**Key words:** venous thromboembolism, occult colon cancer, congested heart failure

## Introduction

For more than a century, cancer-related hypercoagulability is considered to be the underlying mechanism for unprovoked venous thromboembolism (uVTE)[1]. The stage at diagnosis is a major prognostic factor of overall cancer outcome. Because uVTE may be the initial manifestation of cancer, it is an important factor in the identification of potential occult malignancies at an early, curable stage. Several overlapping and interacting mechanisms can explain the increased VTE incidence among patients with cancer. The significance and potential benefits of routine extensive occult cancer screening in patients with acute uVTE have been debated[1,2]. Although recent clinical studies have reported a low rate of occult cancer occurrence (<5%)[3], currently, practice guidelines recommend routine extensive screening for occult cancer for patients with clinically relevant risk factors[4]. These factors included tumor characteristics, anatomic site, degree of aggression, and patient's clinical condition.

## Clinical report

The case being presented is an 81-year-old woman with obesity and a history of type 2 diabetes, hypertension, and thyroid disease receiving treatment of the comorbidities at the Medical Center Hospitals for >10 years. She had general edema for several months, especially in the lower extremities bilaterally. Her treatment for the same included diuretics, beta-blockers, and angiotensin-converting-enzyme inhibitors; other repetitive symptoms such as swelling of her legs and general malaise were not

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investigated.

She was referred to our hospital because of refractory edema of the limbs. At the outpatient department, she complained of shortness of breath, slight orthopnea, and decreased urine output. We noted labored breathing accompanied by the use of accessory respiratory muscles. An initial physical examination revealed bilateral basal rales and pitting edema over both feet. A chest X-ray revealed cardiomegaly (Fig. 1) and electrocardiogram showed normal sinus rhythm with nonspecific ST-T segment changes. A echocardiographic study revealed four-chamber dilatation with preserved left ventricular function. The laboratory test results were as follows: total leukocytes, 9700/μl; hemoglobin, 7.1 g/dl; aspartate transaminase (AST), 69 IU/dl; creatinine, 1.1 mg/dl; estimated glomerular filtration rate, 50.7 mg/dl; sodium, 136 mg/dl; and potassium, 2.9 mg/dl. Myocardial enzymes and brain natriuretic peptide levels (92.3 ng/ml, reference <100 ng/ml) were within normal ranges. Other laboratory findings were as follows: D-Dimer, 3810 ng/ml (reference: <600 ng/ml); total bilirubin, 1.6 mg/dl; and albumin: 2.5 g/dl. Tests for alpha-fetoprotein, hepatitis B, and hepatitis C were negative. The initial diagnosis was peripheral vascular swelling due to deep venous thromboembolism or venous insufficiency and the patient was treated using diuretics and anticoagulant drugs. However, a peripheral arteriovenous ultrasound examination showed no obvious venous thrombosis but lymphedema in the lower extremity. Because the results ruled out venous thrombosis, an abdominal ultrasound examination (Fig. 2A) was arranged, revealing a large hepatic mass with splenomegaly, gallstones, and ascites. Therefore, additional serum tumor marker tests were performed; results were as follows: cancer embryo antigen (CEA), 17,524 ng/ml (reference: <6.2 ng/dl); CA-199, 8261 U/ml (reference: <31 U/ml); and CA-125, 161 U/ml (reference: <21 U/ml). Abdominal computed tomography (CT) and biopsy showed diffuse infiltrative hypodense tumor masses in both hepatic lobes (Fig. 2B), which did not compress the portal vein and inferior vena cava, along with an ascending colon tumor (size 4.1 × 4.2 × 4.8 cm) (Fig. 3). Ultimately, the patient was diagnosed with ascending colon cancer and liver metastasis. Brain CT and bone scan did not reveal

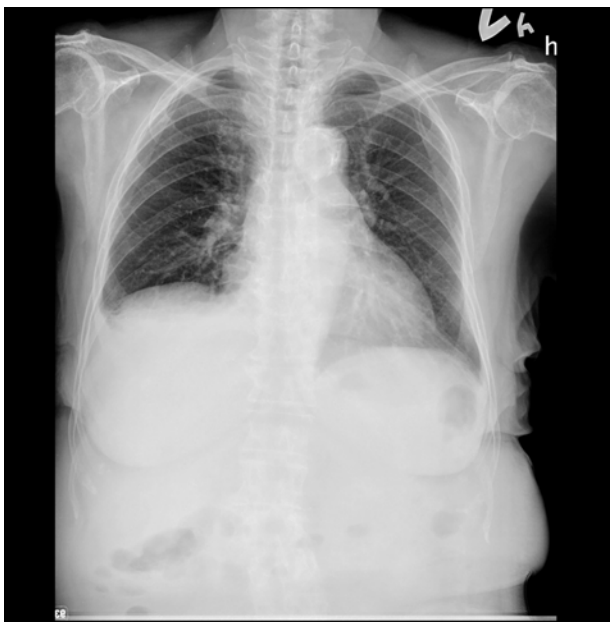

**Fig. 1** Chest X-ray of a patient with recurrent edema showing cardiomegaly with bilateral small pleural effusion. Atherosclerosis of the thoracic aorta was also noted.

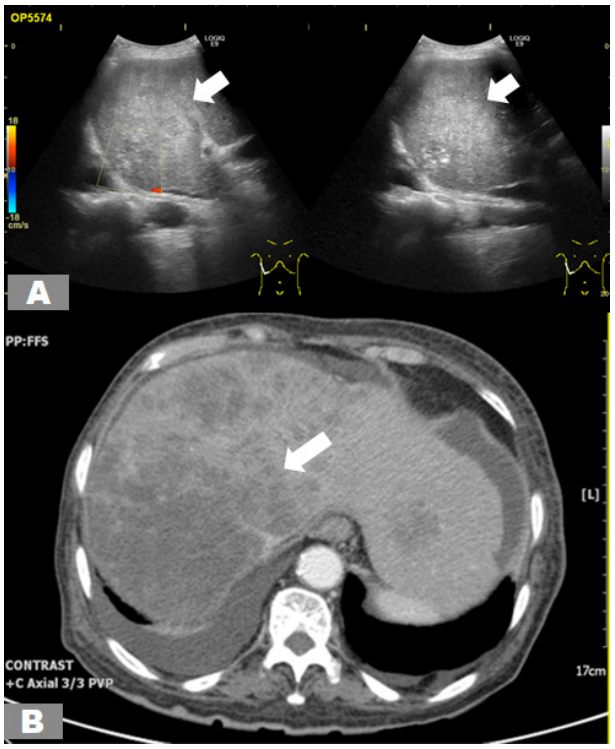


**Fig. 2** (A) Abdominal ultrasound revealed a huge mass-like lesion in the right hepatic lobe and clustered calcifications at the S6. The right portal venous branch is compressed (white arrow). (B) Abdominal computed tomography revealing hepatomegaly with diffuse infiltrative hypodense tumor in both lobes and multiple satellite nodules with heterogeneous enhancement after contrast. The portal vein and inferior vena cava are patent but compressed by the tumor mass (white arrow).

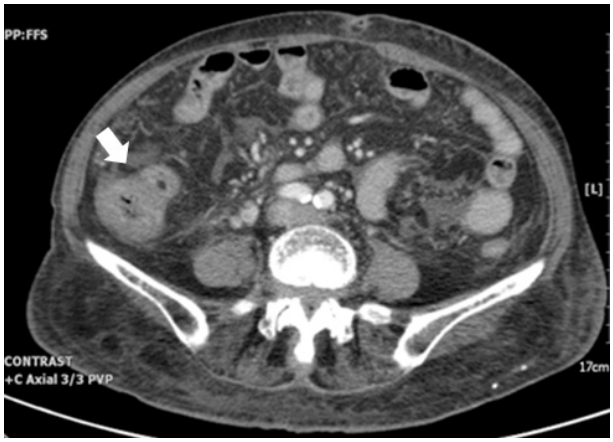


**Fig. 3** Abdominal computed tomography of an ascending colon tumor mass (size 4.1 × 4.2 × 4.8 cm) with thickened walls accompanied by adjacent fat stranding (white arrow).

abnormalities. Immunohistochemical analysis of the liver tissue showed staining of CDX-2 (+) and CK20 (+), indicating a metastatic adenocarcinoma arising from the colon. The patient and her family rejected any interventional procedures, including colonoscopy. Subsequently, she was transferred to the oncology ward where her condition suddenly deteriorated. Her family requested hospice care; the patient eventually passed away in the hospital.

## Discussion

Venous thromboembolism is a dynamic process associated with several risk factors such as advanced age, sex, ethnicity, tumor sites (brain, pancreas, stomach, lung, bladder, gynecological tumors, or hematological origin), disease stage, and initial period after diagnosis. In 1856, Rudolf Virchow first described "Virchow's triad," comprising venous stasis, endothelial injury, and hypercoagulability, in the pathophysiologic process underlying thrombogenesis. The possibility of cancer should be ruled out in patients presenting with uVTE. Activation of blood coagulation in patients with cancer is complex and multifactorial, involving all three aspects of Virchow's triad. Tumor cells can form a mass and compress blood vessels to cause venous stasis; they can also induce inflammation to cause injury and produce procoagulant substances such as thromboplastin (TP), tumor necrosis factor, and vascular endothelial growth factor[5].

Studies have reported that the prevalence of occult cancer in patients with uVTE is as high as 10% [95% confidence intervals (CI): 8.6%–11.3% [2] but the detection rate is low. The incidence of uVTE is much higher in patients with metastatic cancer than in those with local or regional cancer[6]. Most occult cancers are diagnosed within the first few months of uVTE occurrence and the rate of diagnosis gradually declines. A clinical approach screening method is important for accurate occult cancer diagnosis.

The clinical approach for occult cancer screening can be classified into limited and extensive. The limited strategy usually includes a complete medical history, physical examination, and basic laboratory investigations, such as complete blood counts, serum biochemistry (liver function tests and lactate dehydrogenase), and radiographs. The extensive strategy includes the aforementioned investigations as well as one or more CT scans of the thoracic, abdominal, and pelvic regions[3], ultrasonography, gastrointestinal endoscopy, breast mammography, and serum tumor markers such as CEA, prostate-specific antigen for men and CA-125 for women[7]. Recent studies mention that the limited screening strategies are sufficient, although extensive screening slightly increases the rate of detection of occult cancers. There was no significant difference between the limited and extensive cancer-related mortality[3]. However, the current analysis did not specifically adjust for the organ types, stages, treatment decision-making, and chronic comorbidities affecting mortality[8]. Under the Modern Insurance Healthcare System, the limited screening strategy is favored because of its decreased economic cost. The most prevalent cancers among patients with uVTE, including colorectal, breast, cervix, prostate, lymph node, and bone marrow cancers, require advanced diagnostic tests[9,10]. Current guidelines do not oppose an extensive screening strategy, although these recommendations are controversial. Routine extensive screening for occult cancer should be performed for risk assessment of patients or special patient subgroups[4,8].

## References

1. Sorensen HT, Mellemkjaer L, Steffensen FH, Olsen JH, Nielsen GL. The risk of a diagnosis of cancer after primary deep venous thrombosis or pulmonary embolism. N Engl J Med 1998;338:1169-73.

2. Carrier M, Le Gal G, Wells PS, Fergusson D, Ramsay T, Rodger MA. Systematic review: the Trousseau syndrome revisited: should we screen extensively for cancer in patients with venous thromboembolism? Ann Intern Med 2008;149:323-33.
3. Carrier M, Lazo-Langner A, Shivakumar S et al. Screening for Occult Cancer in Unprovoked Venous Thromboembolism. N Engl J Med 2015;373:697-704.
4. Langford N, Stansby G, Avital L. The management of venous thromboembolic diseases and the role of thrombophilia testing: summary of NICE Guideline CG144. Acute Med 2012;11:138-42.
5. Chung I, Lip GY. Virchow's triad revisited: blood constituents. Pathophysiol Haemost Thromb 2003;33:449-54.
6. Alcalay A, Wun T, Khatri V et al. Venous thromboembolism in patients with colorectal cancer: incidence and effect on survival. J Clin Oncol 2006;24:1112-8.
7. Monreal M, Lensing AW, Prins MH et al. Screening for occult cancer in patients with acute deep vein thrombosis or pulmonary embolism. J Thromb Haemost 2004;2: 876-81.
8. Piazza G. Venous thromboembolism and cancer. Circulation 2013;128:2614-8.
9. Blom JW, Vanderschoot JP, Oostindier MJ, Osanto S, van der Meer FJ, Rosendaal FR. Incidence of venous thrombosis in a large cohort of 66,329 cancer patients: results of a record linkage study. J Thromb Haemost 2006;4:529-35.
10. Prandoni P, Lensing AW, Buller HR et al. Deep-vein thrombosis and the incidence of subsequent symptomatic cancer. N Engl J Med 1992;327:1128-33.

# 不明原因靜脈血栓栓塞和隱匿性結腸癌的病例

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**摘要**

不明原因的靜脈血栓栓塞（unprovoked venous thromboembolism）可以是隱匿性癌症的早期表現之一。由於不明原因的靜脈血栓栓塞與癌症之間存在著關連性，對於臨床醫生來說，能夠在患者初次急性發生時，篩檢出可能潛在隱匿性惡性腫瘤，在醫療成效是有助益的。然而，現今的研究大概還是認為是完整醫療歷史，身體理學檢查和基本血液檢驗就已足夠，檢查似乎有侷限性，但例行性的廣泛隱匿性癌症篩檢有待討論，例如電腦斷層攝影，正子攝影斷層攝影等，現今大多數研究顯示例行性廣泛癌症篩選並未能有效的篩選出更多廣泛隱匿的癌症，或是減少可能癌症的誤失來改善整體的相關死亡率。因此，對於所有不明原因靜脈血栓栓塞的患者採取例行性廣泛癌症篩選檢查是仍有爭議的，僅須有選擇性地進行癌症篩檢檢查 , 但在特殊情況下，還是得進行廣泛癌症篩選檢查。臨床醫生仍應根據年齡、性別與所在地區族群的特異性，對於患者篩選可能的癌症，例如結腸，乳腺，子宮頸和前列腺，根據個別情況再進行進階的檢查以利儘早在可治癒期發現，給予治療並預防癌症相關的合併症。因此，我們做此一病例報告及相關當前文獻的回顧。

**關鍵詞：**VTE 、不明原因的靜脈血栓栓塞、隱匿性癌症

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Case Report

# Female Genital Tuberculosis: Report of 2 Unusual Cases

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**Abstract**

From May 2005 to September 2017, two patients with female genital tuberculosis (FGTB) were treated at Taipei Tzu Chi Hospital. FGTB was difficult to diagnose because of its protean clinical manifestations. One patient, a 55-year-old woman, experienced abdominal fullness, leg edema, and general weakness. Computed tomography revealed massive ascites, uterine masses, and right pleural effusion. The acid-fast stains for sputum and ascites yielded negative results. Under suspicion of ovarian malignancy, left salpingo-oophorectomy and endometrial curettage were performed, and frozen pathologic study revealed caseous granuloma. Antituberculosis (anti-TB) drugs were administered, and the patient's status improved. The other patient, an 81-year-old woman, presented with purulent vaginal discharge and bleeding. Dilation and curettage revealed endometrial TB. Anti-TB drugs were administered, but the patient died of other disease. For frail patients, anti-TB drugs may be harmful. The number of FGTB cases in our hospital may be underestimated. Of 12 patients with TB peritonitis, only 1 received FGTB diagnosis. Laparoscopy is useful for FGTB diagnosis in patients with TB peritonitis.

**Key words:** Female, genital, tuberculosis

## Introduction

Tuberculosis (TB) is a major health problem worldwide, although effective treatment has caused a declining trend in mortality. Taiwan was previously an area endemic for TB. In 1947, TB-related deaths accounted for 18,533 persons, which corresponded to 16.23% of all deaths (114,192) in Taiwan [1]. Since 1951, the government of Taiwan has made considerable efforts in TB prevention, including bacilli Calmette-Guérin vaccination. By 1970, the number of TB-related deaths had decreased to 4117 persons per year, which represented 6.04% of all deaths (68,117) in Taiwan [1].

In 1993, the World Health Organization declared a worldwide state of emergency for TB [2]. In 2016 [3], 23 years after this declaration, the incidence of TB in Taiwan was 43.9 per 100,000. Therefore, TB still poses a major threat to public health in Taiwan.

Female genital tuberculosis (FGTB) is an extrapulmonary manifestation of TB. FGTB usually affects the fallopian tubes (in 95% to 100% of cases), endometrium (50% to 60%), ovaries (23% to 30%), or cervix (5% to 10%); it rarely involves the vulva or vagina [4]. The frequency of FGTB among the general population is difficult to determine. In many affected patients, FGTB is asymptomatic and is discovered only incidentally [4]. Tsai and Huang [5] reported a 0.155% overall incidence of FGTB among 21,833 patients who had undergone gynecological surgery between 1960 and 1975. During this study period, the TB-related death decreased from 45.65 deaths per 100,000 in 1960 to 28.38 deaths per 100,000 in 1970 [1]. FGTB may be asymptomatic or may be characterized by

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abnormal vaginal bleeding or discharge, menstrual irregularities, abdominal pain, infertility, postmenopausal bleeding, ascites, or other constitutional symptoms [6]. This study was an investigation of the FGTB cases at Taipei Tzu Chi Hospital, Taipei, Taiwan, and their protean clinical manifestations, diagnosis, and treatment.

From May 2005 to September 2017, two patients with FGTB were treated at Taipei Tzu Chi Hospital. Because no histologic proof of TB involvement in the female genital organs was available, 11 patients with TB peritonitis were excluded from this study.

## Case Presentations

### Case 1

A 55-year-old postmenopausal woman suffered abdominal fullness, bilateral lower limb edema, and general weakness for 3 weeks. She visited our gastrointestinal outpatient department on April 22, 2014. Physical examination revealed soft and ovoid abdomen without tenderness; however, shifting dullness was noted. Abdominal ultrasonography revealed massive ascites, and chest radiographs indicated bilateral interstitial lung infiltration. Blood biochemistry examination and complete blood cell count were normal except for mild anemia (hemoglobin, 10.7 g/dL), and the C-related protein level was 1.93 mg/dL. Abdominal computed tomography on April 24, 2014 (Fig. 1), revealed ascites, an enlarged uterus with multiple myomas, and right pleural effusion. However, no enlarged lymph nodes were observed.

Paracentesis was performed on the same day, and approximately 1600 mL of straw-colored fluid was drained from the peritoneal cavity. Analysis of the drained fluid revealed that the white blood cell count was 594/μL, the lymphocyte proportion was 81%, the total protein level was 5.0 mg/dL, the lactose dehydrogenase level was 317 IU/L, and the glucose level was 83 mg/dL. Acid-fast stain results for sputum and ascites yielded negative findings. Among tumor markers, the carcinoembryonic antigen level was 2.469 ng/mL, the CA 19-9 level was 29.532 U/mL, and the CA-125 level was 285.7 IU/mL. Pelvic examination revealed whitish vaginal discharge, an eroded cervix, and an enlarged uterus. Transvaginal ultrasonography revealed a myomatous uterus and endometrial thickening; the endometrium was approximately 10-mm thick. Because of suspicion of endometrial or ovarian malignancy, the patient was transferred to the gynecologic ward.

Laparotomy was performed on April 27, 2014 (Fig. 2), and approximately 1400 mL of ascites was suctioned out. Severe intestinal adhesions were noted, as were multiple instances of miliary seeding over the adnexa and peritoneum. Left salpingo-oophorectomy and endometrial curettage were performed, and the specimens were sent for frozen pathologic analysis. The endometrium, ovaries, and fallopian tubes demonstrated caseous granuloma; furthermore, the acid-fast stains for all three were positive for mycobacterial bacilli. The patient was subsequently transferred to the infection ward, and anti-TB treatment began in April 29, with ethambutol, 800 mg/day, and the combination of rifampicin, 4 tabs/day; isoniazid, 480 mg/day; and pyrazinamide, 320 mg/day (Rifater, 1000 mg/day). This regimen was followed for the first 2

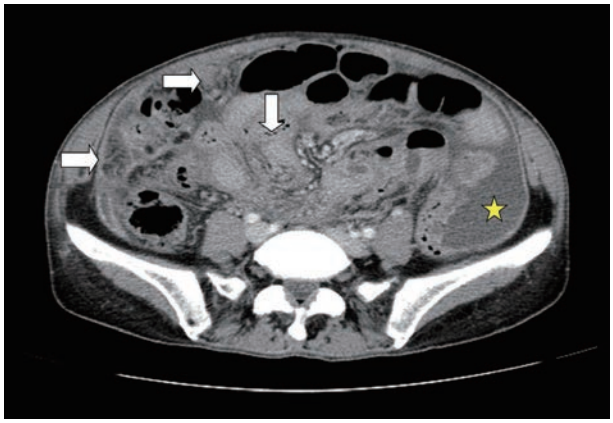

**Fig. 1** Post-contrast medium-enhanced computed tomographic image, exhibiting diffuse enhancement and thickening of the peritoneum with ascites (star) and multiple peritoneal nodules (arrows), which were suggestive of peritoneal carcinomatosis.

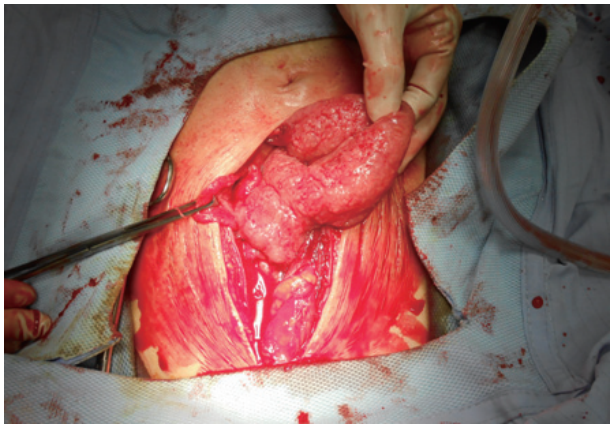

**Fig. 2** Miliary seeding over the intestines.

months, followed by the combination of rifampicin, 3 tabs/day, and isoniazid, 450 mg/day (Rifinah, 300 mg/day) for 7 months. The initial TB sputum culture, on May 30, 2014, revealed *Mycobacterium tuberculosis.* The CA-125 level dropped to 11.2 IU/mL after 5 months of treatment. The patient responded well to the regimen of anti-TB drugs, and the treatment ended on February 6, 2015.

**Case 2**

An 81-year-old postmenopausal woman with underlying hypertension and chronic renal failure was also receiving hemodialysis for end-stage renal disease. She suffered purulent vaginal discharge and bleeding for 3 weeks. Pelvic examination and ultrasonography, performed on July 1, 2014, revealed endometrial thickness of up to 31 mm, and endometrial malignancy was suspected. Magnetic resonance imaging indicated endometrial thickness of 27 mm with myometrium involvement and cystic change at the endometrial cavity. Moreover, a cystic mass 38 × 33 × 26 $mm^3$ in size was observed on the right pelvic side wall. The CA-125 level was 232.3 IU/mL. Endometrial curettage was performed, and pathologic study revealed abundant caseous-like necrosis surrounded by granulomatous inflammation and a few Langerhans giant cells. Furthermore, acid-fast stain of the endometrial tissue yielded positive results, which was compatible with TB; however, the acid-fast stain results for sputum were all negative. No definite malignancy was found.

Because tuberculous endometritis was suspected, the patient was started on anti-TB treatment postoperatively. The regimen included pyridoxine, 50 mg/day; ethambutol, 600 mg three times a week; pyrazinamide, 1000 mg three times a week; and the combination of rifampicin, 300 mg, and isoniazid, 200 mg (Rifinah) daily. Unfortunately, the patient died on September 30, 2014, from hospital-acquired pneumonia and septic shock with multiple-organ failure.

## Discussion

FGTB is an extrapulmonary manifestation of TB. In India, it represents 5% of all female pelvic infections and 10% of pulmonary TB cases [7]. According to recent studies, extrapulmonary TB is relatively rare. Among extrapulmonary TB cases, genital TB cases are even rarer. According to the official statistics released in 2017 by the Taiwan Centers for Disease Control, isolated extrapulmonary TB cases accounted for 5.80% of all TB cases, and genital TB cases accounted for 6.76% of all isolated extrapulmonary TB cases. FGTB is a major cause of morbidity, and it causes short- and long-term sequelae, especially infertility.[8] However, in menopausal women, the clinical presentation can vary. The manifestations include postmenopausal bleeding, abdominal distention, ascites, persistent vaginal discharge, and pyometra. In both our patients, endometrial malignancy and FGTB were initially suspected. However, the actual diagnosis was difficult. The diagnoses of FGTB were not confirmed until surgical intervention had been performed and pathology results had been reported. In cases of no definite diagnosis, surgical intervention, especially minimally invasive laparoscopic surgery, can be performed to make a definite diagnosis. Surgical intervention is not only a vital diagnostic tool but also a treatment option. Timely diagnosis and prompt treatment may prevent infertility and other sequelae of the disease.

Tuberculous peritonitis can also increase serum levels of CA-125. Huang et al [9]. reported that the serum CA-125 level in five patients with pelvic TB ranged from 24.4 to 1093.5 U/mL. The elevation in serum CA-125 level in our first patient was related to the presence of ascites with intra-abdominal miliary TB, not with ovarian malignancy. Both our patients had elevated levels of serum CA-125, which became normal after anti-TB treatment in the first patient. Therefore, CA-125 might be a useful marker in monitoring disease activity of pelvic TB and the response to anti-TB drugs.

The drug therapy for FGTB is similar to the standard treatment regimen used for pulmonary TB. Because the four drugs used—isoniazid, rifampicin, ethambutol, and pyrazinamide—can cause hepatitis, liver function must be monitored [10].

Currently, for FGTB diagnosis, there are no standard guidelines or algorithms, and the diagnosis is usually made after endometrial sampling for acid-fast bacilli microscopy, culture testing, histopathological confirmation of an epithelioid granuloma, a positive result of polymerase chain reaction testing, and endoscopic biopsy [11]. Ascites in women may be caused by ovarian malignancy (50%) or other malignancy or by kidney or liver disease or TB peritonitis. Therefore, nonmalignant ascites must be subjected

to TB screening or culture tests. For diagnosing FGTB, especially for tubal, ovarian, and peritoneal lesions, laparoscopy is the most reliable modality.

In conclusion, the clinical presentation of FGTB can vary. However, a prompt and precise diagnosis and an effective treatment can improve outcomes.

## Acknowledgment

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## References

1. Annual death rate of tuberculosis in Taiwan, p.426, in History of Public Health in Taiwan (I), Ministry of Health, 1995, Taipei.
2. TB: a global emergency. WHO Report on the TB epidemic. WHO/TB/94.177. Geneva: World Health Organization: 1994.
3. Taiwan Tuberculosis Control Report 2016. Center for Disease Control, Ministry of Health and Welfare, 2017, Taipei, Taiwan
4. Sharma JB: Tuberculosis and obstetric and gynecological practice. In Strudd J, Tan SL, Chervenak FA (eds): Progress in Obstetrics and Gynecology. 18th ed. Philadelphia, Pa. Elsevier. 2008. p.395-427.
5. Tsai WS and Huang SC: A review of 34 cases of female genital tuberculosis diagnosed by histology including a case with sonography. J Obstet Gynecol ROC 14:163-170, 1975.
6. Agarwal J, Gupta JK: Female genital tuberculosis – a retrospective clinico-pathologic study of 501 cases. Indian J Pathol Microbiol 1993; 36:389-97.
7. Duggal S, Duggal N, Hans C, Mahajan RK: Female genital TB and HIV co-infection. Indian J Med Microbiol 2009;27: 361-363.
8. Sharma JB: Current diagnosis and management of female genital tuberculosis. J.Obstet Gynaecol India:2015;65: 362-371.
9. YJ Huang, LH Wei, CY Hsieh: Clinical presentation of pelvic tuberculosis imitating ovarian malignancy. Taiwanese J Obstet Gynecol 2004;43(1):29-34.
10. WHO guideline for treatment of tuberculosis. Geneva, WHO, 2010.
11. Sharma JB, Sneha J, Singh US, Kumar S, Roy KK, Singh N, Dharmendra S: Effect of antitubercular treatment on ovarian function in female genital tuberculosis with infertility. J Human Reprod Sci 2016; 9:145-150.

# 婦女生殖道結核之病例報告

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**摘要**

從 2005 年 5 月至 2017 年 9 月，兩名女性生殖器結核病（FGTB）患者在台北慈濟醫院接受治療。結核病至今仍然為我國常見疾病之一。女性生殖器官結核病在骨盆腔炎中並非罕見，然而其臨床表現難以鑑別診斷。此篇報告一名 55 歲的女性出現腹脹，腿部水腫和全身無力的症狀。電腦斷層掃描（CT）顯示大量腹水，子宮肌瘤和右側胸腔積液。痰液和腹水的耐酸性染色 (Acid-fast stain) 呈陰性。懷疑卵巢惡性腫瘤，進行了左側輸卵管卵巢切除術和子宮內膜刮除術，冷凍病理學顯示為乾酪性肉芽腫。給予抗結核藥物，目前復原狀況很好。另一名 81 歲的女性患有膿性陰道分泌物和出血。 子宮刮搔術後病理診斷為子宮內膜結核感染（TB）。給予抗結核藥物治療但最終不幸過世。對於虛弱的患者，抗結核藥物可能是有害的。腹腔鏡檢查可用於診斷結核性腹膜炎中的生殖器結核病（FGTB）。

**關鍵詞**：女性、生殖道、結核病

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Case Report

# Prenatal Diagnosis of Aberrant Right Subclavian Artery: A Case Report and Review of Literature

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**Abstract**

Aberrant right subclavian artery (ARSA) is a rare congenital aortic arch anomaly that can be detected prenatally using the three-vessels and trachea (3VT) view during routine ultrasound and power Doppler ultrasound.

Here, we report a case of prenatal diagnosis of ARSA in a singleton pregnancy with normal karyotype during the second trimester. Detection of ARSA should be followed up with a detailed ultrasound examination for other cardiac defects or ultrasound markers. Chromosomal investigation is advisable due to the increased positive likelihood ratio (LR) for aneuploidy.

**Key words:** aberrant right subclavian artery, prenatal diagnosis

## Introduction

During embryogenesis, the aortic arch normally develops into the left aortic arch with three branches of arteries arising from it. The first branch is the brachiocephalic artery, which bifurcates into the right common carotid and right subclavian arteries, the second branch is the left common carotid artery, and the third branch is the left subclavian artery. However, the right subclavian artery may develop an aberrant right subclavian artery (ARSA) when the right subclavian artery abnormally arises as a fourth branch of the aortic arch instead of the brachiocephalic artery. The incidence of ARSA is approximately 0.4% to 1.4% [1,2]. ARSA is thought to be a prenatal ultrasound marker of Down syndrome (DS) since the prevalence of the aberrant artery was 23.6% in fetuses with DS [2–5]. In 2015, a meta-analysis reported a positive likelihood ratio of 26.93 when an ARSA was viewed as an independent ultrasound marker for DS [3].

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## Case report

A 34-year-old multiparous female in week 22 of gestation was evaluated at our perinatal ultrasound unit for an elective prenatal level 2 ultrasonography. An abnormal continuous flow was detected outwards from the transducer with the patient in a supine position using Doppler ultrasound scan (2.5 MHz, Voluson S10, GE) rightward of the aortic echo, which is a sign of blood flow and was compatible with an isolated ARSA (Fig. 1). No other structural anomalies were detected. Amniocentesis was performed at 26 weeks of gestation and revealed a normal karyotype (46, XY). The mother had received regular prenatal care and the prenatal visits were unremarkable. The baby was delivered by caesarean breech birth at 38 weeks of gestation with a body weight of 3800 g, and the postnatal survey showed no other neonatal abnormalities.

## Discussion

During embryonic development, the primitive heart tube is comprised of a double aortic arch that

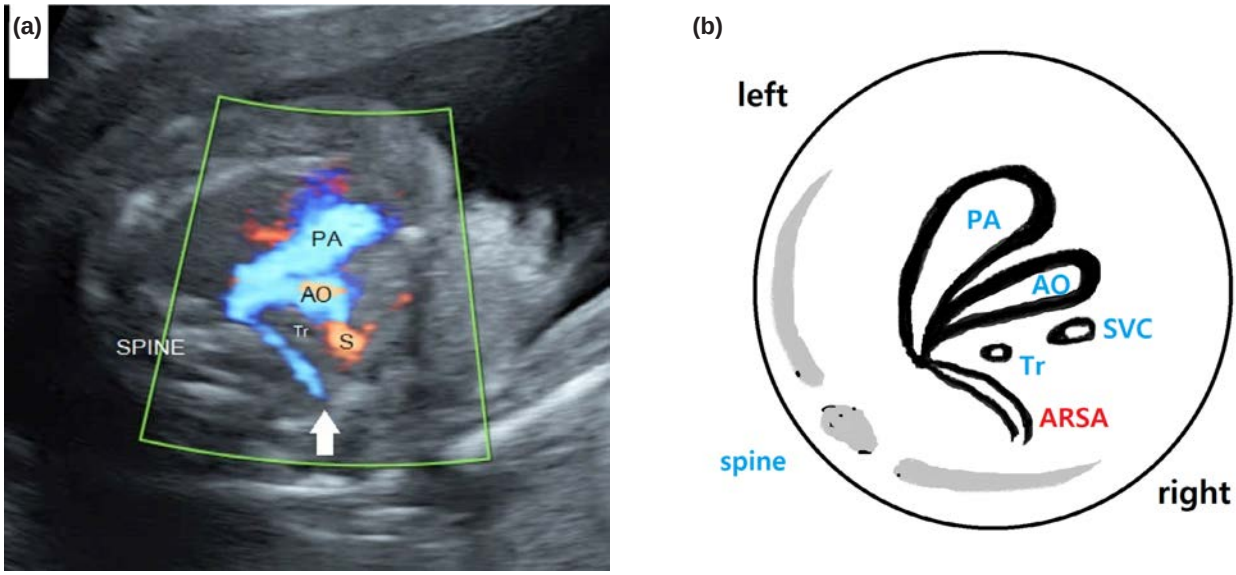


**Fig. 1** Power Doppler ultrasound image showing aberrant right subclavian artery (ARSA). (a) Three-vessel and trachea view revealed an ARSA (arrows) arising from the descending aorta. (b) Schematic diagram of ARSA. AO, aorta; PA, pulmonary artery; S, superior vena cava; Tr, trachea

gives rise to a common carotid artery and subclavian artery. Normally, the right side arch regresses distally and the left side arch persistently develops into the left aortic arch with three branches: brachiocephalic artery, left common carotid artery, and left subclavian artery. However, when the regression process is interrupted, variations of aortic arch development result in aortic arch anomalies. The most common aortic arch anomaly is ARSA, which is characterized by a left aortic arch with four branches: right common carotid artery, left common carotid artery, left subclavian artery, and right subclavian artery.

The incidence of ARSA is around 0.4% to 1.4% in the general population [1,2]. While combined fetal defects have been reported, most are isolated findings. Chromosomal investigation is advisable since ARSA is present in 16% to 35% of cases of Down syndrome (DS) [2,6], and it is recommended as a second-trimester ultrasound marker of fetal DS [3,4]. Combined fetal defects have been reported [7–9], such as a branching pattern of the great vessels arising from the aortic arch, as the ductus arteriosus closes postnatally, affecting the great vessels. Moreover, tracheoesophageal compression by the ARSA has been reported since the route of ARSA enters to the right arm retrospect to the trachea [10].

Therefore, detection of ARSA should be followed up by careful exclusion of other potential defects via careful history taking, astute physical examination, laboratory tests, and imaging studies, while maintaining a high level of suspicion.

## Conclusions

While ARSA is a rare variation of aortic arch, clinicians should be aware that it may exist either alone or in combination with other congenital defects. Therefore, further prenatal counselling may be indicative. Prenatal diagnosis of ARSA is challenging during the second trimester ultrasound examination, and the three-vessel and tracheal view plus power Doppler may provide a clear and specific visualization to reveal any aberrant vessels of the aortic arch.

## References

1. Song MJ, Han BH, Kim Y-H, et al. Prenatal diagnosis of aberrant right subclavian artery in an unselected population. Ultrasonography 2017;36:278-83.
2. Zalel Y, Achiron R, Yagel S, Kivilevitch Z. Fetal aberrant right subclavian artery in normal and Down syndrome fetuses. Ultrasound Obstet Gynecol 2008;31:25-9.
3. Scala C, Leone Roberti Maggiore U, Candiani M, et al. Aberrant right subclavian artery in fetuses with Down syndrome: a systematic review and meta-analysis. Ultrasound Obstet Gynecol 2015;46:266-76.
4. Agathokleous M, Chaveeva P, Poon LC, Kosinski P, Nicolaides KH. Meta-analysis of second-trimester markers for trisomy 21. Ultrasound Obstet Gynecol 2013;41:247-61.
5. De Leon-Luis J, Gamez F, Bravo C, et al. Second-trimester fetal aberrant right subclavian artery: original study, systematic review and meta-analysis of performance in

detection of Down syndrome. Ultrasound Obstet Gynecol 2014;44:147-53.
6. Lo NS, Leung PM, Lau KC, Yeung CY. Congenital cardiovascular malformations in Chinese children with Down's syndrome. Chin Med J (Engl) 1989;102:382-86.
7. Tschirch E, Chaoui R, Wauer RR, Schneider M, Rudiger M. Perinatal management of right aortic arch with aberrant left subclavian artery associated with critical stenosis of the subclavian artery in a newborn. Ultrasound Obstet Gynecol 2005;25:296-8.
8. Bravo C, Gamez F, Perez R, Aguaron A, De Leon-Luis J. Prenatal diagnosis of Potocki-Lupski syndrome in a fetus with hypoplastic left heart and aberrant right subclavian artery. J Perinatol 2013;33:394-6.
9. Tormettino B, Ricci C, Rossi C, Schettino MT, Torella M, Russo MG. A particular association: aberrant right subclavian artery, persistent left superior vena cava and a dilatation of pulmonary artery in a dysmorphic SGA fetus. Minerva Ginecol 2015;67:297-9.
10. Hassan W, Omrani AA, Neimatallah M, Fadley FA, Halees ZA. Dysphagia lusoria caused by aberrant right subclavian artery, Kommerell's diverticulum, legamentum ring, right descending aorta, and absent left pulmonary artery: a report of a unique vascular congenital disease undetected until adulthood and a review of the literature. Pediatr Cardiol 2005;26:851-5.

# 產前診斷右側異生性鎖骨下動脈：案例報告及文獻回顧

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**摘要**

右側異生性鎖骨下動脈是一種少見之主動脈弓發育異常，可以藉由高層次超音波結合彩色杜卜勒超音波於胎兒心臟三血管及氣管切面的異常成像達成產前診斷。

我們報告一位於第二孕期發現羊水染色體正常合併右側異生性鎖骨下動脈之產前診斷個案。根據文獻回顧，右側異生性鎖骨下動脈常合併其他先天性心臟結構異常或超音波異常，而且合併染色體異常的機率也會增加。

**關鍵詞：**右側異生性鎖骨下動脈、產前診斷

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Case Report

# A Case Report of a Female Patient Who Presented a Hepatic Mesenchymal Hamartoma that Grew Since Childhood

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**Abstract**

Hepatic mesenchymal hamartoma (HMH) is commonly observed in pediatric patients aged below 2 years, and it accounts for about 3%–8% of all primary liver tumors in children. HMH usually presents as a cystic tumor with multiple septa and variable solid components. However, the whole tumor may sometimes appear as a solid mass. This type of tumor is rarely observed in adults, and only about 46 adult cases were reported. Herein, we discuss the case of a 23-year-old woman diagnosed with HMH at the age of 5 years via surgical biopsy. Because the tumor could not be resected at that time, liver transplantation was recommended. However, the parents refused to let their child undergo the procedure. Several years after the initial diagnosis, the patient did not receive any management for her HMH, and she only sought treatment after recently experiencing progressive abdominal discomfort. Thus, da Vinci robotic-assisted central hepatectomy with total tumor excision was performed.

**Key words:** Hepatic mesenchymal hamartoma (HMH), Benign liver tumor

## Introduction

Hepatic mesenchymal hamartoma (HMH) is a rare condition. However, it is the second most common benign hepatic tumor in the pediatric population after infantile hemangioendothelioma[1]. It is commonly observed in pediatric patients aged below 2 years and is more predominant in men than in women (male:female = 2:1). The right lobe of the liver is more likely to be involved than the left lobe (right:left = 6:1)[2]. HMH usually presents as a large multiloculated cystic tumor. Multiple septa along with solid components may be observed inside the tumor. Some mesenchymal hamartomas may present as a solid tumor, and they are more common in adult than in pediatric patients, with a prevalence rate of less than 50%[3]. Since the tumor may be extremely large, it may reach up to 20–30 cm in diameter and weigh over 3 kg. It can also cause symptoms, such as portal hypertension, anorexia, and respiratory distress, due to compression of the adjacent structures or organs in the pediatric population. Surgical excision is usually the treatment of choice, and complete tumor removal usually yields good outcomes.

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## Case Report

A 23-year-old female patient presented with a palpable ping-pong sized tumor in the right upper quadrant of the abdomen at the age of 5 years. A serial workup was conducted, and based on the results, the initial diagnosis was hepatoblastoma. A port-A-catheter was inserted at that time to prepare the patient for chemotherapy treatment. However, the surgical biopsy results were indicative of hepatic mesenchymal hamartoma, and chemotherapy was not indicated for this diagnosis. The surgeon informed the parents that liver transplantation was a treatment option as the

patient would be at higher risk if she underwent surgical tumor excision. However, the patients refused. Hence, no treatment was initiated from the time of her initial diagnosis. Recently, the patient presented with progressive abdominal distension and evident protrusion on the right upper abdomen. The levels of tumor markers, including alpha-fetoprotein (a-FP), were normal. Plain radiography revealed several coarse calcifications (1–2 cm) in the right subphrenic area (Fig. 1). Contrast-enhanced magnetic resonance imaging (MRI) (Fig. 2) showed a huge hypointense solid mass on T1-weighted image (T1WI), mild hyperintense lesion on T2-weighted image (T2WI), and some band-like bright signals interspersed inside the tumor. The lesion appeared as heterogeneous dark signal intensity on diffusion-weighted imaging (DWI) and as heterogeneous bright signal intensity on apparent diffusion coefficient (ADC) map. Some dark signals scattered in the upper part of the tumor were observed on all pulse sequences, which were correlated to the coarse calcifications in the right subphrenic space on plain film. Dynamic enhanced MRI revealed progressive inhomogeneous delay enhancement of this tumor, which is limited to the septa and

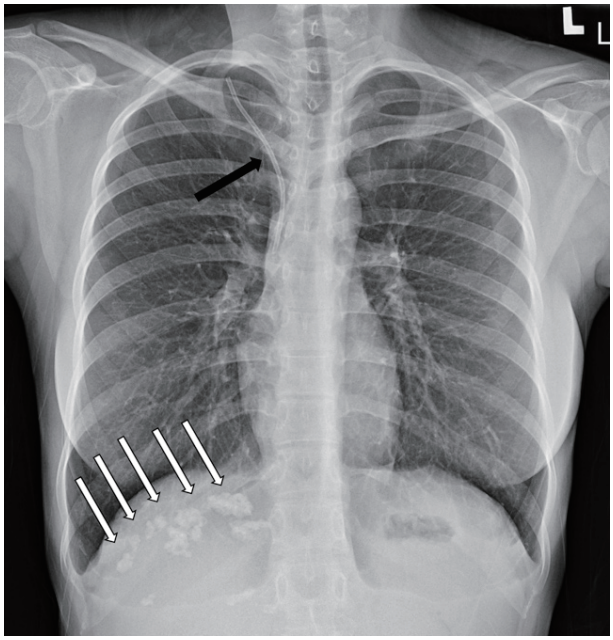

**Fig. 1** Chest PA view revealed several large coarse calcifications (white arrows) in the right subphrenic area, representing unusual calcifications within the hepatic mesenchymal hamartoma. A ruptured catheter (black arrow) was noted inside the superior venal cava due to a failed retrieval of the port-A-catheter that was inserted when the patient was still a child.

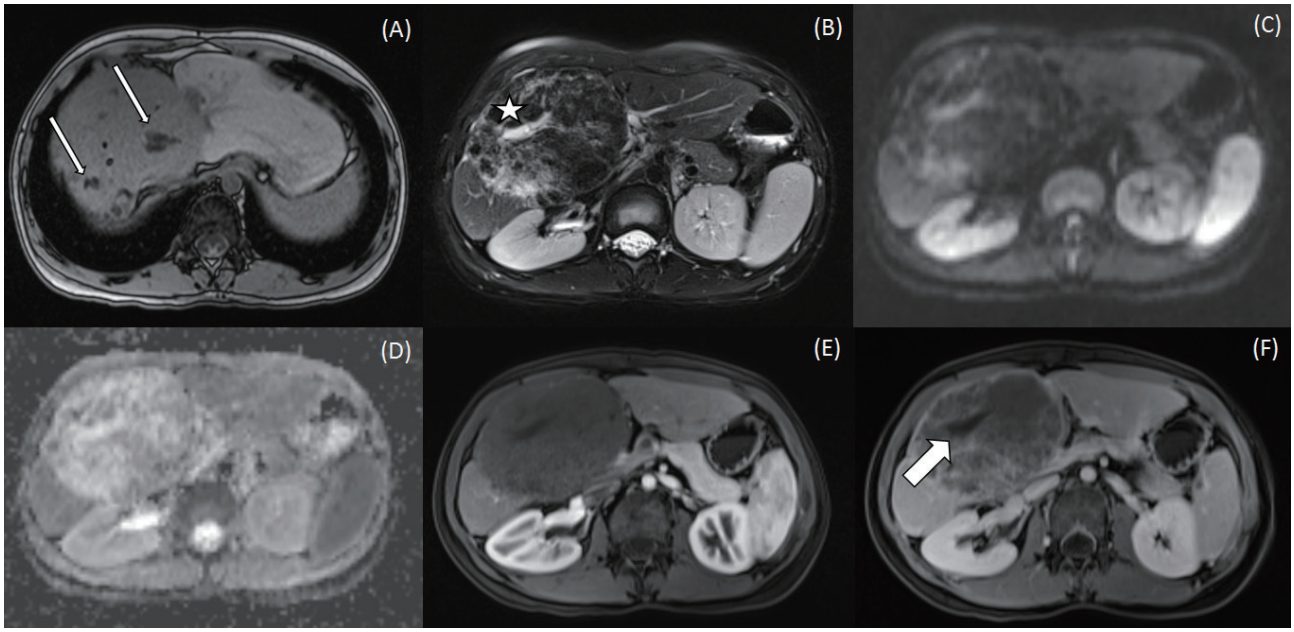


**Fig. 2** (A) Magnetic resonance imaging (MRI) with axial T1-weighted image (T1WI) showed a large homogeneous hypointense mass with several dark signals (white arrows) in segments 4 and 8. These dark signals represent the coarse calcifications noted on chest radiography. (B) MRI with axial T2-weighted image (T2WI) with fat saturation revealed a heterogeneous hyperintense tumor. Central necrosis (asterisk) presented as an irregular cavity inside the tumor. (C) MRI with diffusion-weighted imaging (DWI) showed heterogeneous dark signal intensity, and (D) apparent diffusion coefficient (ADC) map revealed heterogeneous bright signal intensity. (E) MRI with contrast enhancement in the arterial phase showed no evident tumor enhancement. (F) Contrast-enhanced MRI in the venous phase revealed mild inhomogeneous enhancement, which is limited to the septa and stromal components.

stromal components. Due to the large tumor size and its associated symptoms, da Vinci robotic-assisted laparoscopic central hepatectomy with resection of segments 4, 5, and 8 was performed. Pathological examination showed a 14.2 x 12.5 x 9.8-cm tumor weighing 758 g, and the tumor was well encapsulated. Proliferation of mature bile ducts, mesenchymal cells, calcifications, vessels, and smooth muscles were observed throughout the whole tumor (Fig. 3). The final diagnosis was mesenchymal hamartoma. Bile leakage was noted after surgery and was successfully managed with a stent placed in the bile duct.

## Discussion

HMH is rarely observed in adult patients. That is, there are only 46 sporadic cases reported in the literature. The oldest patient reported was aged 87 years[4]. Adult patients have a different gender distribution compared with pediatric patients. In adult cases, it is observed predominantly in women[4]. Although the tumor patterns can be predominantly cystic to solid, the solid mass is more frequently observed in adult patients with a prevalence rate of less than 50%. Tumor calcifications are not common findings in HMH[2]. In this specific case, there were several coarse calcifications in the upper part of the tumor noted on plain film radiography. Since HMH can be predominantly cystic and mixed cystic and have a solid and predominantly solid appearance, the imaging findings were based on the cystic versus solid compositions of the tumor and the fluid content of the cysts. On ultrasonography (US), this tumor usually appeared as a large intrahepatic tumor with solid and

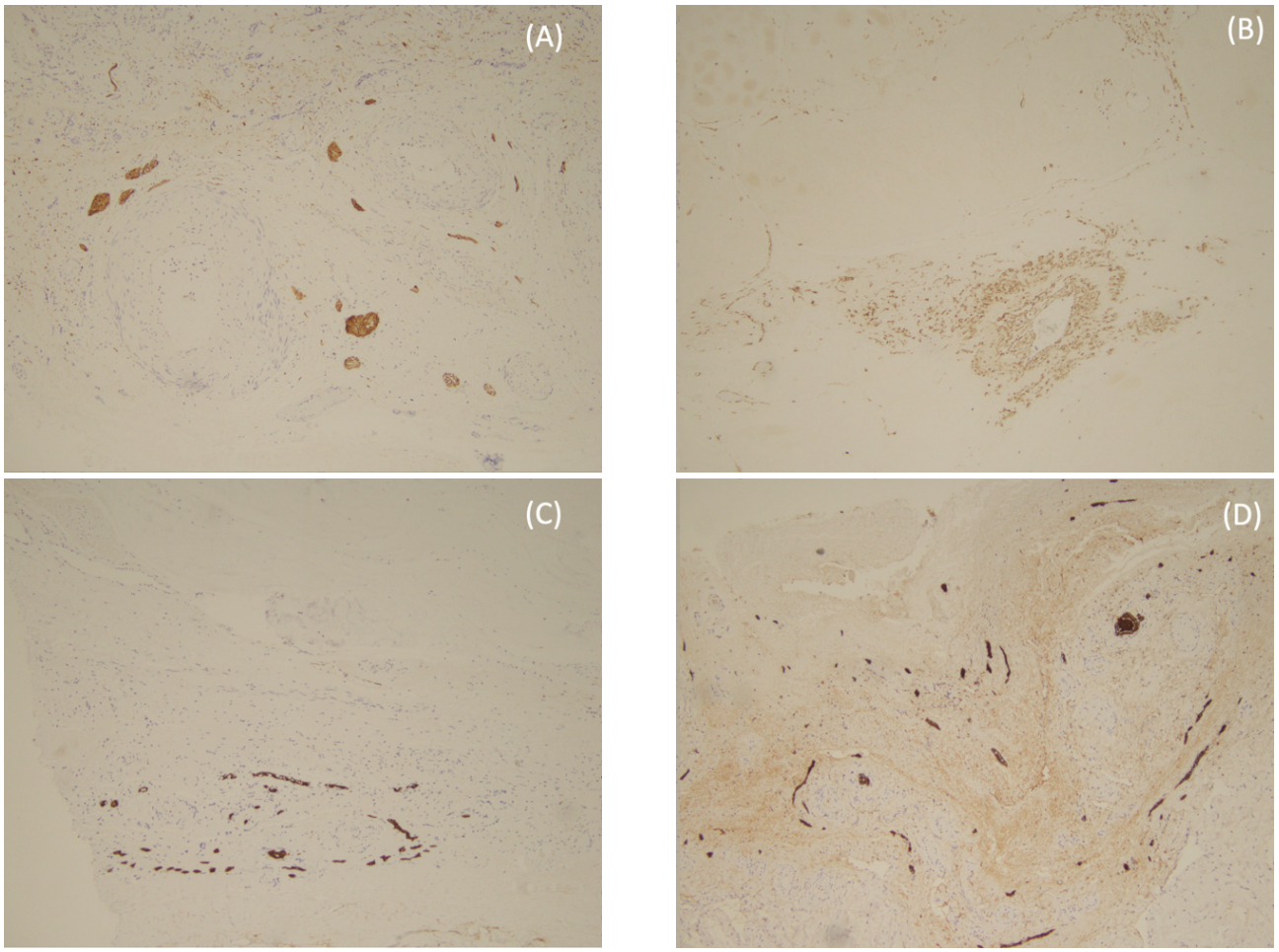


**Fig. 3** (A) The mass mainly comprised loose mesenchymal tissues, and some interspersed nerve tissues were noted and confirmed via positive staining for S100 (original magnification, × 200). (B) The stromal area also contained vessels with rims of hyalinized fibrous tissues surrounding their walls, and this finding was confirmed via positive staining for smooth muscle actin (original magnification, × 200) (C) (D) and proliferation of mature bile ducts that were positive for cytokeratin 7 (original magnification, × 200).

multiple variable cystic components with some septa. On computed tomography (CT) scan, this tumor usually presents as a complex cystic mass with heterogeneous appearance and scattered fluid-attenuation areas. Peripheral and septal enhancements are often observed after contrast injection. Hemorrhage or calcifications may occur but rare. In the predominantly cystic type, MRI may reveal multicystic components with variable high signal intensities in different cystic parts on T2WI. In the mixed cystic and solid type, MRI may show heterogeneous low signal intensities on T1WI and more heterogeneous high signal intensities on T2WI due to the scattered cystic foci inside the solid stromal components. In the solid type (as in our case), MRI may reveal a slightly low signal intensity on T1WI, heterogeneous high signal intensity on T2WI, and some higher band- or septal-like signal intensities inside. The DWI/ADC map did not show evident water restriction, which could be attributed to the loose mesenchymal tissues throughout the tumor. Most HMHs are hypovascular[5], and only few tumors are hypervascular. The enhancement of this tumor is usually mild and delayed. In our case, there was a progressive faint inhomogeneous enhancement in the portal venous and delayed phases, and the enhancement was more evident along the tumor borders and septa than in the stromal components.

The tumor marker levels are usually normal in most cases[4]. However, the a-FP level is sometimes elevated [1], and this finding can be confused with hepatoblastoma, which usually presents with an elevated a-FP level[6]. Some patients were misdiagnosed with hepatoblastoma and consequently received neoadjuvant chemotherapy before a definite diagnosis of HMH could be established based on an elevated a-FP level[6]. Our patient had a port-A-catheter inserted through her right subclavian vein in preparation for neoadjuvant chemotherapy. However, she was fortunate that she did not receive the non-indicated chemotherapy because her surgical biopsy results came back before the treatment was initiated. Patients with HMH may have elevated a-FP levels, which will return to normal levels after tumor resection. Liver transplantation was indicated in this case as the patient would be at high risk if she underwent tumor excision surgery. However, the parents refused the treatment. Only four cases of liver transplantation for this type of tumor were recorded[4]. Most HMHs can be completely removed with a one-stage surgery via anatomic or non-anatomic resection[7]. Some authors recommended other treatments, such as nucleation, marsupialization, and sequential resection, as possible alternatives[1]. Complications after HMH surgery are not common. However, hemorrhage or bile duct injury may occur[1]. Our patient presented with bile leakage after surgery and was treated by placing a temporary common bile duct stent. To prevent tumor rupture during delivery or development of hydrops, prenatal treatment of HMH via US-guided aspiration of cystic components or pigtail drainage of the fluid inside the tumor has been performed in a few cases[8]. Only nine HMH cases involving spontaneously regression without treatment were reported. Most of these cases are similar. That is, they are usually hypervascular and solid. Although the nine cases involved some degree of tumor regression, no tumor completely disappeared [1]. HMHs are typically well circumscribed and surrounded by displaced hepatic parenchyma but without a true capsule. Microscopically, tumor cysts are separated by fibrous septa and surrounded by loose mesenchymal tissues, which contain bile ducts, blood vessels, and some hepatocytes. Mesenchymal hamartomas in adults are more likely to have hyalinized fibrous tissues and fewer ductal structures and hypervascular than those in pediatric patients[9]. Some HMHs have similar genetic abnormalities involving the chromosome 19q13.4 region, which is similar to malignant undifferentiated embryonal sarcoma (UES)[10]. Moreover, some HMH tumors co-existed with UES or malignantly transformed to a UES based on the surgical specimens obtained. Moreover, they were found occasionally with long-term follow-up[1].

In conclusion, HMH is a benign mesenchymal tumor found almost exclusively in pediatric patients. Therefore, these tumors are extremely rare in adults. Most HMHs present as a large, multicystic hypovascular mass with some septa. However, calcifications and tumors with a solid appearance are not common findings in adults.

## References

1. Stringer MD, Alizai NK. Mesenchymal hamartoma of the liver: a systematic review. J Pediatr Surg 2005;40:1681-90.
2. Chiorean L, Cui XW, Tannapfel A, Franke D, Stenzel M, Kosiak W, et al. Benign liver tumors in pediatric patients - Review with emphasis on imaging features. World J Gastroenterol 2015;21:8541-61.

3. Hernandez JC, Alfonso C, Gonzalez L, Samada M, Ramos L, Cepero-Valdez M, et al. Solid mesenchymal hamartoma in an adult: a case report. J Clin Pathol 2006;59:542-5.
4. Li J, Cai JZ, Guo QJ, Li JJ, Sun XY, Hu ZD, et al. Liver transplantation for a giant mesenchymal hamartoma of the liver in an adult: Case report and review of the literature. World J Gastroenterol 2015;21:6409-16.
5. Chung EM, Cube R, Lewis RB, Conran RM. From the archives of the AFIP: Pediatric liver masses: radiologic-pathologic correlation part 1. Benign tumors. Radiographics 2010;30:801-26.
6. Boman F, Bossard C, Fabre M, Diab N, Bonnevalle M, Boccon-Gibod L. Mesenchymal hamartomas of the liver may be associated with increased serum alpha foetoprotein concentrations and mimic hepatoblastomas. Eur J Pediatr Surg 2004;14:63-6.
7. Qureshi SS, Bhagat M, Kembhavi S, Vora T, Ramadwar M, Chinnaswamy G, et al. Benign liver tumors in children: outcomes after resection. Pediatr Surg Int 2015;31:1145-9.
8. Tsao K, Hirose S, Sydorak R, Goldstein RB, Machin GA, Albanese CT, et al. Fetal therapy for giant hepatic cysts. J Pediatr Surg 2002;37:E31.
9. Cook JR, Pfeifer JD, Dehner LP. Mesenchymal hamartoma of the liver in the adult: association with distinct clinical features and histological changes. Hum Pathol 2002;33: 893-8.
10. Bove KE, Blough RI, Soukup S. Third report of t(19q)(13.4) in mesenchymal hamartoma of liver with comments on link to embryonal sarcoma. Pediatr Dev Pathol 1998;1: 438-42.

# 自幼發現之實質樣肝臟間葉缺陷瘤：一個成年女性之罕見個案報告

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**摘要**

肝臟間葉缺陷瘤（HMH）通常發生在 2 歲以下的小兒病患。它們佔所有小兒原發性肝腫瘤的百分之三～八。肝臟間葉缺陷瘤通常表現為具有多個隔膜和多樣實質構造所組成的囊狀腫瘤。 少數肝臟間葉缺陷瘤可能表現為實質狀腫塊。 肝臟間葉缺陷瘤在成人中發現的案例很少。目前僅報告 46 例成人病例。在本報告中，我們討論了一名 23 歲的女性案例，她在 5 歲時經由手術活檢診斷出患有肝臟間葉缺陷瘤。由於當時的技術無法安全切除整個腫瘤，於是建議進行肝臟移植，但病患父母當時拒絕了肝臟移植這項手術。在診斷後的這十幾年間，患者沒有再接受過任何有關她肝臟間葉缺陷瘤的治療。最近由於患者逐漸感到腹部不適後才又尋求治療。在本院她接受了達文西機器手臂輔助的中央肝臟切除手術，順利將整個腫瘤切除。

**關鍵詞：**肝臟間葉缺陷瘤、良性肝臟腫瘤

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Image

# Pseudomelanosis of the Stomach and Duodenum

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**Abstract**

Pseudomelanosis of the stomach and duodenum is a rare and generally benign disease. However, the disease mechanism remains unclear. Here, we report the case of a 74-year-old man with a history of chronic kidney disease and hypertension. He was admitted due to end-stage renal disease with uremic syndrome and received hemodialysis. A gastroenterologist was consulted for severe anemia and positive fecal occult blood test. Upper endoscopy resulted in the incidental discovery of multiple discrete tiny black spot lesions in the antrum and duodenum; a biopsy was performed at the same time. Histological assessment showed hemosiderin-laden macrophages and moderately mixed inflammatory infiltrate consisting of lymphocytes, plasma cells, and eosinophils in the lamina propria. The iron stain revealed hemosiderin pigment deposition. These findings were consistent with the diagnosis of pseudomelanosis of the stomach and duodenum. This disease is not associated with significant clinical impact or long-term complications. Treatment is discontinuation of medication as described in the article.

**Key words:** Chronic renal failure, Anti hypertensive drugs, Pseudomelanosis duodeni, Pigmentation, Iron, Melanin

A 74-year-old man was admitted to our hospital with suspected end-stage renal disease with uremic syndrome where he received hemodialysis. A gastroenterologist was consulted for severe anemia and positive fecal occult blood test. He had a history of chronic kidney disease and hypertension for more than 10 years. He took iron supplements, folic acid, doxazosin, bisoprolol, amlodipine, and hydralazine HCl over a long period based on prescriptions from both nephrology and cardiology services. After an esophagogastroduodenoscopy, multiple discrete tiny black spot lesions in the antrum (Fig. 1A) and duodenum (Fig. 1B, C) were discovered incidentally. A biopsy was performed at the same time, which revealed hemosiderin-laden macrophages and moderately mixed inflammatory infiltrate consisting of lymphocytes, plasma cells, and eosinophils in the lamina propria (Fig. 2). No evidence of malignancy was observed. The iron stain revealed hemosiderin pigment deposition (Fig. 2B, D). These results indicated a diagnosis of pseudomelanosis of the stomach and duodenum.

Pseudomelanosis duodeni is a rare benign condition first described by Bisordi and Kleinman in 1976 [1], and gastric pseudomelanosis was first described by Treeprasertuk et al. in 2000 [2]. These diseases are characterized by a collection of pigment-laden macrophages within the lamina propria, but the pathogenesis is still unclear. However, this condition is strongly associated with other diseases, such as chronic kidney disease, hypertension, diabetes mellitus, and gastrointestinal bleeding, as well as some medications, such as ferrous sulfate, hydralazine, propranolol, thiazide, furosemide, methyldopa, and digoxin [3]. This condition is often diagnosed by incidental endoscopy findings and has no significant clinical impact. It is not associated with long-term complications and does not require specific therapy or follow-up. Treatment is discontinuation of the medication as mentioned earlier.

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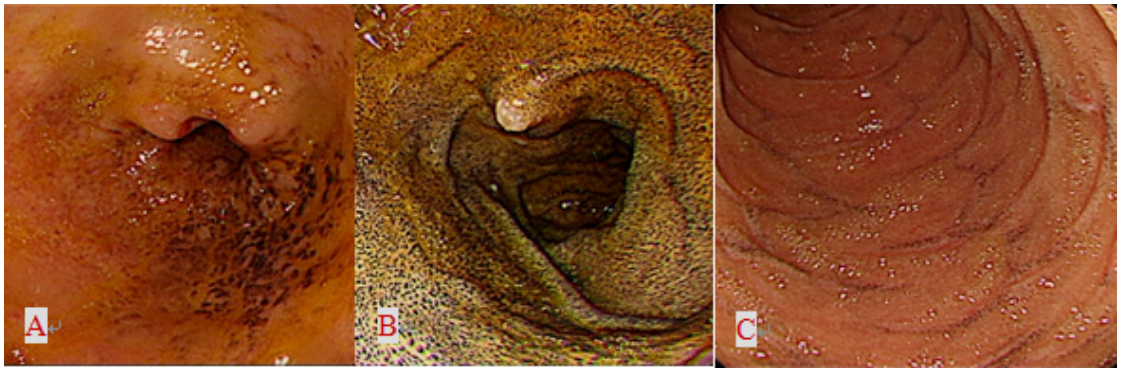


**Fig. 1** Upper gastrointestinal endoscopy revealed multiple discrete, tiny, black spot lesions. (A) Gastric antrum; (B) Duodenal bulb; (C) Second portion of the duodenum.

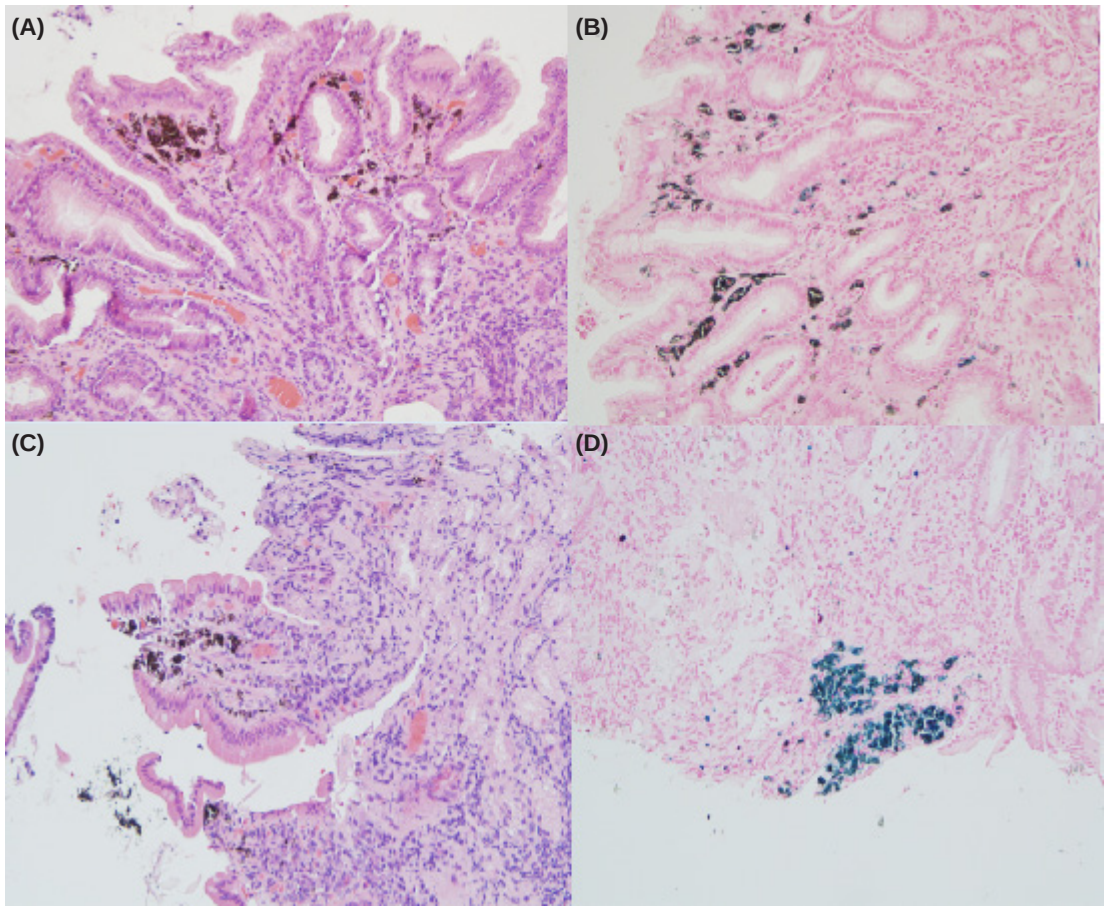


**Fig. 2** (A) Gastric antrum, hematoxylin-eosin staining; 100×, focal hemosiderin-like deposition and inflammatory cell infiltration in the superficial mucosa; (B) Iron stain-positive, 100×, gastric antrum; (C) Duodenal bulb, hematoxylin-eosin staining; 100×, hemosiderin-laden macrophages and moderately mixed inflammatory infiltrate consisting of lymphocytes, plasma cells, and eosinophils in the lamina propria; (D) Iron stain positive, 100×, duodenal bulb.

## References

1. Bisordi WM, Kleinman MS. Melanosis Duodeni. Gastrointest Endosc 1976; 23: 37-38.
2. Treeprasertuk S, Thong-Ngam D, Suwangool P et al. Pseudomelanosis duodeni: association with hypertension and chronic renal failure: case report. J Med Assoc Thai 2000; 83: 964-968.
3. Kang JY, Wu AY, Chia JL, Wee A, Sutherland IH, Hori R. Clinical and ultrastructural studies in duodenal pseudomelanosis. Gut 1987; 28: 1673-1681.

# 胃與十二指腸偽黑色素沉著症

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**摘要**

胃與十二指腸偽黑色素沉著症是罕見良性的狀況。目前還不知道它真正的機轉。我們報告一個 74 歲本身有慢性腎衰竭和高血壓的男性病人，此次住院是因為慢性腎衰竭併尿毒症而需要住院洗腎。住院中因為嚴重的貧血和糞便潛血反應陽性而會診腸胃科。上消化道內視鏡發現胃竇和十二腸有廣泛散布黑褐色細小斑點。病理切片顯示，在固有層（lamina propia）內有許多的發炎細胞和深褐色的色素顆粒聚集在巨噬細胞（macrophage）內，這些顆粒對鐵染色呈現陽性反應。根據以上的發現診斷為胃與十二指腸偽黑色素沉著症。本病症通常不會造成病人之不適，也不會有長期併發症，無須特別治療，只要停用相關之藥物或可避免加重黑色素沉著。

**關鍵詞：**慢性腎衰竭、高血壓用藥、十二指腸偽黑色素沉著症、色素沉著、鐵、黑色素

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Image

# Epiploic Appendagitis: A Benign Mimicker of Appendicitis

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**Abstract**

Abdominal pain can represent a spectrum of conditions, ranging from benign and self-limited disease to surgical emergencies. Differential diagnosis of right lower quadrant pain includes appendicitis, colitis, diverticulitis, and epiploic appendagitis. Here, we report the case of a male patient who was transferred to the emergency department from a clinic owing to suspected appendicitis. Although his symptoms were typical, laboratory reports and abdominal ultrasonography indicated the need for further investigation using computed tomography (CT). CT scan showed a pericolonic enhanced fat-mass-like lesion and stranding at the ileocecum in the coronal and transverse views; epiploic appendagitis was the diagnosis. Epiploic appendagitis is usually considered a benign, self-limiting disease that spontaneously resolves within days to weeks and can be conservatively treated with anti-inflammatory medications. Abdominal CT is a helpful tool for diagnosing this disease while excluding other causes of abdominal pain and plays an important role in preventing unnecessary surgery.

**Key words:** abdominal pain, appendicitis, epiploic appendagitis

## Introduction

Abdominal pain is one of the common reasons owing to which patients visit the emergency department (ED). It can represent a spectrum of conditions, ranging from benign and self-limited disease to surgical emergencies. Differential diagnosis of right lower quadrant pain includes appendicitis, colitis, diverticulitis, and epiploic appendagitis[1,2]. Pelvic inflammatory disease, tubo-ovarian abscess, ovarian torsion, and ruptured corpus luteal cyst should also be considered if the patient is a female. Epiploic appendagitis can be conservatively treated, but surgical intervention may be needed if the appendicitis is highly suspected. Computed tomography (CT) plays an important role in diagnosing appendagitis and preventing unnecessary surgery[3].

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## Case Report

A 42-year-old man was transferred to the ED from a local clinic owing to the chief complaint of right lower quadrant pain that persisted for 2 days. He had no surgical history, and his medical history was unremarkable. On physical examination, he exhibited tenderness in the right iliac fossa; however, he did not have fever. The pain was localized but worsened while walking. The Rovsing's and obturator signs were also positive. Laboratory findings did not show leukocytosis, although C-reactive protein level was mildly elevated (0.69 mg/dL). An abdominal CT was performed at the ED. CT revealed a pericolonic enhanced fat-mass-like lesion and adjacent stranding at the iliocecum (Fig. 1). The patient was diagnosed with epiploic appendagitis. He was conservatively managed with nonsteroidal anti-inflammatory medications, and his symptoms totally resolved 3 days later.

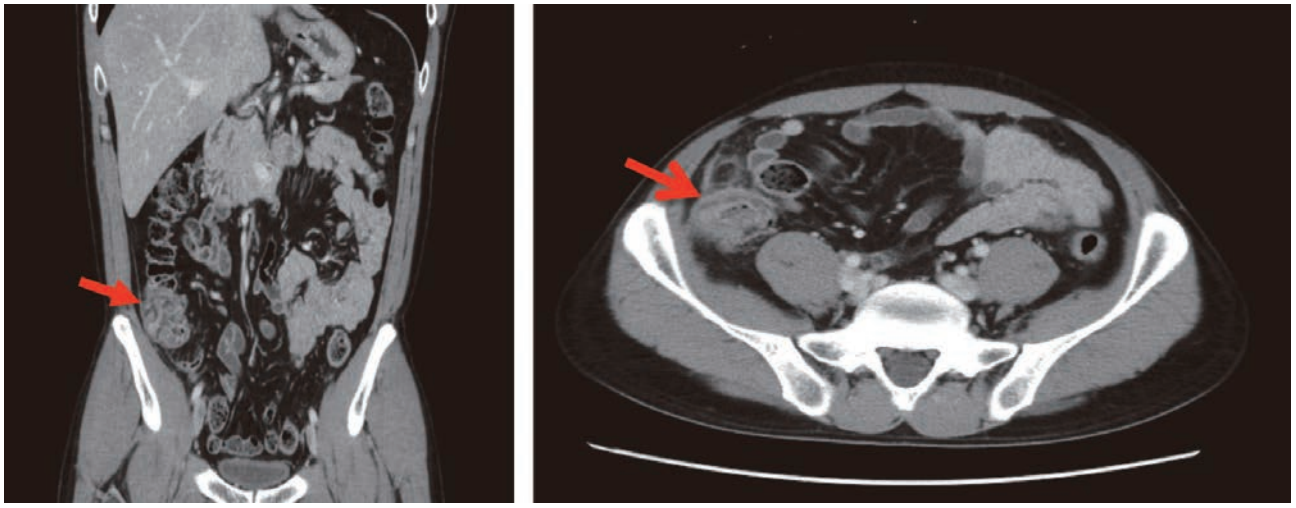

**Fig. 1.** Computed tomograms (coronal and transverse views) show a pericolonic enhanced fat-mass-like lesion (arrows) and stranding at the ileocecum.

## Discussion

Epiploic appendagitis is an ischemic infarction of an epiploic appendage caused by torsion or spontaneous thrombosis of the epiploic appendage central draining vein. Epiploic appendagitis has been reported in 2%–7% of patients who were initially suspected to have acute diverticulitis and in 0.3%–1% of those suspected to have acute appendicitis[1]. It may occur in any segment of the colon. In a surgical case series, 57% of the cases had appendagitis in the rectosigmoid, 26% had in the ileocecum, 9% had in the ascending colon, 6% had in the transverse colon, and 2% had in the descending colon[4]. Radiological examination plays an important role in the differential diagnosis. Abdominal ultrasonography is highly operator-dependent and is suitable for patients with a thin body shape. Generally, epiploic appendagitis presents as a noncompressible hyperechoic oval-shaped mass. Abdominal CT is helpful in diagnosing this disease while excluding other causes of abdominal pain[3]. Epiploic appendagitis is usually considered a benign, self-limiting disease that spontaneously resolves within days to weeks and can be conservatively treated with anti-inflammatory medications[2]. Accurate diagnosis of the disease can help in preventing unnecessary antibiotic therapy or surgery.

## Conflicts of interest

All authors have no conflicts of interest to declare.

## References

1. Schnedl WJ, Krause R, Tafeit E, Tillich M, Lipp RW, Wallner-Liebmann SJ. Insights into epiploic appendagitis. Nature Reviews Gastroenterology and Hepatology 2011;8:45-9.
2. Schnedl WJ, Krause R, Wallner-Liebmann SJ, Tafeit E, Mangge H, Tillich M. Primary epiploic appendagitis and successful outpatient management. Medical science monitor: international medical journal of experimental and clinical research 2012;18:CS48.
3. Horton KM, Corl FM, Fishman EK. CT evaluation of the colon: inflammatory disease. Radiographics 2000;20: 399-418.
4. Macari M, Laks S, Hajdu C, Babb J. Caecal epiploic appendagitis: an unlikely occurrence. Clinical radiology 2008; 63:895-900.

# 闌尾炎的良性模仿者：腸脂垂炎

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**摘要**

腹痛可以包含良性、自限性疾病到需緊急手術的一系列病症。右下腹痛的鑑別診斷包括闌尾炎、結腸炎、憩室炎和腸脂垂炎。我們報告一位開業醫無法排除闌尾炎的個案轉入我院進一步檢查。其理學檢查症狀確實很典型，但血液報告和腹部超音波檢查讓我們想進一步借助電腦斷層掃描。從電腦斷層的冠狀切面和橫斷切面顯示，在迴盲部出現增強性脂肪團塊樣病灶及脂肪組織的發炎，初步診斷為腸脂垂炎。腸脂垂炎通常被認為是一種良性的自限性疾病，可用消炎藥物保守治療，數天至數週內自發消退。腹部電腦斷層掃描除了可以診斷疾病，同時亦可排除其他腹痛原因，也是診斷腸脂垂炎的重要依據且可避免不必要的手術。

**關鍵詞**：腹痛、闌尾炎、腸脂垂炎

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2. References in the text should be placed where relevant. When a reference article is cited, only the primary author is cited; however, if only two authors are present, both should be listed.
3. Citation should show as [numbers] and use Superscript mark.

## Examples of Reference:

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   Yang KTA, Chen HD: A semi-automated method for edge detection in the evaluation of left ventricular function using ECG-gated single-photon emission tomography. Eur J Nucl Med 1994;21:1206-11.

2. Monographs:

   Plum F, Posner JB: Diagnosis of Stupor and Coma. 3rd ed. Philadelphia: Davis, 1980:132-3.

3. Monographs with multiple authors:

   Levinsky NG: Fluid and electrolytes. In: Thorn GW, Adams RD, Braunwald E, Isselbacher K, Petersdprf RG eds. Harrison's Principles of Internal Medicine, 8th ed. New York: Mcgraw-Hill, 1977:364-75.

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4. 本刊對於原稿經徵得著者之同意得伸縮或修改之。如不合本刊宗旨者，得退還之。
5. 凡刊載於本雜誌之著作，若涉及「研究用人體檢體採集」及「人體試驗」等情事，應遵守該注意事項並於文章中註明 IRB 編號〔需含機構名稱〕；病例報告及影像判讀等文章需取得病人知情同意並於內文標註，以落實保障受檢人權益。
6. 論文中如涉及使用脊椎動物進行科學應用計畫者，應檢附該計畫業經所屬機構動物實驗管理小組審議認可之文件，以落實實驗動物之人道管理。

## 貳、寫作原則

1. 原著論文（Original Articles）按下列順序撰寫：摘要、前言、材料與方法、結果、討論與結論、誌謝、參考文獻、附表、圖片說明、圖片（含照片）。每篇字數 3000 字以內，摘要 300 字以內，參考文獻 40 篇以內。
2. 病例報告（Case Reports）按下列順序撰寫：摘要、前言、病例、討論、參考文獻、附表、圖片說明、附圖、照片。凡病患顏面部位之相片必須遮去眼睛部位，表示尊重隱私。診療資料或臨床經過之圖表，原則上均限六個月以內。每篇字數 1500 字以內，摘要 150 字以內，參考文獻 10 篇以內。
3. 綜論（Review Articles）不必按原著論文格式撰寫，但每篇字數 3500 字以內，摘要 300 字以內，參考文獻 60 篇以內。

4. 短論（Brief Communications），臨床上、技術上的精簡論著，每篇字數 750 字以內，摘要 150 字以內，參考文獻 7 篇以內。
5. 影像判讀（Images）、臨床病理討論（Pathology Page）圖例說明每篇字數 500 字以內，摘要 150 字以內，參考文獻 3 篇以內。
6. 編者的話（Editorials），每篇字數 2000 字以內，摘要 150 字以內，參考文獻 7 篇以內。
7. 其他細節，請參閱國際指導委員會（International Steering Committee）發表之生物醫學雜誌稿件統一規格（Uniform Requirements for Manuscripts Submitted to Biomedical Journals，見 The New England Journal of Medicine 336:309-315,1997）。
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| 病例報告 (Case Report) | ≦ 150 | ≦ 1500 | ≦ 10 | ≦ 3 |
| 綜論 (Review Article) | ≦ 300 | ≦ 3500 | ≦ 60 | ≦ 6 |
| 短論 (Brief Communication) | ≦ 150 | ≦ 750 | ≦ 7 | ≦ 1 |
| 影像判讀 (Images)、<br>臨床病理討論 (Pathology Page) | ≦ 150 | ≦ 500 | ≦ 3 | ≦ 2 |
| 編者的話 (Editorial) | ≦ 150 | ≦ 2000 | ≦ 7 | ≦ 1 |

## 參、投稿須知

1. 稿件須符合「生物醫學雜誌投稿之統一規定」[1]，請以電腦隔行 double space 書寫，並編行號及頁碼，中文字型以標楷體，英文字型以 Time New Roman 12 號字大小，稿紙之左右緣爲 2.54 公分，上下緣爲 3.17 公分。
2. 第一頁爲標題頁，須列出中文及英文之論文題目、中英文作者姓名、所屬機構及單位之中英文稱號（分屬不同單位，請以阿拉伯數字標出作者與單位）、聯絡人姓名、電話及中英文通訊錄。
3. 第二、三頁爲中文及英文之摘要及關鍵詞（請提供 3 至 5 個關鍵詞或簡短片語），中英文摘要須完全相同，摘要分段撰寫，依序爲背景及目的（Background and purpose）、方法（Methods）、結果（Results）及討論（Discussion）。
4. 相同貢獻作者請加註說明，如研究主題的設定、參與決定研究設計、進行統計分析、詮釋研究結果、以及各章節撰稿等貢獻。
5. 圖表應專業製作，一張紙僅一個附圖或附表，依引用順序以阿拉伯數字標出排列。附表須有標題及說明且不可以照片形式。圖片或照片電子檔（.jpg）必須清晰、分明。附圖須有簡單說明（Legend），並另頁撰寫。光學或電子顯微鏡照片，請註明擴大倍率或比例。

註：[1] 根據「生物醫學雜誌投稿之統一規定」第五版，刊載於 Annals of Internal Medicine 1997;126(1): 36-47.

## 肆、參考文獻

未經發表之論文或摘要不得列爲參考文獻，但可於本文中說明並註明「未發表」（unpublished observations）。博碩士論文可引用。已被任何雜誌接受刊發但仍未發表之著作，請列出雜誌名稱及

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原著論文、病例報告、綜論、短論、影像判讀、臨床病理討論、編著的話按下列格式撰寫：

A.雜誌及期刊

中文例〔作者姓名：題目。雜誌簡稱 年號；卷數：起訖頁數〕

薛玉梅、陳建仁：皮膚砷癌之流行性病學特徵與危險因子。中華衛誌 1996; 15: 1-26。

英文例〔英文原稿中引用的參考文獻，其雜誌或期刊之簡稱應參照 Index Medicus 型式〕

1. Feely J, Wilkinson GR, Wood AJ. Reduction of liver blood flow and propranonol metabolism by cimetidine. N Engl J Med 1981;304:691-6.
2. Kaplan NM. Coronary heart disease risk factors and antihypertensive drug selection. J cardiovasc Pharmacol 1982; 4(suppl 2): 186-365.（引用雜誌附冊時）
3. Tada A, Hisada K, Suzuki T, Kadoya S. Volume measurement of intracranial hematoma by computedtomography. Neurol surg (Tokyo) 1981; 9: 251-6.〔In Japanese: English abstract〕（引用文獻之作者之本文爲非英文，但有英文摘要）。
4. Bhasin S, Storer TW, Berman N, Callegari C, Clecenger B, Phillips J, et al. The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. N Engl J Med 1996; 335: 1-7.（作者超過 6 位時，只須列出前 6 位，其它以「等」(et al) 代替）

＊期刊若有「數位物件識別碼 (digital object identifier, DOI)」，則於文獻末。

＊＊內文文獻標示以中括號、數字、上標呈現。

B.單行本：

中文例 [ 作者姓名：書名，版數（卷數）。發行地；出版公司，年代：引用部份頁數 ]。

楊志良：生物統計學新論，一版。台北；巨流圖書公司，1984：33-8.

英文例 [ 英文單行本的書名，除介系詞及連接詞外，第一字母需大寫 ]

(1) Plum F, Posner JB. Diagnosis of Stupor and Coma. 3rd ed., Philadelphia: Davis, 1980:132-3.

C.多重作者之單行本：

中文例 [ 有關文章作者姓名：題目。編輯者姓名：書名。版數（卷數）。發行地：出版公司，年代；引用部份頁數 ]。

蔣欣欣：護理與健康。顧乃平：護理專業導論。一版。台北：匯華出版公司，1991：83-121。

英文例 Levinsky NG: Fluid and electrolytes. In: Thorn GW, Adams RD, Braunwald E, lsselbacher K, Petersdprf RG eds. Harrison’s Principles of Internal Medicine. 8th ed. New York: Mcgraw-Hill, 1977;364-75.

D.參考文獻引用時，若兩名以下作者請列出姓氏。兩名以上則列出第一名之姓氏，其他以「等」(et al) 代替，並以阿拉伯數字方括弧表示於引用之後。

例：One of the first well documented reports of ECH poisoning with fatality in young children was reported by Miller et al. in 1970[2].

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第十四卷　第一期　　民國 109 年 01-06 月

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