INPLASY

The prevalence, disease characteristics, and diagnosis of Von Hippel-Lindau (VHL) syndrome in China: a scoping review and meta-analysis

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ADMINISTRATIVE INFORMATION

Support - V&I, MSD China.

Review Stage at time of this submission - The review has not yet started.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 15 June 2026 and was last updated on 15 June 2026.

INTRODUCTION

Review question / Objective To systematically review and analysis the prevalence of VHL syndrome in China;
To systematically review and analysis the disease characteristics and diagnosis of VHL syndrome in China.

Background Von Hippel-Lindau (VHL) syndrome is a rare autosomal dominant hereditary disease triggered by germline mutations of the VHL tumour suppressor gene located on the short arm of chromosome 3. Functional deficiency of VHL protein blocks ubiquitination and degradation of HIF-2α. Accumulated HIF-2α upregulates a series of oncogenic targets such as VEGF, MET, mTOR and EGFR, which jointly promote angiogenesis, cell proliferation, EMT, invasive migration, anaerobic glycolysis, lipid deposition, immune suppression and chemotherapy resistance to drive multifocal tumour progression.

Global prevalence ranges from 1 in 36,000 live births in the UK to 1 in 38,951 individuals in Germany, yet reliable nationwide epidemiological statistics for the Chinese population are still unavailable. VHL damages multiple organ systems, generating common lesions including central nervous system and retinal hemangioblastomas (RH), clear cell renal cell carcinoma (ccRCC), pheochromocytoma/paraganglioma (PPGL), pancreatic cysts and pancreatic neuroendocrine tumours (pNETs). Typical clinical traits encompass early disease onset at an average age of 26 years, shortened life expectancy (62 years for men, 69 years for women) and genetic anticipation. Earlier symptom onset usually corresponds to more severe manifestations; as an incurable lifelong condition, repeated tumour relapses frequently result in permanent disability or premature mortality. Disease phenotypes are determined by mutation categories: Type 1 loss-of-function variants confer low PPGL risk but high susceptibility to renal and hemangioblastic lesions, while Type 2 almost exclusively missense

mutations bring high PPGL risk and three separate subcategories of severity and organ involvement.

Diagnosis depends on either typical multisystem tumour clinical presentations or germline VHL gene genetic verification, the latter serving as the gold standard for definitive confirmation. Historically, management relied on long-term surveillance follow-up plus surgical excision of space-occupying masses to alleviate symptoms and slow progression. The selective HIF-2α inhibitor belzutifan has drastically upgraded treatment paradigms. Global pivotal phase 2 trial LITESPARK-004 yielded a 49% objective response rate (ORR) for ccRCC, and Chinese cohort LITESPARK-015 B1 achieved an impressive 83% ORR for renal lesions and 100% overall disease control across all tumour types. This agent has gained FDA, EMA and NMPA approval as first-line systemic therapy for adult VHL patients unsuitable for immediate surgery or local intervention.

Remarkable ethnic disparities exist between Chinese and Western Caucasian patients. Chinese RH involvement (27.9%, sometimes as low as 10% in individual families) is markedly lower than Western rates of 37.6%–73%, whereas ccRCC incidence (57.8%) greatly exceeds Western figures of 28%–35%. Genetically, large complete deletions account for 32.5% of East Asian mutations versus only 10.5% in Western populations; conversely, missense (40.9% vs 52.0%) and frameshift (8.4% vs 13.0%) variants are less prevalent domestically. The de novo mutation rate among Chinese patients hits 47.4%, more than double the ~20% Western rate, with two-thirds of these spontaneous mutations emerging in families with no prior VHL history. Distinct local hotspot mutations including p.S65W, p.N78S, p.R161Q and subtype-correlated p.R167W are frequently detected in China.

Nevertheless, high-quality national evidence remains scarce. Most domestic publications are small-scale, single-centre retrospective analyses lacking nationwide prevalence data. This evidence gap hinders rapid clinical suspicion, cross-specialty referral and accurate early diagnosis, obstructs multidisciplinary design of personalised strategies covering surveillance, surgery and targeted therapy, and delays the formulation, popularisation and optimisation of unified national standardised diagnosis and care pathways for VHL syndrome.

Rationale VHL syndrome is a rare, multisystem genetic disorder characterized by complex clinical manifestations, a heterogeneous disease course, and limited established treatment paradigms. In China, critical knowledge gaps persist in epidemiological data and large-scale disease characteristics, including organ-specific involvement patterns, age at onset, disease prevalence, associated disability burden, and long-term mortality. Furthermore, optimal treatment approaches and progression patterns across affected organs remain poorly defined.
Following the approval of Belzutifan for the treatment of VHL syndrome in China in 2024, there is an urgent and timely need to enhance disease awareness among healthcare providers and the general public,and to further standardize diagnostic pathways for this rare condition. Such efforts are critical to improving early identification, reducing diagnostic delay, and ultimately optimizing clinical outcomes for Chinese patients with VHL syndrome.
To establish standardized diagnostic protocols, guide evidence-based clinical practice, refine multidisciplinary disease management, and facilitate equitable access to appropriate care, a comprehensive systematic review and meta analysis is warranted. This study will systematically synthesize available evidence to support clinical decision-making, healthcare policy development, and future research focused on Chinese patients with VHL syndrome.

METHODS

Strategy of data synthesis Search Strategy :
A comprehensive literature search will be conducted in the following databases to identify all relevant
studies: the Cochrane Library, PubMed, Embase, Web of Science, China Biology Medicine (CBM), China
National Knowledge Infrastructure (CNKI), WANFANG Data, and China Science and Technology
Journal Database (VIP). Aligned with the PICOTS framework, the search terms will focus on keywords
related to “VHL syndrome” and "China" to ensure targeted retrieval.
• PubMed
#1 Von Hippel-Lindau or von Hippel-Lindau syndrome or von Hippel-Lindau disease or VHL syndrome or VHL disease or Hippel-Lindau disease [Title/Abstract]
#2 China OR Chinese OR Taiwan OR Taiwanese OR "Hong kong" OR Hongkong OR Macau OR Macao OR Beijing OR Shanghai OR Tianjin OR Chongqing OR "Inner Mongolia" OR Tibet OR Guangxi OR Sinkiang OR Ningxia OR Xinjiang OR Hebei OR Shanxi OR Liaoning OR Jilin OR Heilongjiang OR Jiangsu OR Zhejiang OR Anhui

OR Fujian OR Jiangxi OR Shandong OR Henan OR Hubei OR Hunan OR Guangdong OR Hainan OR Sichuan OR Guizhou OR Yunnan OR Shaanxi OR Gansu OR Qinghai
#3 "Animals"[Mesh] NOT ("Humans"[Mesh] AND "Animals"[Mesh])
#4 #1 AND #2 NOT #3.

Eligibility criteria Inclusion Criteria:
Population(s): Chinese individuals with VHL syndrome
Interventions/Comparisons: None
Outcomes:
1.Prevalence of VHL syndrome in China (including the proportion of VHL syndrome among CNS hemangioblastomas, RH, PPGL and RCC)
2. Disease characteristics of VHL syndrome in China: gender distribution; age at symptom onset, age at diagnosis, age at death; cause of death; organ involvement (distribution, organ-specific age at symptom onset, organ specific age at diagnosis, clinical manifestations); mutation characteristics; VHL subtype; primary affected organ
3.Diagnostic patterns of VHL syndrome in China: initial-to-definitive diagnosis time (if applicable); symptom onset-to-first visit time; clinical vs. genetic diagnosis proportion; family history proportion (index cases without de novo mutations); genetic testing timing (pre- vs. post-diagnosis).
Time: No limitation
Study design: Prevalence of VHL syndrome in China: cross sectional studies, cohort studies
Disease characteristics or diagnostic patterns of VHL syndrome in China: observational studies
Exclusion criteria:
Population(s): Non-Chinese patients with VHL syndrome
Interventions/Comparisons: None
Outcomes: Outcomes not of interest or studies focusing exclusively on the efficacy and safety of interventions
Time: None
Study design: Randomized controlled trials (RCT); clinical controlled trials (CCT); case report; reviews.

Source of evidence screening and selection All articles retrieved from the databases will be screened by two independent reviewers. The eligibility of each identified citation will first be assessed based on titles and abstracts. For all citations deemed eligible after abstract screening, full-text publications will be further retrieved and reviewed. Any disagreements between the two reviewers will be resolved through discussion, or with the assistance of a third independent reviewer if necessary. A study flow diagram will be generated to illustrate the literature screening process.

Data management Data extraction will be independently conducted by two investigators with disagreements resolved through discussion or with the assistance from a third independent reviewer if necessary. Where possible, the following information will be extracted: 1) Basic study information: First author's name, year of publication, and study design; sampling region, sampling period, and total sample size; VHL syndrome screening approaches (e.g., proactive screening of high-risk families, population-based census); diagnostic criteria for VHL syndrome; and follow-up time.
2) Prevalence of VHL syndrome in China: crude prevalence in the general Chinese population; age specific prevalence (if reported); regional/ethnic-specific prevalence (if reported); the proportion of VHL syndrome among patients with CNS hemangioblastomas; and prevalence differences between familial and sporadic VHL syndrome (if reported).
3) Disease characteristics of VHL syndrome in Chinese population
Demographic and survival traits: gender distribution, age at symptom onset, age at diagnosis, age at death (for deceased patients), causes of death, and survival metrics (e.g., overall survival rate, progression-free survival).
Organ involvement profiles: Overall distribution of organ involvement; age at symptom onset, age at diagnosis and clinical manifestations of involvement in specific organs (e.g., RH, renal lesions, pancreatic lesions); initial involved organ(s); and time interval from single-organ involvement to multi-organ involvement (if reported).
Genetic and Phenotypic Classification: Phenotypic subtypes of VHL syndrome; genetic mutation characteristics of the VHL gene (e.g., mutation type, locus, frequency) (if reported).
4) Diagnostic patterns of VHL syndrome in China (if applicable): Time interval from initial clinical diagnosis to definitive confirmation; time from symptom onset to the patient's first medical consultation; proportion of clinical diagnoses versus genetic diagnoses; proportion of patients with a positive family history (i.e., index cases not arising from de novo mutations); and details of genetic testing timing (proportion of genetic tests performed pre-diagnosis versus post-diagnosis).

Reporting results / Analysis of the evidence Statistical Analysis for Pairwise Meta-Analysis:

Chinese VHL syndrome prevalenceMeta-analysis via R random-effects model is applied for homogeneous prevalence studies. Pooled prevalence and 95% CIs are calculated; event and total patient counts are extracted if original studies lack direct rates. Analyses shift to tabular descriptive summaries when fewer than three eligible studies exist or quantitative effect sizes are unavailable.
Clinical features of Chinese VHL patientsSynthesized data cover demographics (age metrics, sex ratio, mortality causes), organ lesion profiles (organ involvement distribution, onset/diagnosis age per organ, presentations, predominant lesion site), and genotype-phenotype links. Mutation disparities between Chinese and Caucasian cohorts and VHL subtypes are highlighted for later discussion comparison.
Diagnostic profiles in Chinese VHL cases Aggregated diagnostic data include key time intervals (symptom onset to consultation and confirmed diagnosis), split ratios of clinical vs genetic diagnosis, positive family history rates (index patients excluding de novo variants), and sequencing timing (genetic testing before or after clinical confirmation).
Subgroup Analyses and Meta-Regression :
For epidemiological prevalence analysis, subgroup analyses will be performed according to 1) diagnostic methods (clinical criteria vs. genetic testing); 2) study period.
For baseline analysis, subgroup analyses will be performed according to diagnostic methods (clinical criteria vs. genetic testing).
Sensitivity Analysis :
In order to measure the robustness of our findings, a sensitivity analysis will be conducted based on the different levels of bias defined by utilized quality assessment tools and different characteristics of patients. We will subsequently remove studies in different levels of risk of bias and re-calculate the pooled effects using leave-one-out method.

Presentation of the results The results from the SR activities will be described in one literature synthesis technical report. This report
will include a description of the rationale of the review, the applied methods, and results. The results for
each objective will be separately described in the report. More specifically, the report will detail the
methodological aspects, participants and outcomes across the included studies, and a narrative descriptive
summary of the study findings.

Language restriction None.

Country(ies) involved China.

Keywords VHL syndrome; China; Disease characteristics; Diagnosis.

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