Presentation, management, and clinical outcomes of von Hippel–Lindau syndrome

Athena YH Lee #, David KW Leung #, CH Leung, Kelly HY Tsang, Alvina Yiu, Chloe YK Ho, Jason MK Ho, CF Ng *

A B S T R A C T

Introduction: von Hippel–Lindau (VHL) syndrome is a rare autosomal dominant genetic disorder that typically leads to the development of multiple tumours in various organs. This study describes the lifetime journey of VHL patients in terms of their hospitalisation, surgery, and functional impairment, and aims to examine the local presentation patterns, treatment courses, and clinical outcomes associated with the condition.

Methods: Thirty-two patients with VHL syndrome (mean age=27.9 ± 12.6 years) were retrospectively identified from five local public hospitals managed between 1 January 1993 and 30 September 2024, with a follow-up duration of 18.0 ± 10.8 years. Patient demographics, disease presentation, length of hospital stay, and treatments received were recorded and analysed.

Results: Over a total of 575.9 person-years, 17 patients (53.1%) developed renal tumours and 10 (31.3%) underwent partial or radical nephrectomy. Twenty-four patients (75.0%) underwent central nervous system (CNS) surgery for haemangioma. Eleven patients (34.4%) had phaeochromocytoma, and eight (25.0%) underwent adrenalectomy. Nine patients (28.1%) had retinal haemangioma. During the study period, 368 emergency department visits, 1209 inpatient admissions, 192 intensive care unit days, and 5635 hospitalisation days were recorded. In total, 116 surgeries were performed involving the kidneys (n=17), pancreas (n=6), adrenal glands (n=10), and CNS (n=83). Six patients required dialysis; 4373 dialysis sessions were performed. Fifteen patients died. Among the nine who died of VHL syndrome, eight had developed cerebral haemangioblastoma, three had phaeochromocytoma, and four had renal tumours.

Conclusion: Patients with VHL syndrome often experience early-onset and recurrent diseases affecting multiple organ systems, leading to substantial morbidity and mortality. A multidisciplinary approach, along with the introduction of novel treatments, may improve disease control and clinical outcomes.

Hong Kong Med J 2025;31:Epub
https://doi.org/10.12809/hkmj2412496

[1,2] **AYH Lee #,** MB, ChB
[1] **DKW Leung #,** MB, ChB, FRCS
[1] **CH Leung,** MSc
[1] **KHY Tsang**
[1] **A Yiu**
[1] **CYK Ho**
[3] **JMK Ho,** FHKAM (Surgery), FRCSEd (Neurosurgery)
[1,4] **CF Ng *,** MD, FHKAM (Surgery)

1 *Division of Urology, Department of Surgery, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, China*
2 *Cardio-Oncology Research Unit, Cardiovascular Analytics Group, Hong Kong, China–UK Collaboration, Hong Kong SAR, China*
3 *Division of Neurosurgery, Department of Surgery, Tuen Mun Hospital, Hong Kong SAR, China*
4 *SH Ho Urology Centre, The Chinese University of Hong Kong, Hong Kong SAR, China*

* Corresponding author: ngcf@surgery.cuhk.edu.hk

# Equal contribution

This article was published on 28 Aug 2025 at www.hkmj.org.

This version may differ from the print version.

Introduction

von Hippel–Lindau (VHL) syndrome is a rare autosomal dominant genetic disorder characterised by benign and malignant tumours, including clear cell renal cell carcinoma (RCC), adrenal phaeochromocytoma, pancreatic neuroendocrine tumour, and retinal and central nervous system haemangioblastoma (CNS-Hb).[1] According to a 2017 study, its incidence is estimated to be one in 27 300 live births.[2] The multi-system manifestations of VHL typically require repeated admissions, multidisciplinary care, and long-term follow-up, placing a substantial socio-economic burden on healthcare systems. Recently, belzutifan, a second-generation hypoxia-inducible factor (HIF)-2α inhibitor, has shown promising results in a phase 2 study involving Western populations.[3] However, its applications and benefits for Asian patients remain poorly understood.

This multi-centre retrospective cohort study investigated VHL patients to examine local presentation patterns, treatment courses, and clinical and functional outcomes. The findings aim to provide insight into the presentation and management of VHL in Asian patients and, more importantly, to inform resource allocation.

希林氏病的臨床表現、治療及結果

李昕曉、梁家偉、梁志豪、曾晞榣、姚蔚、何悅喬、何文傑、吳志輝

引言：希佩爾—林道病（簡稱「希林氏病」）為罕見的常染色體顯性遺傳病，常累及多個器官並導致多個腫瘤。本研究討論希林氏病患者的住院情況、手術及面對的功能障礙，以探討此病在香港的臨床表現、治療策略及結果。

方法：本回顧性隊列研究納入1993年1月1日至2024年9月30日期間五所本地公立醫院共32例希林氏病患者（平均年齡：27.9 ± 12.6歲），隨訪平均18.0 ± 10.8年。我們記錄患者的人口學資料、臨床表現、住院情況及治療細節，並進行分析。

結果：累計575.9人年期間， 17例（53.1%）發生腎腫瘤，10例（31.3%）進行部分或根治性腎切除。 24例（75.0%）接受中樞神經系統出血管瘤手術。 11例（34.4%）發生嗜鉻細胞瘤，8例（25.0%）進行腎上腺切除。 9例（28.1%）出現視網膜血管瘤。研究期內共錄得368次急診、1209次住院、192日進入深切治療部及5635住院日數，並進行了116次手術（腎臟17例、胰臟6例、腎上腺10例及腦神經83例）。6例進展至終末期腎衰，需4373次透析。15例死亡，其中9例直接因希林氏病相關腫瘤死亡，包括8例腦部血管瘤、3例嗜鉻瘤及4例腎腫瘤。

結論：希林氏病患者多於青壯年發病，終身多個器官反覆累及，罹患率高且需重複入院與手術，致顯著病殘及死亡率。跨專科團隊合作及引入新療法或能改善疾病控制及臨床預後。

Methods

This study identified patients with VHL syndrome from five local public hospitals—Prince of Wales Hospital, Alice Ho Miu Ling Nethersole Hospital, North District Hospital, Tuen Mun Hospital, and Pok Oi Hospital—managed between 1 January 1993 and 31 December 2023, with follow-up data collected up to 30 September 2024. The Clinical Data Analysis and Reporting System, a local online platform recording clinical data from all public hospitals in Hong Kong, was used for patient identification. Patient demographics and clinical information regarding disease course and treatment outcomes were retrieved from the Clinical Management System, an online database storing electronic patient records for public hospitals in Hong Kong. The following data were collected for each included patient: demographic factors (age, sex, body mass index, performance status, and co-morbidities); disease characteristics (initial presentation, time of diagnosis, lag time to diagnosis, number and size of renal and extrarenal lesions, and response or recurrence patterns); treatment details (number and frequency of surgical or ablative interventions, hospital length of stay, intensive care unit [ICU] admissions, associated costs, and resultant complications and disabilities); and health outcomes (health-adjusted life years, quality of life estimates, and economic parameters related to hospitalisations, outpatient services, and medical and surgical care).

The study endpoints included rates of VHL-spectrum disease (CNS-Hb, choroid plexus papilloma, retinal haemangioma, endolymphatic sac tumour, RCC, renal cyst, renal angiomyolipoma, phaeochromocytoma, paraganglioma, pancreatic cyst, pancreatic neuroendocrine tumour, pancreatic adenocarcinoma, and liver cyst), emergency department (ED) attendance, admissions, surgeries, and functional outcomes (independent in activities of daily living, wheelchair-bound, or bedbound). According to the local public healthcare system in Hong Kong, the mean cost per ambulatory

New knowledge added by this study

- This study examined the disease journey of von Hippel–Lindau (VHL) patients in Hong Kong, providing insights into disease presentation patterns, the number of treatments and procedures required, treatment outcomes, and morbidity data.
- The study analysed the substantial healthcare costs incurred in managing VHL syndrome, highlighting the economic burden on healthcare systems due to repeated admissions, multidisciplinary care, long-term follow-up, surgeries, and other interventions, notably VHL syndrome–related renal cell carcinoma treatment and kidney dialysis.
- The study emphasises the potential benefits of novel treatments such as belzutifan in managing VHL syndrome among local patients, with promising results that could transform the treatment landscape for this rare genetic disorder, thus reducing disease burden and improving the quality of life of patients.

Implications for clinical practice or policy

- Given the cross-specialty manifestations of VHL syndrome, the study underscores the importance of a multidisciplinary approach in its management, thereby demonstrating the value of collaborative care in improving clinical outcomes.
- The study's findings may prompt policymakers to re-evaluate existing healthcare policies related to rare genetic disorders such as VHL syndrome, particularly in expanding access to innovative treatments by adding belzutifan to the Hospital Authority Drug Formulary.
- The study highlights the need for dedicated funding to establish local VHL syndrome registries, thereby supporting further clinical trials and large-scale research. The creation of patient support programmes may also contribute to a healthcare environment that addresses the unique challenges faced by VHL patients and fosters a holistic approach to care.

emergency attendance and per hospitalisation day was HK$750 (US$96.2) and HK$3440 (US$441), respectively.[4] The total cost of hospital attendance was defined as the sum of ED and inpatient attendance costs. Descriptive statistics, including mean, standard deviation, median, and interquartile range, were used to summarise the data.

Results

Demographics

Initially, 87 patients were identified. After manual review of the medical records, 52 were excluded due to incorrect diagnoses (three non-VHL, two Cowden syndrome, 17 Peutz–Jeghers syndrome, 28 Sturge–Weber syndrome, one hamartoma, and one duplicate record). Two additional patients were excluded due to incomplete data, and one further duplicate was removed. The incorrect diagnoses were likely due to similarities and overlaps in the diagnostic codes used for these conditions.

In total, 32 patients were deemed eligible for inclusion, of whom 21 (65.6%) were male. The mean age at first presentation was 27.9 ± 12.6 years and the mean follow-up duration was 18.0 ± 10.8 years. All patients developed tumours. Seventeen patients (53.1%) had renal tumours, and 10 (31.3%) underwent partial or radical nephrectomy. Twenty-four patients (75.0%) underwent CNS surgery for haemangioma. Eleven patients (34.4%) had phaeochromocytoma, and eight (25.0%) underwent adrenalectomy. Retinal haemangioma occurred in nine patients (28.1%). Demographic and disease prevalence data within the VHL syndrome spectrum are summarised in Table 1.

TABLE 1. Demographic and prevalence data of lesions in von Hippel–Lindau syndrome (n=32)*

	No. of patients (n=32)	Mean age, y	Male (n=21)
Cerebellar haemangioblastoma	25 (78.1%)	28.6 ± 11.6	17 (68.0%)
Cerebral haemangioblastoma	6 (18.8%)	23.8 ± 19.0	3 (50.0%)
Brainstem haemangioblastoma	9 (28.1%)	22.6 ± 8.1	5 (55.6%)
Spinal haemangioblastoma	13 (40.6%)	24.4 ± 7.8	8 (61.5%)
Retinal haemangioblastoma	9 (28.1%)	23.2 ± 7.1	5 (55.6%)
Renal cell carcinoma	17 (53.1%)	27.4 ± 11.3	13 (76.5%)
Cystic renal lesions	4 (12.5%)	27.5 ± 15.0	1 (25.0%)
Phaeochromocytoma	11 (34.4%)	29.5 ± 13.9	9 (81.8%)
Pancreatic tumour	5 (15.6%)	38.6 ± 13.3	2 (40.0%)
Cystic pancreatic lesion	14 (43.8%)	25.4 ± 7.9	9 (64.3%)
Epididymal cystadenoma	2 (6.3%)	22.5 ± 2.1	2 (100%)

* Data are shown as No. (%), unless otherwise specified

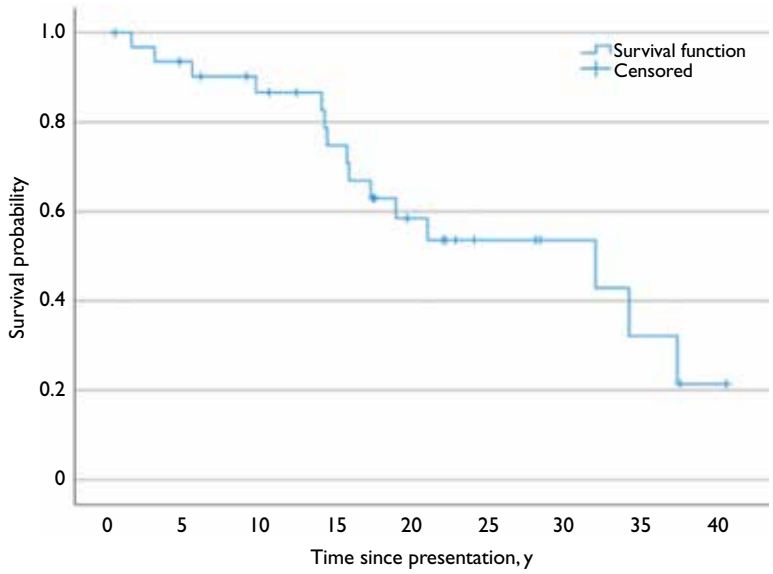

FIG 1. Kaplan-Meier curve demonstrating all-cause mortality over time since presentation

von Hippel–Lindau syndrome–related mortality

Over a total of 575.9 person-years, 15 patients died. Causes of death were VHL syndrome in nine (60%), pneumonia in three (20%), metastatic lung cancer in one (6.7%), sepsis in one (6.7%), and congestive heart failure in one (6.7%). Among those who died of VHL syndrome–related tumours, eight had CNS haemangioma, three had phaeochromocytoma, and four had renal tumours. Even in patients whose causes of death were not directly related to VHL, strong associations were observed with the sequelae of VHL-spectrum diseases and treatments. All three patients who died of chest infections were wheelchair-bound after neurosurgical treatment of CNS-Hb; one of them required long-term steroids following bilateral adrenalectomy. The patient who died of sepsis had paraplegia after spinal surgery and end-stage renal failure (ESRF) requiring peritoneal dialysis. The source of sepsis was likely peritoneal dialysis–related peritonitis. All-cause mortality and VHL syndrome–related mortality over time since presentation are shown in Figures 1 and 2, respectively.

von Hippel–Lindau syndrome–related morbidity

Nine patients (28.1%) developed chronic kidney disease, of whom six progressed to ESRF (estimated glomerular filtration rate <15 mL/min/1.73 m^2). All six (18.8%) required renal replacement therapy—three underwent haemodialysis, one received peritoneal dialysis, and two began peritoneal dialysis before switching to haemodialysis.

By the last follow-up, 15 patients had died, whereas 17 remained independent in their activities of daily living. None of the 17 surviving patients were wheelchair-bound or bedbound.

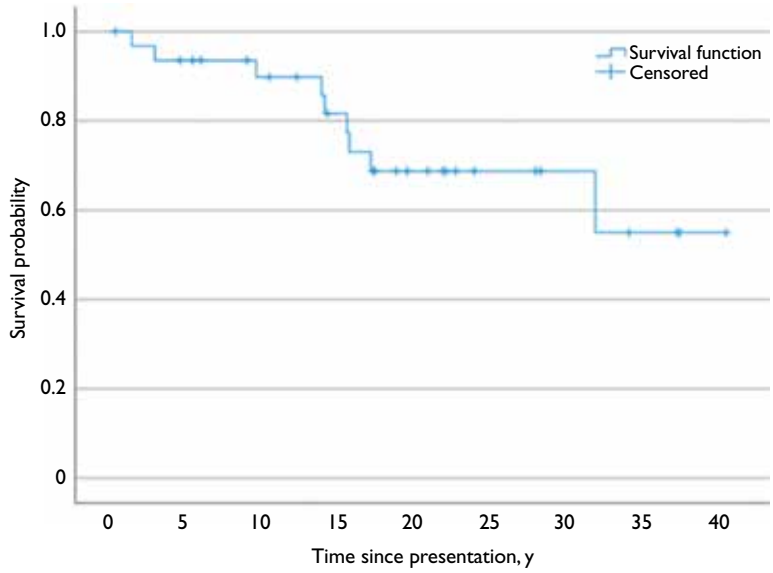

FIG 2. Kaplan-Meier curve demonstrating von Hippel–Lindau syndrome–related mortality over time since presentation

Belzutifan usage

Belzutifan was prescribed to three patients. The mean age at presentation was 26.3 years, with the youngest at 17 years and the oldest at 35 years. The average duration from initial presentation to the initiation of belzutifan therapy was 22.9 years. All three patients had CNS haemangioma, with one experiencing multiple recurrences. One patient also had phaeochromocytoma, and another had a renal tumour. Patient characteristics are summarised in Table 2. The duration of belzutifan therapy ranged from 1 to 7.6 months. Of the three patients, two required dose reductions due to adverse events—specifically, anaemia and deranged liver function.

von Hippel–Lindau syndrome–attributable healthcare costs

During the study period, a total of 368 ED visits, 1209 inpatient admissions, and 5635 days of hospitalisation were recorded. In total, 21 patients had ICU stays, amounting to 192 ICU days. These utilisation patterns translated to an annualised per-patient ED visit–related cost of HK$8625 and an annualised per-patient inpatient admission–related cost of HK$129 968.[4] Six patients required dialysis, and 4373 dialysis sessions were performed during the study period, resulting in a total cost of HK$28.8 million (HK$6580 per dialysis session).[4] For the belzutifan patient cohort, no ED visits or inpatient admissions were recorded after initiation of belzutifan therapy, likely due to the short follow-up duration after the prescription of this drug newly approved by the United States Food and Drug Administration. Consequently, we could not directly compare the healthcare cost burden between belzutifan users and non-users.

TABLE 2. Characteristics of belzutifan users

	Patient 1	Patient 2	Patient 3
Age at diagnosis, y	17	27	35
Description of VHL syndrome	Multiple cerebellar and spinal haemangiomas, 2 unilateral phaeochromocytomas (maximum diameter 3.9 cm, 2.2 cm), retinal haemangioblastoma	4 CNS haemangioma	2 CNS haemangiomas with spinal cord haemorrhage, retinal haemangioma, bilateral RCC >1 cm (Fuhrman grade 2), 2 bilateral phaeochromocytomas (maximum diameter 2.7 cm, 2.0 cm), pancreatic cyst
Treatment received	Phenoxybenzamine, adrenalectomy, laser surgery for retinal haemangioblastoma	Surgical excision of cerebral haemangioblastoma	Phenoxybenzamine, resection of RCC, laminectomy of T7 to relieve cord compression
Baseline eGFR, mL/min/1.73 m^2	>90	>90	84
Baseline haemangioblastoma, g/L	12.4	51	46
Baseline ALT, U/L	16	49	72
Age at first prescription of belzutifan, y	27	49	72
Belzutifan regimen	PO 120 mg daily	PO 120 mg daily	PO 120 mg daily
Duration of belzutifan, d	36	169	229
Reason for stopping belzutifan	Withheld since 10 April 2024 due to liver derangement; resumed at 40 mg daily since 23 July 2024		Withheld since 17 February 2024 due to anaemia; resumed at 80 mg daily since 7 April 2024

Abbreviations: ALT = alanine transaminase; CNS = central nervous system; eGFR = estimated glomerular filtration rate; PO = per os; RCC = renal cell carcinoma; VHL syndrome = von Hippel–Lindau syndrome

The pattern of tumour-related surgeries and accident and emergency admissions in VHL patients was highly variable; some patients experienced periods of intense activity followed by quieter phases, suggesting non-linear disease progression. Tumour-related operations and deaths since diagnosis are shown in Figure 3, whereas accident and emergency admissions are presented in Figure 4, highlighting individual disease burden. Monitoring and management should be tailored to address these fluctuating needs.

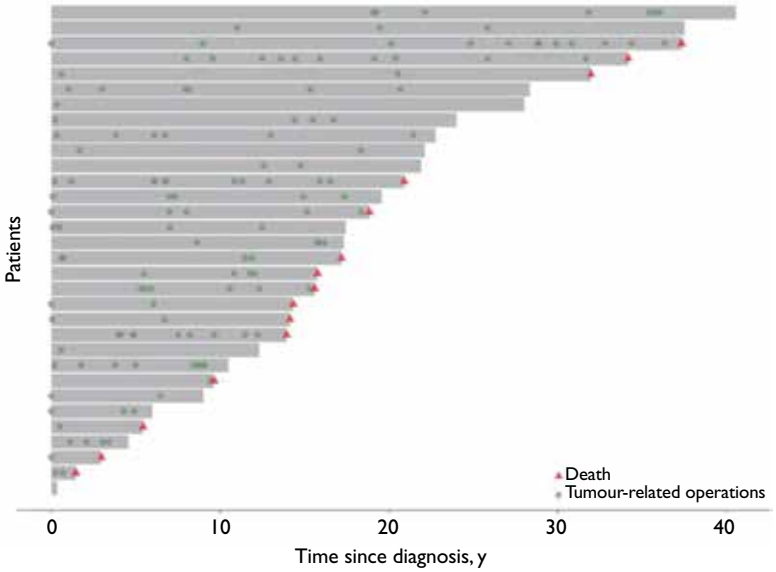

FIG 3. Event plot showing tumour-related operations for individual patients with von Hippel–Lindau syndrome since diagnosis

Discussion

From this review, we observed that VHL-spectrum diseases emerged at a young age and recurred throughout patients' lives, leading to considerable morbidity and mortality. This finding is consistent with existing literature. There is a pressing need to improve the current care of VHL syndrome in Hong Kong to enhance patients' life trajectories and quality of life.

Pathophysiology

The VHL protein normally functions as an E3 ubiquitin ligase that facilitates ubiquitination of the alpha subunit of HIF, leading to its proteolysis.[5] In VHL patients, genetic alterations reduce VHL protein activity, thereby disinhibiting HIF-mediated transcription. Consequently, the overexpression of vascular endothelial growth factor, cyclin D1, glucose transporter 1, and erythropoietin promotes neoplastic growth.[5,6] The resultant tissue overgrowth leads to early-onset, recurrent, and multi-system benign and malignant neoplasms.[1]

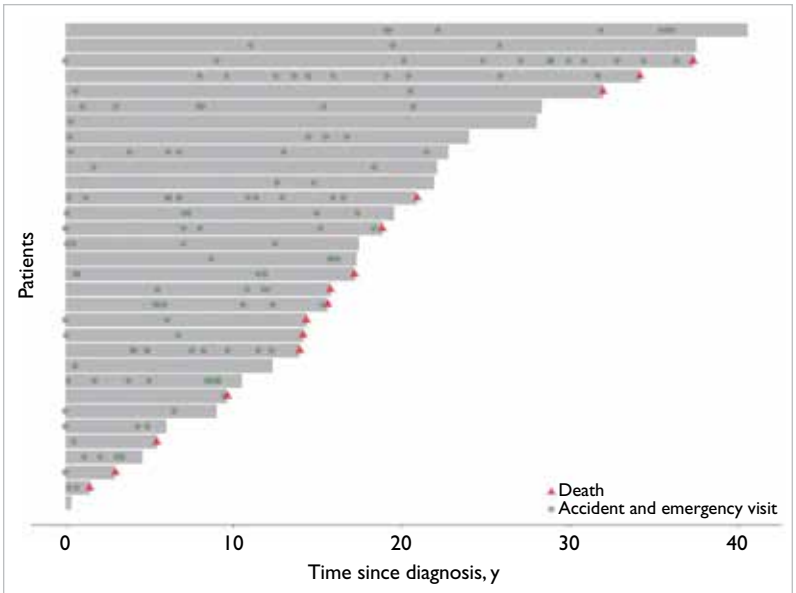

FIG 4. Event plot showing accident and emergency visits for individual patients with von Hippel–Lindau syndrome since diagnosis

Functional impairment in patients

Patients with VHL syndrome experience a lifelong journey with the disease, characterised by substantial morbidity and mortality.

An Italian study of 128 VHL patients showed that the natural history varied according to disease manifestations.[7] For RCC, the median age at first presentation was 31 years,[7] similar to our cohort, which had a median age of 27.4 years. The first progression typically occurred after 7 to 8 years; a second progression followed 1 to 2 years later. von Hippel–Lindau syndrome–related cerebellar haemangioblastomas generally developed at a median age of 30 years and progressed relatively consistently every 3.5 years. The cumulative incidences of disability were 26.5% for CNS involvement, 16.4% for visual disturbance, 12.5% for hearing loss, 10.9% for adrenergic dysfunction, 4.6% for pancreatic morbidity, and 1.5% for renal impairment.[7] One patient died of metastatic RCC (0.8%), another entered a vegetative state after a CNS procedure (0.8%), and five died of postoperative complications (3.9%).[7] Overall, the average Karnofsky performance status was 80% at the end of follow-up.[7]

In contrast, in our cohort, the nine patients who died of VHL syndrome–related tumours succumbed to the disease itself, rather than postoperative complications. This highlights the substantial impact of such tumours on patient mortality, underscoring the need for vigilant monitoring and comprehensive management strategies to improve outcomes.

Surgery and radiosurgery for von Hippel–Lindau syndrome–related tumours

Central nervous system haemangioblastomas represent a major and disabling manifestation of VHL syndrome. A prospective natural history study focusing on stereotactic radiosurgery for CNS-Hb in VHL patients reported outcomes from 20 individuals treated for 44 lesions.[8] Most lesions were located in the cerebellum (n=39), and five in the brainstem. The mean age at treatment was 37.5 ± 12.0 years.[8] All patients were alive at a mean follow-up interval of 8.5 years. Tumours (mean volume: 0.5 ± 0.7 cm^3) were treated with a mean prescription dose of 18.9 Gy (range, 12-24) to the tumour margin, resulting in local control rates of 91%, 83%, 61%, and 51% at 2, 5, 10, and 15 years, respectively.[8] Despite the favourable early response to stereotactic radiosurgery, VHL syndrome–related haemangioblastomas tend to progress during long-term follow-up.

With respect to the treatment of VHL syndrome–related RCC (ie, VHL-RCC), the rule of thumb is to strike a balance between oncological control and renal function preservation to avoid or delay ESRF. Common strategies include nephron-sparing surgery and ablative therapies. A retrospective review of VHL-RCC by Duffey et al[9] suggested that 3 cm was a reasonable cutoff, beyond which metastasis may occur earlier; therefore, nephron-sparing surgery would be indicated. In a cohort of 54 VHL patients who underwent nephron-sparing surgery, nephrectomy, or thermal ablation for RCC,[10] 97 kidney treatments were performed. Nephron-sparing surgery was adopted in 96% of first and 67% of second interventions. The probabilities of a second surgery were 21% at 5 years and 42% at 10 years. The overall survival and cancer-specific survival rates were 82.5% and 90.5%, respectively, at the 10-year follow-up. No metastasis was observed for RCCs with a maximum diameter smaller than 4 cm.[10]

Systemic therapies for von Hippel–Lindau syndrome

With greater understanding of the genetics and pathophysiology of VHL syndrome, researchers have been actively developing effective systemic therapies. The advent of belzutifan has revolutionised systemic therapy for VHL syndrome. This HIF-2α inhibitor demonstrated satisfactory objective response rates for RCC (49%), pancreatic lesions (77%), and CNS-Hb (30%), along with an acceptable safety profile—anaemia and fatigue were the most common side-effects.[2] On 13 August 2021, belzutifan was approved by the United States Food and Drug Administration for use in adult VHL patients who need treatment for associated RCC, CNS-Hb, or pancreatic neuroendocrine tumours not requiring immediate surgery.[11]

The LITESPARK-004 (MK-6482-004) phase 2 study further supports the clinical benefits of belzutifan in patients with VHL syndrome.[12] With over 2 years of follow-up data, the study demonstrated sustained efficacy in reducing tumour burden across multiple organs.[12] Objective response rates were consistent with earlier findings: 49% for RCC, 77% for pancreatic lesions, and 30% for CNS-Hb.[12] Notably, the responses were durable, with many patients experiencing prolonged disease control without surgical intervention. The safety profile remained acceptable; anaemia and fatigue were the most common adverse events.[12] These findings reinforce belzutifan's potential as a transformative systemic therapy, offering a non-invasive alternative to repeated surgeries and improving patient quality of life. Continued research and access to such therapies, particularly in Asian populations, are essential.

Socio-economic impact

von Hippel–Lindau syndrome–related RCC is a notable malignancy within the disease spectrum. In our cohort, the annualised per-patient ED visit–related cost for VHL-RCC patients was HK$2070, and the annualised inpatient admission cost was HK$23 965. In comparison, an American study reported that VHL-RCC patients (n=160) incurred US$36 450 more annually than the control group (n=800), including US$21 123 more for RCC management.[13] Among complications, ESRF was the most costly, requiring US$65 338 over 6 months post-nephrectomy.[13] Similarly, our cohort incurred approximately HK$28.8 million during the study period for repeated dialysis in six patients with ESRF.

Another claims-based study showed that CNS-Hb and pancreatic neuroendocrine tumours due to VHL syndrome similarly increased annual healthcare costs by US$49 645 compared with the control group.[14] These findings underscore the importance of novel therapies that can alleviate both clinical and economic burdens.

In our local hospital system, the estimated annualised per-patient ED visit–related cost was HK$8625, and the annualised per-patient inpatient admission–related cost was HK$129 968. Additionally, dialysis for the six patients with ESRF required an additional HK$28.8 million. We did not include calculations for the surgical treatment of all tumours and related management due to the practical difficulties of cost estimation within the public hospital system. Nevertheless, we expect these costs to be substantial. Although the current drug cost for belzutifan is high (estimated at around CAD$17 920 per 28 days[15]), the medical expenses associated with the natural course of VHL syndrome are also considerable. Evidence regarding the cost-effectiveness of medical therapies, including

belzutifan, is still emerging; it is important to consider the composite outcomes of mortality, healthcare-related costs, irreversible morbidities, and social dysfunction. Further economic studies are warranted to quantify the potential cost savings associated with this novel treatment.

Future directions to optimise care

von Hippel–Lindau syndrome greatly affects patients' clinical outcomes and quality of life. Frequent hospitalisations, repeated medical and surgical therapies, and recurrent tumours contribute to cumulative morbidities and mortality. The need for multidisciplinary care, ongoing surveillance for recurrence, and genetic counselling further add to the disease burden. Thus, VHL patients require improved access to novel medications.

As our results suggest, the management of VHL syndrome should be holistic. Patients with multiple VHL syndrome–related conditions should be discussed at multidisciplinary meetings to facilitate treatment prioritisation. A sensible approach would be to address the most life-threatening and symptomatic disease first.

The initial local experience of using belzutifan was promising, with manageable toxicity profiles. With the advent of its coverage by the Samaritan Fund for eligible patients,[16] the role of belzutifan is expected to rise in local VHL management. While its safety and efficacy have been demonstrated in Western populations, its benefits for Asian patients remain to be fully defined. This retrospective study showed that one belzutifan user in the cohort developed fewer new-onset VHL syndrome–related conditions than non-users. However, the small sample size (three belzutifan users among 32 VHL patients) limits generalisability. Nevertheless, the encouraging initial results of belzutifan in controlling tumour growth in the kidneys, CNS, retina, and pancreas support the need for coordinated efforts in resource allocation and the establishment of subsidy schemes.[3] With increased use of the medication, overall healthcare costs are expected to decline due to reductions in surgeries and hospitalisations. Given the rarity of VHL syndrome, future clinical trials should ideally be multi-national and multi-centre. Local registries should also be established to facilitate long-term follow-up, clinical trial enrolment, and policy development for this patient group. Additionally, patient support groups, social support initiatives, and increased attention to psychological well-being would help provide holistic care for VHL patients. Addressing the financial and disease-related burdens faced by this vulnerable population is essential to improving their quality of life and long-term outcomes.

Limitations

Our cohort did not include all VHL patients in Hong Kong. Assuming an incidence of one in 27 300[17] and a total population of 7 million in Hong Kong,[18] the estimated number of VHL patients in this locality is approximately 250, excluding those who did not present to the participating hospitals or whose follow-up data were unavailable. Nevertheless, our study offers the first insight into the clinical journey of local VHL patients.

Conclusion

Overall, VHL patients experience early-onset and recurrent multi-systemic illness, with a substantial risk of irreversible morbidity and mortality. Multidisciplinary care and the promotion of effective treatments such as belzutifan may improve the management of this rare but important disease.

Author contributions

Concept or design: AYH Lee, DKW Leung.
Acquisition of data: CH Leung, KHY Tsang, A Yiu, CYK Ho.
Analysis or interpretation of data: AYH Lee, DKW Leung, CH Leung.
Drafting of the manuscript: AYH Lee, DKW Leung.
Critical revision of the manuscript for important intellectual content: JMK Ho, CF Ng.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

As an editor of the journal, CF Ng was not involved in the peer review process. Other authors have disclosed no conflicts of interest.

Acknowledgement

The authors thank the following contributors for their expertise and support in the research: Dr Jeffrey SK Chan and Dr Esther TW Cheng of the Cardio-Oncology Research Unit, Cardiovascular Analytics Group, Hong Kong, China–UK Collaboration; and Dr Brian WH Siu, Dr Ivan CH Ko, Dr Chris HM Wong, and Dr Alex Liu of the Division of Urology, Department of Surgery, Faculty of Medicine, The Chinese University of Hong Kong.

Funding/support

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Ethics approval

This research was approved by the Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee, Hong Kong (Ref No.: 2024.435). A waiver of patient consent was granted by the Committee due to the retrospective nature of the research.

References

1. Couch V, Lindor NM, Karnes PS, Michels VV. von Hippel–Lindau disease. Mayo Clin Proc 2000;75:265-72.
2. Binderup ML, Galanakis M, Budtz-Jørgensen E, Kosteljanetz M, Luise Bisgaard M. Prevalence, birth incidence, and penetrance of von Hippel–Lindau disease (vHL) in Denmark. Eur J Hum Genet 2017;25:301-7.
3. Jonasch E, Donskov F, Iliopoulos O, et al. Belzutifan for renal cell carcinoma in von Hippel–Lindau disease. N Engl J Med 2021;385:2036-46.
4. Hospital Authority, Hong Kong. Hospital Authority Annual Report 2007-2008. Available from: https://www.ha.org.hk/ho/corpcomm/Annual%20Report/2007-08.pdf. Accessed 10 Oct 2024.
5. Choueiri TK, Kaelin WG Jr. Targeting the HIF2-VEGF axis in renal cell carcinoma. Nat Med 2020;26:1519-30.
6. Haase VH. The VHL tumor suppressor: master regulator of HIF. Curr Pharm Des 2009;15:3895-903.
7. Feletti A, Anglani M, Scarpa B, et al. von Hippel–Lindau disease: an evaluation of natural history and functional disability. Neuro Oncol 2016;18:1011-20.
8. Asthagiri AR, Mehta GU, Zach L, et al. Prospective evaluation of radiosurgery for hemangioblastomas in von Hippel–Lindau disease. Neuro Oncol 2010;12:80-6.
9. Duffey BG, Choyke PL, Glenn G, et al. The relationship between renal tumor size and metastases in patients with von Hippel–Lindau disease. J Urol 2004;172:63-5.
10. Jilg CA, Neumann HP, Gläsker S, et al. Nephron sparing surgery in von Hippel–Lindau associated renal cell carcinoma; clinicopathological long-term follow-up. Fam Cancer 2012;11:387-94.
11. United States Food and Drug Administration. FDA approves belzutifan for cancers associated with von Hippel–Lindau disease. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-belzutifan-cancers-associated-von-hippel-lindau-disease. Accessed 6 Aug 2025.
12. Jonasch E, Iliopoulos O, Kimryn Rathmell W, et al. LITESPARK-004 (MK-6482-004) phase 2 study of belzutifan, an oral hypoxia-inducible factor 2α inhibitor (HIF-2α), for von Hippel–Lindau (VHL) disease: update with more than two years of follow-up data. J Clin Oncol 2022;40 (Suppl):4546.
13. Jonasch E, Song Y, Freimark J, et al. Epidemiology and economic burden of von Hippel–Lindau disease–associated renal cell carcinoma in the United States. Clin Genitourin Cancer 2023;21:238-47.
14. Jonasch E, Song Y, Freimark J, et al. Epidemiology and economic burden of von Hippel–Lindau disease–associated central nervous system hemangioblastomas and pancreatic neuroendocrine tumors in the United States. Orphanet J Rare Dis 2024;19:73.
15. Belzutifan (Welireg): CADTH Reimbursement Review: Therapeutic area: von Hippel–Lindau disease–associated tumours [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2023 Nov. Pharmacoeconomic Review. Available from: https://www.ncbi.nlm.nih.gov/books/NBK599999/. Accessed 10 Oct 2024.
16. Samaritan Fund. Items supported by the Samaritan Fund. Available from: https://www.ha.org.hk/haho/ho/sf/SF_Items_en.pdf. Accessed 18 Aug 2025.
17. Rare Disease Hong Kong. von Hippel–Lindau Disease. About Rare Diseases Rare Disease Wiki. Available from: https://rdhk.org/post/data?mid=15&id=13471&lang=en. Accessed 10 Oct 2024.
18. Census and Statistics Department, Hong Kong SAR Government. Year-end Population for 2023 [20 Feb 2024]. Available from: https://www.censtatd.gov.hk/en/press_release_detail.html?id=5386. Accessed 10 Oct 2024.

