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The "China model" for rare disease governance: Policy framework, local implementation, and pathways for optimization

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SUMMARY: Globally, the prevention and treatment of rare diseases is still constrained by limited diagnostic and therapeutic capacity, restricted drug accessibility, and disparities in medical security systems. In response, China has developed a distinct "China Model" of rare disease governance, characterized by national policy leadership and coordinated local implementation. This study systematically reviews policies issued between 2009 and 2026 and it analyzes five domains: *i*) prevention and screening, *ii*) list-based governance, *iii*) clinical diagnosis and treatment systems, *iv*) drug accessibility, and *v*) payment guarantees. Shandong Province is examined as a representative case. Findings show that the central government has established unified standards through two nationally endorsed rare disease lists covering 207 conditions, supported by clinical guidelines and a national collaborative network for diagnosis and treatment of those diseases. Regulatory incentives for drug review and approval have facilitated the inclusion of 126 treatments for patients with rare diseases in the National Basic Medical Insurance reimbursement list, forming an integrated policy framework spanning identification, diagnosis, treatment, and financial protection. At the provincial level, Shandong is aligned with national directives by integrating its case registration system with the national platform, enhancing quality control across its clinical network and developing a multilevel payment mechanism. The core of the "China Model" is the enhancement of clinical capacity through standardized systems and networked organizations, combined with multilevel risk-sharing mechanisms. However, governance challenges persist, including weak inter-organizational policy coordination, barriers to drug accessibility, fragmented coverage schemes, and an underdeveloped data governance infrastructure. Addressing these challenges requires enhanced end-to-end policy implementation and institution of effective local practices at the national level.

Keywords: rare diseases, China model, collaborative network for diagnosis and treatment, case registration, drug accessibility, medical security

1. Introduction

Rare diseases are a heterogeneous group of conditions characterized by a low prevalence, multisystem involvement, and high risks of disability and mortality. More than 7,000 rare diseases have been identified globally. Patients with rare diseases face four interrelated challenges: delayed or inaccurate diagnosis, limited therapeutic options, high treatment costs, and substantial long-term caregiving burdens (*1,2*). In China, approximately 20 million individuals are living with rare diseases, with approximately 200,000 new cases reported annually. This trend places sustained pressure on healthcare capacity, drug accessibility, and the sustainability of multilevel medical security systems (*3*).

In response, China has developed a distinct "China Model" of rare disease governance, characterized by national policy leadership and provincial implementation. Shandong Province provides a representative case of institutional evolution. As a populous province with strong healthcare capacity, Shandong has implemented several reforms, including the "4+X" newborn screening model, a provincial clinical collaborative network, a mandatory case registration system, and a drug reimbursement mechanism under the critical illness insurance scheme. These initiatives support evidence-informed governance. This study reviews national policy development (2009–2026) alongside Shandong's experience with its implementation, it examines the structural framework of rare disease governance, and it

analyzes how subnational actors adjust administrative mandates and resource allocation to overcome persistent barriers in "last-mile service delivery."

2. National policy framework: A five-pillar institutional architecture

At the national level, China has established a policy framework with five pillars: prevention and screening; list-based governance; clinical diagnosis and treatment systems; drug accessibility; and financial protection. This framework spans the full continuum from disease identification to health outcomes. It standardizes governance through a national rare disease list, regulates service delivery *via* clinical guidelines and coordinated care networks, enables surveillance through mandatory case registration, aligns incentives across the drug development-approval-reimbursement continuum, and reduces financial risk through a multilevel medical insurance system. The overall framework and operational logic of the system are shown in Figure 1.

2.1. Prevention and screening: Embedded entry points and fragile links

Within China's three-tier system to prevent birth defects, detection of rare diseases is integrated into maternal and child health (MCH) care. The 2017 amendment of the Maternal and Infant Healthcare Law and the 2023 regulations implementing that law incorporated premarital examinations, prenatal diagnosis, diagnosis of genetic disorders, and newborn screening in the statutory scope of MCH care, thereby formalizing risk identification and health education within an existing infrastructure (*4,5*). The 2019 revision of the Administrative Measures on Prenatal Diagnosis, the 2009 Administrative Measures on Newborn Disease Screening, and related technical standards established a combined "regulatory framework + technical specifications" system that defines screening protocols, institutional accreditation, and quality assurance requirements (*6-8*).

This integrated approach enables broad population coverage and efficient incorporation into routine clinical workflows, functioning as a "lead generation entry point" for rare disease identification. However, several limitations remain. The scope of conditions included in routine screening only partially aligns with the national Rare Disease List. In addition, post-screening processes - such as confirmation of a diagnosis, coordination of referrals, case registration, follow-up, and financial coverage - remain inconsistent across regions in terms of specificity, implementation, and interoperability. Consequently, initial screening "leads" do not consistently translate into standardized care pathways. Recent policies, including the Plan to Enhance Birth Defect Detection Capacity (2023–2027) and updated quality control indicators, emphasize enhancing the "diagnosis-and-intervention" phase after positive screening results (*9,10*). These measures aim to operationalize the full continuum from screening to diagnosis, treatment, and rehabilitation, with particular emphasis on enhancing the "smooth transition" from detection to clinical management.

2.2. List governance: Defining boundaries, setting priorities, and establishing a shared language

In the absence of comprehensive epidemiological data and a unified prevalence threshold, China has adopted

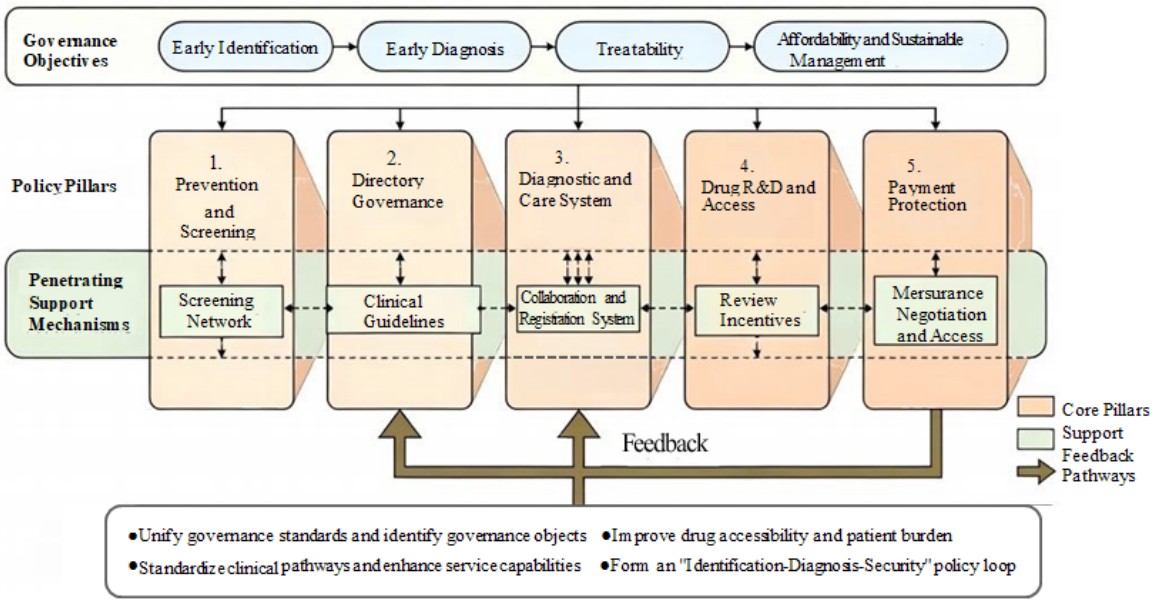

Figure 1. Overall framework and operational logic of China's rare disease governance model.

a "disease list"-based approach to define the scope of rare disease governance. The first national list, issued in 2018, included 121 diseases; the second, issued in 2023, added 86, bringing the total to 207. This list functions as a cross-departmental "common reference framework" for policy coordination (*11,12*). Its institutional value is reflected in two dimensions. First, it defines governance boundaries and priorities, enabling alignment among clinical guidelines, care networks, case registration systems, drug approval processes, and reimbursement policies. Second, it provides subnational authorities with a standardized "language system" framework that reduces transaction costs in policy implementation.

However, list-based governance must deal with two key sources of tension. The first involves balancing regulatory consistency with the need for timely updates based on emerging clinical evidence. The second concerns strengthening the link between the list as a "definitional tool" and as a "catalyst for patient-level entitlements." Only when the list is systematically integrated into clinical standards, registration systems, drug approval criteria, and reimbursement policies can it evolve from a "unified reference point" into an actionable, patient-centered governance tool.

2.3. Diagnosis and care system: An integrated institutional architecture of guidelines, networks, and registration

To address persistent bottlenecks, including misdiagnosis and delayed diagnosis, China has implemented a tripartite institutional strategy consisting of clinical guidelines, a collaborative care network, and a mandatory case registration system. This approach enhances supply-side capacity for rare disease care. At the normative level, the Guidelines for the Diagnosis and Treatment of Rare Diseases (2019) established standardized pathways for the 121 initial conditions, while the 2025 update extended coverage to 86 additional diseases, achieving full alignment with the expanded list (*13,14*).

At the organizational level, the National Collaborative Network for the Diagnosis and Treatment of Rare Diseases - composed of national- and provincial-level leading hospitals and affiliated institutions - supports centralized diagnosis, bidirectional referrals, and sharing of resources. Together with the National Rare Disease Medical Centers, it forms a tiered system characterized by "center-led guidance and network-enabled collaboration" (*15,16*). At the level of data, the mandatory case registration system aggregates standardized clinical data, enabling case management, longitudinal follow-up, quality control, and the generation of natural history and real-world evidence (*17*).

The core logic of this strategy is the coordination of fragmented resources: clinical guidelines standardize care pathways, the collaborative network reduces interinstitutional barriers, and the registration system establishes a feedback loop for continuous quality improvement. The central challenge is no longer the existence of these tools, but whether data can be effectively used to facilitate quality assurance, train providers, optimize referrals, and allocate resources, thereby completing the "data → governance → improvement" cycle.

2.4. Drug development and access: From accelerated review to predictable returns

The pharmaceutical sector represents a key site of "chain friction" in rare disease governance, driven by high research and development (R&D) uncertainty, unmet clinical need, limited patient populations, and methodological constraints in evidence generation. Even after market authorization, therapies frequently encounter downstream barriers, including limited hospital adoption, inconsistent supply, and misaligned reimbursement mechanisms.

In response, national policy has evolved towards a comprehensive framework integrating "methodological support," "economic incentives," and "expectations of predictable returns." At the methodological level, the National Medical Products Administration has issued technical guidance on drug development, statistical approaches, natural history studies, and decentralized clinical trials. These measures reduce regulatory uncertainty and promote "patient-centered" development models that incorporate patient perspectives throughout the R&D lifecycle. At the regulatory level, innovative therapies qualify for priority review, and the 2020 revision of the Administrative Measures on Drug Registration improved transparency and predictability (*18*). Economically, preferential value-added tax policies and tariff adjustments reduce production and import costs, improving expected returns (*19*). In terms of intellectual property policy, the 2026 revision of the Regulations implementing the Drug Administration Law introduces market exclusivity of up to seven years, contingent on commitments to ensure consistent supply. This establishes an institutional linkage of "reliable supply—exclusivity as a reward" (*20*).

Collectively, these policies aim to provide credible signals that reduce investment risk. However, effectiveness depends on seamless integration across the access pathway: "approval → listing → hospital adoption → reliable supply → physician prescription → insurance reimbursement." Disruptions in any stage may limit access for patients with rare diseases despite regulatory progress upstream.

2.5. Payment protection: Expanding coverage despite structural gaps

China has established a three-tier payment framework consisting of basic medical insurance, critical illness

insurance, and medical assistance. As outlined in the Opinions on Further Reform of the Medical Security System, this "triple-protection" structure aims to enhance risk pooling for catastrophic expenditures and explore targeted mechanisms for rare disease drug coverage (*21*). Within this framework, coverage has expanded through dynamic updates to the National Reimbursed Drug List (NRDL), price negotiations for high-cost therapies, and active price regulation. By December 2024, 126 drugs for patients with rare diseases were included, covering 68 conditions. Several high-cost therapies have undergone substantial price reductions through national negotiation, improving patient access (*3*).

Despite these advances, structural gaps remain. First, disparities between listed and unlisted drugs expose patients to high out-of-pocket costs for effective but unreimbursed therapies. Second, long-term sustainability and equity require stronger empirical support. If registration data, real-world evidence, and budget impact analysis are not systematically integrated into policy adjustment processes, regional variations may persist, leading to fragmented and unequal access across jurisdictions.

3. Shandong's implementation pathway: Operationalizing top-level design and establishing an integrated service chain

Within the national policy framework, Shandong Province has instituted a locally operated model by using the MCH system to expand screening and enhance early detection; integrating provincial case registration with the national platform to support collaborative diagnosis and treatment; enhancing standardization through a regional network of collaborative care, designated hospitals, and quality control centers; and ensuring affordability by anchoring coverage in basic medical insurance while incorporating diversified payment mechanisms. Across five interlinked domains - prevention and screening, case registration, diagnosis and treatment, drug accessibility, and payment security - this approach demonstrates how provincial implementation can bridge systemic gaps and establish a closed-loop service model (Table 1).

3.1. Prevention and screening: Localized "entry expansion" and structured referral mechanisms

Building on the national three-tier framework for prevention of birth defects, Shandong has enhanced risk identification and early intervention from pregnancy through the neonatal period *via* provincial initiatives. Management protocols post-screening have been instituted to ensure systematic referral to diagnosis and treatment pathways.

In terms of prenatal screening, a free provincial program launched in 2017 established a "closed loop" of services for "screening-genetic counseling-referral-follow-up," providing a standardized model for managing high-risk populations, including those at risk for Down syndrome (*22*). In 2025, the Administrative Measures on Prenatal Diagnostic Techniques formally defined prenatal diagnosis as the assessment of fetal congenital anomalies and inherited disorders. The policy regulates core components, including genetic counseling, imaging, biochemical and immunological testing, cytogenetics, and molecular genetics, as well as specific modalities (*e.g.*, serum screening, non-invasive prenatal testing, and ultrasound). It also establishes institutional accreditation standards, technical protocols, and quality control requirements, enhancing the continuum of "a condition is suspected based on screening → standardized confirmation → timely referral and intervention" (*23*).

For newborn screening, the province issued the Administrative Measures on Newborn Screening in 2021, mandating screening for four core conditions: phenylketonuria (PKU), congenital hypothyroidism, congenital adrenal hyperplasia, and glucose-6-phosphate dehydrogenase deficiency. The program has been expanded to include tandem mass spectrometry-based screening for inborn errors of metabolism and universal hearing screening, supported by governance and quality assurance mechanisms (*24*). Shandong applies a differentiated "4+X" model: the "4" denotes the four fully subsidized conditions, while the "X" represents additional conditions selected by prefecture-level cities based on fiscal capacity and disease burden. Some cities have expanded coverage to 36–48 conditions. Although this multilevel financing structure has accelerated expansion, it has also introduced regional disparities in subsidies and cost burdens, highlighting the need for improved equity and fiscal efficiency (*25-27*).

3.2. List governance and case registration: Enabling collaborative clinical operations through standardized terminology and provincial-level registration

To enhance the identification of cases of rare diseases and improve the efficiency of inter-institutional referrals, Shandong Province has established a provincial registration system centered on terminology standardization—thereby ensuring effective alignment with the national Collaborative Network for the Diagnosis and Treatment of Rare Diseases and its associated registration framework.

In 2010, the Shandong Association for Rare Disease Prevention and Control was founded to advance academic research, physician training, and public education, providing sustained support to enhance clinical capacity in rare disease identification. In 2017, Shandong became the first province in China to implement a provincial-level rare disease case registration system, covering 53 tertiary hospitals and maternal and child healthcare facilities. This initiative laid the foundation for a cross-institutional infrastructure for aggregation of standardized

Table 1. A comparative analysis of the design and implementation of national policies on rare diseases in Shandong Province

Governance phase	National policy instruments	Implementation in Shandong Province	Mechanism of local modification
Prevention and screening	The Newborn Screening Measures (2009) explicitly delineate requirements for screening, diagnosis, referral, follow-up, and quality control; the Program to Enhance Birth Defect Detection Capacity (2023) enhances the integrated "screening-diagnosis-intervention" continuum.	The Shandong Plan to Implement Free Prenatal Screening (2017) and the Regulations for the Implementation of Administrative Measures on Newborn Disease Screening (2021) promote the standardized implementation of prenatal screening, prenatal diagnosis, genetic counseling, and newborn screening.	Converts national front-end identification requirements into provincial-level entry points for the "screening-consultation-referral-intervention" process.
Disease-specific list management	The Notice on the First Installment of the Disease List (2018) and Notice on the Second Installment of the Disease List (2023) jointly established a unified definition of the target population for rare disease management, thereby instituting a standardized list and delineating clear policy boundaries.	Building on this harmonized framework—which encompasses 207 designated rare diseases drawn from both installments of the list—substantial progress has been made in advancing diagnosis and treatment protocols, case registration systems, health insurance coverage, and legislative research.	These national list standards have been operationalized as a common reference language to facilitate consistent internal identification, collaboration, and effective policy implementation across provinces.
Diagnosis and treatment system	The Collaborative Network Notice (2019) established a national collaborative network and referral mechanism; the Diagnosis and Treatment Guidelines (2019/2025) provided standardized diagnostic and treatment pathways.	Established a provincial-level collaborative network for diagnosis and treatment consisting of 53 member hospitals; the Provincial Hospital is designated as the lead institution to establish a provincial quality control center, and the development of multidisciplinary teams (MDTs) and disease-specific outpatient clinics are promoted.	Adapted the national Collaborative Network and Guidelines framework into a provincially implemented, tiered diagnosis and treatment system in the form of "Collaborative Network- Member Hospitals-Quality Control Centers-MDTs."
Case registration system	The Information System Management Plan (2019) mandates that hospitals in the collaborative network implement standardized case registration, systematic data collection, and rigorous quality control measures and establish a unified, interoperable information platform.	The provincial system for registration of cases of rare diseases was launched in 2017, with continuous improvement of the database. Public responses indicate that 87,600 patients and 207 disease categories have been registered.	The national registration system is being transformed into a comprehensive governance support platform, serving as the foundational infrastructure for provincial databases, routine reporting, and statistical analysis.
Drug development and accessibility	The Opinions on Reforming Review and Approval Procedures (2017) encourage innovation; the VAT Notice (2019) provides tax incentives; the Administrative Measures on Drug Registration (2020) improve review rules; and the Regulations for Implementation (2026) establish a priority review pathway and stipulate a maximum period of market exclusivity of seven years.	The Shandong Biomedical Innovation Action Plan (2024) supports research and development, clinical trials, regulatory review services, and medical insurance coverage of innovative drugs for rare diseases while also facilitating the integration of the "dual-channel" pharmaceutical supply system; the R&D Subsidy Notice (2026) provides subsidies for clinical trials of Class I new drugs.	A provincial-level translational value chain – consisting of R&D subsidies, clinical trials, regulatory review and approval, and linkage to medical insurance - shall be established.
Medical security policy	The Opinions on Medical Insurance Reform (2020) established a three-tiered medical security system consisting of basic medical insurance, critical illness insurance, and medical assistance; the Opinions on Dual-channel Mechanism (2021) promoted the alignment of drug supply and payment for negotiated medications.	The newly added orphan drugs will be incorporated into the dual-channel system; outpatient treatment for 10 rare diseases will be covered under a dedicated, separate payment scheme; and financial burdens will be mitigated through coordinated support from critical illness insurance and medical assistance programs.	The national unified reimbursement framework has been refined into province-level integrated medical security – consisting of the dual-channel system, separate outpatient payment, critical illness insurance, and medical assistance.

Note: In the table, both national policies and their implementation in Shandong Province are referred to using the standardized format "document abbreviation + year." Full document titles are provided either in the main text or in the references. For certain implementation practices in Shandong Province—where no single, dedicated regulatory document exists—the descriptions are synthesized from relevant action plans, official departmental responses, or internal working documents.

case data (*28*). In 2019, 22 medical facilities—including Shandong Provincial Hospital as the lead—joined the National Collaborative Network for the Diagnosis and Treatment of Rare Diseases, successfully integrating the provincial registration platform with the national system. Concurrently, the scope of registered conditions was expanded to encompass all 207 diseases listed across the two officially issued installments of the National Rare Disease List, thereby establishing a unified, interoperable data foundation to support coordination of intra-provincial referrals and evidence-informed optimization of policy (*15*).

As of the most recent reporting period, the provincial registration system has a total of 83,600 confirmed cases of rare diseases. Of those, 92.68% come from four key clinical departments: endocrinology, neurology, respiratory medicine, and hematology (according to data from the Shandong System for Registration of Cases of Rare Diseases). This not only reflects the clinical characteristic of rare diseases involving multiple systems but also offers clear guidance for subsequent training in targeted identification and management of follow-up by key departments.

3.3. Diagnosis and treatment system: A collaborative network, designated hospitals, and a quality control center promoting standardized care

To improve accessibility and standardization, Shandong has developed an integrated system consisting of a collaborative network, designated hospitals, expert teams, and a provincial quality control center. This model is grounded in multidisciplinary collaboration and structured referral mechanisms.

In 2019, the provincial Collaborative Network for the Diagnosis and Treatment of Rare Diseases was established, incorporating all Grade-3 general hospitals and Grade-3 MCH hospitals to support cross-institutional consultations and tiered referrals (*29*). In 2021, the Shandong Province Plan for the Prevention and Control of Rare Diseases designated specialized hospitals and established an expert panel to support complex case management (*30*). In 2022, the province established the first provincial Center for the Quality Control of Medical Care for Rare Diseases, introducing a three-tier coordinated system involving a lead hospital, member hospitals, and downstream institutions. This system supports standard development, training, assessment of competency, and cyclical quality evaluation, thereby advancing standardization. It also promotes multidisciplinary outpatient clinics, improving comprehensive care capacity (*31*).

At the institutional level, Shandong Provincial Hospital has established 69 multidisciplinary teams, including 25 dedicated rare disease teams, that provide more than 100 interdisciplinary consultations annually. The number of rare disease diagnoses increased from 108 in 2021 to 131 in 2024, demonstrating expanded diagnostic and treatment capacity (according to data from Shandong Province's Center for the Quality Control of Medical Care for Rare Diseases).

3.4. Drug supply and clinical accessibility: Industrial strength despite persistent gaps in R&D capacity and in-hospital availability

Drug accessibility remains affected by cumulative friction along the "access–procurement–entry into hospitals–supply–reimbursement" pathway. In 2024, Shandong issued the Shandong Biomedical Innovation Action Plan, supporting the R&D and translation of innovative drugs through rare disease clinical trials, review services, and the integration with medical insurance and the "dual-channel" system. Shandong has a strong pharmaceutical base, with 5,924 biopharmaceutical enterprises as of 2023; these are concentrated in Jinan, Qingdao, Heze, Yantai, and Zibo and are supported by established manufacturing capacity (*32*). In the area of rare diseases, however, research and industrial capacity remain limited. Of more than 800 globally approved drugs for rare diseases, only 252 are marketed in China, nearly 60% of which are imported, and only six are domestically developed innovative drugs. Although two drugs have been launched by Shandong-based enterprises, production capacity is limited, and most firms focus on generics, indicating limited capacity for upstream innovation (*33,34*).

Policy support for rare disease drug and device development remains insufficient. Provincial regulatory frameworks and incentive mechanisms are underdeveloped, and systems supporting collaboration among academia, industry, and clinical practice are incomplete. Market approval represents only the initial stage; sustained access requires coordination across provincial lists, inclusion in hospital formularies, prescribing systems, supply chains, and reimbursement. Currently, supply depends heavily on imports, and local production capacity is limited. Persistent challenges include restricted entry into hospitals, regional shortages, and high prices, which disrupt treatment continuity for patients with rare diseases, particularly in primary care. Moreover, surveillance systems, stockpiling mechanisms, and emergency allocation protocols remain underdeveloped, further limiting availability and diminishing system reliability.

3.5. Payment protection: A multi-tiered financing framework anchored in basic medical insurance—with persistent gaps between listed and unlisted therapies

Recognizing the high cost of drugs for rare diseases and the need for lifelong treatment, Shandong Province has established a multi-tiered payment system anchored in basic medical insurance, reinforced by cost-sharing

mechanisms, and supplemented by diversified financing instruments to improve affordability and treatment continuity.

Basic medical insurance serves as the foundation. Complete alignment with the NRDL is maintained, and all listed drugs for rare diseases are covered. Through national price negotiations, these drugs have been reduced in price by an average of over 60%. Additionally, 35 costly rare diseases are included in the program for outpatient care for chronic and specified diseases, enabling coordinated reimbursement between outpatient and inpatient care (*35*).

The critical illness insurance scheme functions as a secondary safety net. For high-cost drugs not included in the NRDL, including those for Gaucher disease and Fabry disease, a segmented reimbursement model applies: a deductible of 20,000 RMB; 80% reimbursement for costs between 20,000–400,000 RMB; and 85% reimbursement for costs over 400,000 RMB, with an annual ceiling of 900,000 RMB (*36*).

Medical assistance provides targeted protection for vulnerable populations. Individuals receiving special hardship allowances or minimum livelihood support are exempt from deductibles, with reimbursement rates of at least 70%. Medicinal foods for patients with PKU are included and reimbursed at 75% (*37,38*). At the supplementary level, inclusive commercial insurance products have been introduced; by 2024, these covered 11 rare diseases (*39*).

In 2024, the specified drug program under critical illness insurance covered 155 patients, with total expenditures of 86.84 million RMB (approximately 560,000 RMB per patient). Inclusive commercial insurance disbursed 37.18 million RMB to 384 patients (approximately 100,000 RMB per patient) (according to data from the Medical Security Bureau of Shandong Province). Despite these gains, structural challenges remain: access to certain innovative, unlisted therapies is limited; out-of-pocket costs remain high for many patients; and the long-term sustainability and equity of the financing system require further refinement.

4. Challenges and limitations

Although China has established a "China Model" of rare disease governance characterized by national coordination and local implementation and although Shandong Province has demonstrated notable institutional innovation, several challenges remain. First, there is still inconsistency across the care continuum. Post-screening processes, including diagnosis confirmation, referral, and follow-up, vary across regions in terms of standardization and operations (*40*), limiting the conversion of early detection of cases ("identification") into standardized clinical management. While case registration systems aggregate data nationally, their use in quality improvement and resource allocation remains limited. Second, access to treatment remains constrained. Even when drugs are approved or included in reimbursement lists, barriers such as "hospitals that are difficult to enter," variations in regional supply (*41*), and inconsistent supply reduce effective access in the "last mile." Third, financing structures remain fragmented. Although the affordability of listed drugs has improved, clinically necessary unlisted therapies lack consistent financing mechanisms, resulting in continued high out-of-pocket costs for patients with rare diseases (*42-43*). Fourth, data governance remains underdeveloped. Variability in hospital information systems, lack of unified data standards, and the sensitivity of genomic data impede data integration and sharing. Balancing data accessibility with privacy protection remains a critical policy challenge.

5. Policy recommendations

Based on these findings, four policy priorities are proposed. First, enhance integration across the "positive results in screening → confirmation of the diagnosis → referral → follow-up" pathway by clarifying responsibilities and standardizing processes. This should include capacity-building initiatives and the use of real-world data to identify system bottlenecks and expand collaborative networks. Second, enhance pharmaceutical supply security through integrated mechanisms, including real-time monitoring, strategic stockpiling, and emergency allocation. Concurrently implement incentives such as market exclusivity to support domestic innovation and increase production capacity. Third, promote precise financing by incorporating real-world evidence in dynamic assessment of drug value and adjustment of reimbursements. Develop targeted payment mechanisms for high-cost, unlisted therapies, aligning reimbursement with clinical value and fiscal sustainability, while diversifying funding sources to reduce the pressure on basic medical insurance. Fourth, establish a unified and secure framework for data governance. This should include standardized data collection and interoperability protocols, adoption of privacy-enhancing technologies (*e.g.*, secure multi-party computation and federated learning); and tiered access to de-identified data. These measures will support clinical research and policy evaluation while ensuring ethical and legal compliance.

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From presence to provenance: Building substantive infrastructure for China's rare disease ecosystem

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SUMMARY: International collaboration is indispensable in rare diseases, yet its depth and impact vary widely. In recent years, China has expanded its engagement in global rare-disease initiatives, but not all efforts translate into lasting progress. This Policy Forum examines China's evolving role through the lens of symbolic versus substantive collaboration. While symbolic efforts enhance visibility, substantive collaboration builds durable infrastructures—such as standardized terminologies, interoperable data systems and registries, and sustained clinical and research networks. Drawing on policy-relevant case examples, this article shows how patient-centered, infrastructure-building approaches can transform episodic engagement into systemic capacity. Looking ahead, the next phase of collaboration must focus on embedding global standards into health information systems, registries, and reimbursement frameworks. With its population scale, growing scientific capacity, and expanding global interaction, China is well positioned to evolve from a participant to a co-shaper of a truly global rare-disease ecosystem.

Keywords: rare disease innovation, China's rare disease advantage, patient-initiated research, Lesch-Nyhan Syndrom (LNS), Hemophilia Home of China (HHC), rare disease infrastructure building

1. Introduction

Rare diseases, though individually "rare", represent a global public health priority of staggering proportions (*1-3*). No single nation possesses the patient volume or specialized expertise to address these conditions in isolation, and international collaboration is not merely an advantage; it is a necessity.

In China, the sheer scale of the population (1.4 billion) transforms rare prevalence into high absolute patient numbers regardless of which definition is used (*3-5*). While these conditions remained on the periphery of the national health agenda for decades, the last ten years have marked a radical policy pivot (*6-9*). Beginning with the 13th Five-Year Plan for Health and Wellness (2017) (*10*) and the landmark release of the National Rare Disease Catalog (2018) (*11*), the Chinese government embarked upon a systematic, cross-sectoral approach. This era of "explosive growth" was underscored by the allocation of substantial state funding to initiatives such as the National Rare Disease Cohort Study (*12,13*).

The initial phase of China's rare disease evolution was characterized by "inbound" collaboration—a vital period of knowledge importation where Chinese stakeholders adopted global best practices in patient care, clinical guidelines, advocacy, and genomics from the U.S., Europe, and Japan. This foundation was solidified through pivotal international engagements. Academic research collaboration and the "Haigui" (returnee) phenomenon have successfully ignited China's biotech infrastructure (*14*), yet a critical distinction must be made between isolated research successes and substantive, systemic progress.

This Policy Forum argues that the next frontier for China—and the global community—lies in moving beyond symbolic gestures toward collaborative infrastructure-building. By analyzing unique case studies in patient-led networks and technology standards, this article examines the structural and regulatory shifts necessary to build an enduring, interoperable rare disease collaborative ecosystem.

2. Symbolic *vs.* substantive efforts

Not all forms of collaboration deliver equal impact. In rare diseases, where data is scarce and time is a luxury, it's important to distinguish between symbolic and substantive efforts (Table 1).

Symbolic collaborations, are often highly visible but

Table 1. Comparison of symbolic *vs* substantive collaboration in rare diseases

Feature	Symbolic Collaboration	Substantive Collaboration
Primary goal	Visibility, prestige, short-term wins	Utility, scalability, long-term efficiency
Type of output	Press release, conference, MOUs, halo publication	Shared data standards, shared protocol/ methodology, clinical trial network, registry useful for research and drug development
Data strategy	Siloed or proprietary	Interoperable, sharable *via* open data standards
Duration	Transient, dissipates once the event or funding ends	Durable, outlasts the initial project or individuals
Barrier to entry	Low, requires consensus on a public message	High, requires legal, technical and regulatory alignment
Policy implication	Low	High, generate evidence base for standard of care or reimbursement changes
Impact on patient	Indirect, unsubstantiated hope rarely changes patient outcomes	Direct, reduction in the diagnostic odyssey, access to global trials/ treatment, and improved standard of care

functionally shallow. They generate headlines and short-term visibility, but rarely "move the needle" on patient outcomes. In many cases, they create an opportunity cost—consuming precious resources and stakeholder attention while leaving little behind once the spotlight fades.

By contrast, substantive collaborations produce durable infrastructure and systems with far-reaching effects. These initiatives prioritize what can be described as "the plumbing of progresses": inherently harder, slower, and often less glamorous than symbolic gestures. It often requires navigating complex regulatory frameworks and aligning disparate institutional interest. However, it is precisely this groundwork that enables progress to be systematic, scalable, and reproducible across borders.

The substantive collaboration efforts can originate as grassroots initiatives but snowball into institutional forces that could shape policy changes.

2.1. Patient advocacy

Patient advocacy in rare diseases is born of necessity. Historically, in the United States and Europe, advocacy was the fundamental prerequisite for establishing medical and legislative recognition (*15,16*). Prior to formal mobilization, rare diseases were often dismissed as "marginalized problems" lacking commercial or clinical visibility (*17*). In China, this trajectory is compressed but equally transformative. As recent as 30 years ago, the healthcare system was ill-equipped to recognize or treat most rare conditions, with expertise concentrated in a few tertiary hospitals in big cities. Patients were medically underserved and subjected to social stigma (*17*). Within this environment, patient advocacy emerged as the first "visible bridge" connecting Chinese patients to global expertise.

2.2. From patient support to trial-ready networks

China's patient advocacy evolved from grassroots support to "trial-ready" infrastructure, exemplified by the Hemophilia Home of China (HHC) (*18-20*). Supported by the World Federation of Hemophilia (WFH), and buoyed by favorable policy tailwinds, HHC collaborated with clinical experts to establish China's Hemophilia Treatment Center Collaborative Network of China (HTCCNC) (*19*). The network expanded from 6 centers in 2004 to 115 in 2019, building a National Hemophilia Registration System with tens and thousands of patients (*19,20*).

Leveraging its registry for patient identification and enrollment, HHC partnered with Belief Biomed (BBM). Their partnership enabled the 2025 NMPA approval of BBM-H901, China's first domestically developed gene therapy (*21*). Today, HHC's digital platforms facilitate centralized recruitment and standardized AAV antibody testing—shifting the role from "support beneficiary" to "sophisticated co-development partner."

2.3. Lesch-Nyhan syndrome (LNS) – From serendipity to leading global research

While HHC illustrates the power of national networks for higher-prevalence rare diseases, Lesch-Nyhan Syndrome (LNS)—with an incidence of 1 in 380,000—demonstrates how substantive collaboration can achieve global impact in ultra-rare, resource-constrained contexts.

The China LNS Patient Group emerged from the "Wonder Sir" digital platform (*22*), founded by Dr. Yiwei Chen, a molecular geneticist and "returnee" (haigui) from Heidelberg University in Germany. Her academic background bridged the gap between laboratory research and clinical needs, enabled her to grow a small WeChat group with just three families into the world's largest LNS community with over 100 patients in just eight months.

Beyond providing mutual support, the community has

built a robust medical infrastructure: a national clinical and research network in China, and LNS Diagnostic Guidelines, aligned with GeneReviews standards (*23*). With direct support from the world's top LNS expert, Dr. Hyder A. Jinnah, the initiative now entered into a new phase: advancing basic research and co-designing clinical trials with Chinese clinicians and researchers. The resulting work is currently being developed into a graduate thesis under the supervision of a principal investigator (PI) (*24*). Serving as an outside graduate advisor, Dr. Chen plays a key role in ensuring that grassroots data collection is translated into academically rigorous output capable of meeting international peer review standards.

As a trail blazer, LNS group has encountered a range of structural challenges. Securing funding for patient-initiated research remains particularly difficult. Despite her strong academic background, Dr. Chen is at disadvantage when applying for government grants, which are typically awarded to PIs affiliated with established institutions. Regulatory barriers further complicate the landscape: strict rules governing human genetic materials, along with limitation on non-for-profit organizations receiving foreign funding, significantly restrict access to diverse funding sources.

Collaboration with hospital-based researchers presents an additional hurdle as rare disease research is perceived as a "non-essential" clinical activity. Neither institutions nor physicians are incentivized to engage deeply as existing rare disease reporting mandates focus solely on avoiding penalties for "non-compliance" rather than awarding excellence. Consequently, hospital participation remains largely performative, fulfilling administrative quotas without advancing clinical depth.

This systemic apathy, however, is not merely a failure of wills, but a failure of infrastructure. The friction encountered by the LNS case reveals the structural gaps in our current healthcare infrastructure – gaps that cannot be bridged by advocacy alone but require a fundamental shift on how rare disease research is recognized and valued.

2.4. The infrastructure of visibility: Standardized terminologies

To move rare disease collaboration from symbolic gestures to substantive impact, data must be both visible and computable across disparate systems and throughout the disease lifecycle. A shared global vocabulary is the only mechanism capable of transcending technical and linguistic barriers to aggregate these rare and highly valuable data points. By standardizing clinical data, we transform isolated anecdotes into a powerful engine for timely diagnosis, treatment development, and for deepening our understanding of the physiology and pathology of cellular networks (*25-30*). Furthermore, this standardization enables insights on disease prevalence, the natural history of rare conditions, and the socioeconomic burdens on families and health systems. The Human Phenotype Ontology (HPO) (*25-27*) and Orphanet Nomenclature of Rare Diseases (ORPHACode) (*28-30*) serve as the two foundational pillars of this global infrastructure.

2.4.1. CHPO: Standardizing the clinical narrative

The Human Phenotype Ontology (HPO) was constructed with the goal of covering all phenotypic abnormalities that are commonly encountered in human monogenic diseases (*25-27*). Originally developed in English, its usage in China was limited until the grassroots creation of the Chinese Human Phenotype Ontology (CHPO) (*31*). Led by a volunteer consortium of experts including Professors Weihong Gu, Shangzhi Huang, and Kai Wang—with the direct support of HPO creator Peter Robinson—the CHPO allows Chinese clinicians to document phenotypes in their native language while remaining fully interoperable with the global system.

CHPO is more than a language translation; it is a reciprocal infrastructure. As CHPO updates in parallel with HPO, Chinese clinical feedback flows back into the global data registry, ensuring that the diverse phenotypic expressions of 1.4 billion people are represented in world science (*32*).

The Chinese Human Phenotype Ontology (CHPO) is being used to support rare disease research, genomic analysis, and emerging AI-driven diagnostic tools (Table 2) (*33-35*). Its strongest adoption is in leading academic and clinical centers, where it enables structured phenotyping, facilitates genotype–phenotype correlation, and improves data interoperability in research settings (*33-35*). However, CHPO is not yet widely integrated into routine hospital information systems, which continue to rely on ICD-based coding and local clinical terminologies. As a result, its clinical use is often indirect, supported by natural language processing and AI-based tools that map unstructured Chinese clinical records to CHPO terms (*34-35*). This reflects a broader transitional model in China, where ontology-based standards are advancing rapidly in research and data infrastructure, while clinical implementation is being enabled through intermediary technologies rather than direct system-level integration.

2.4.2. Orphanet Nomenclature of Rare Diseases (ORPHACode): Making the invisible visible

While CHPO standardizes symptoms, ORPHACode is the gold standard for rare disease nomenclature (Table 2) (*28-30*). It is formalized in key institutional documents, such as The WHA Resolution (May 24, 2025) (*36*), and European Commission Guidelines (2024) (*37,38*).

ICD10 is notoriously poor for rare diseases. Most conditions are lumped to "Other Specified" catch-all codes (*e.g.* Q87.8). The result is rare disease patients become invisible in health statistics. "For rare diseases to

Table 2. Comparison of the CHPO and ORPHACode translation projects

	HPO Localization (CHPO)	ORPHACode Chinese Translation
Description	Record Chinese phenotypes in the native Chinese languages leveraging HPO's interoperable and computable data structure	Label rare disease in registry or public health system
Current status	Continue to be updated, and locally maintained	No update since the initial release in June 2021; Centrally maintained by Orphanet
Features	Used in leading academic and research centers in rare disease research, genomic analysis and AI diagnostics. Chinese data flow back into the global registry	Currently no recorded implementation in China. Only used as a reference in NRDRS: when a new case is submitted to NRDRS, the disease name needs to be consistent with the ORPHACode translation
Future direction	Implement in the electronic medical record (EMR) systems	Implement in the health systems, registries, and reimbursement systems

Table 3. Comparison – Electronic vehicle industry *vs* rare disease research

Feature	Electronic Vehicle (EV) Industry	Rare Disease (RD) Ecosystem
Initial market status	Niche, high-cost, "unprofitable" for traditional automakers	Niche, "non-essential", high risk / low return for traditional hospital / pharma
Strategic value	Testing ground for battery tech, AI and autonomous driving	Testing ground for gene and cell therapy, AI diagnosis, precision medicine
The plumbing	National charging networks and standardized battery connectors	Standardized terminologies (HPO / ORPHACode), and interoperable data repositories
Role of policy	From subsidiaries (symbolic / initial) to mandatory fleet shifts and infrastructure (substantive)	From "direct report" mandates (symbolic) to integrated "trial-ready" networks and stimulative measures for innovations (substantive). System-wide implementation of terminology maximize data intelligence
Grassroots influence	Early adopters and tech-disruptor (*e.g.* Tesla/NIO forcing policy change	Grossroot initiative (HHC, LNS) fill critical gaps and brings valuable patient insight, drive regulatory changes
Global dynamics	China's manufacturing prowess creates global export standards	Chinese vast patient data generates global scientific evidence

count, we need to count rare diseases" (*30*).

ICD-11 was developed in close collaboration with Orphanet. It adopts a much more granular approach that mirrors the ORPHACode structure. Compatibility between the systems is a major driver for the adoption of ICD-11 (*36*).

In December 2020, I initiated and led the Chinese translation of ORPHACode, supported by the China Alliance for Rare Diseases (CHARD). Teams at Fudan University Children's Hospital and Peking Union Medical College Hospital (PUMCH) completed the translation work in June 2021. However, a critical gap remains: while the translation is complete, it has yet to be implemented in China's National Rare Disease Registration System (NRDRS) or hospital information systems, which are still using ICD-10.

3. Conclusion and recommendations: Toward a substantive global ecosystem

To realize the full potential of the rare disease ecosystem, China should transition from a compliance-driven regulatory model toward an "Innovation-First" framework. In much the same way that the electric vehicle industry served as a catalyst for transforming the broader automotive and energy infrastructure, rare disease research acts as the "EV sector" of healthcare—a high-tech laboratory for the next generation of precision medicine and digital health systems (Table 3).

Investing in the "plumbing" of this sector—from standardized terminologies to patient - initiated rare disease research and to trial-ready networks, —offers far-reaching strategic value that transcends the rare disease community. I propose that policy incentives be redesigned to foster innovation at both the institutional and grassroots levels.

3.1. Elevate rare disease to "National Strategic Asset"

Policy must evolve beyond baseline administrative mandates toward a framework that integrates rare disease research into the fundamental value proposition of the

national healthcare system. By recognizing rare disease research and clinical trials as primary drivers of medical innovation-analogous to "New Energy" benchmarks in the industrial sector—the government can incentivize hospital leaders to prioritize these efforts as core institutional strengths rather than peripheral "nice-to-have" obligations.

Rare disease research represents a unique "frontier territory" where the boundaries between basic science and clinical care dissolve. They provide an unparalleled window into human biology, offering insights that catalyze breakthroughs in common diseases, oncology and regenerative medicine.

China possesses a distinct structure advantage in this global race: the high concentration of healthcare resources within major tertiary hospitals in mega-cities. While this centralization presents access challenges for patients, it has created an unparalleled density of rare disease cohorts that exists nowhere else in the world. This "concentration effect" allows for the rapid recruitment of patient groups even in the ultra-rare conditions like LNS - effectively turning China's leading medical centers into global hubs for accelerated clinical validation, treating these concentrated patient populations as vital resources for national scientific sovereignty and global biopharmaceutical leadership.

3.2. Incentivize the "grassroots-to-institution" pipeline

Strategic value is often generated at the initiation level by "trail-blazers" like the LNS and HHC groups. The future of rare disease research may depend on recognizing and integrating these grassroots, yet highly substantive, forms of collaboration into formal policy and funding frameworks. Future policy should provide clear pathways for these grassroots, patient-led initiatives to access government research grants and formalize their role as "trial-ready" partners. By allowing more flexible regulatory pathways for patient-initiated research and facilitating international data-sharing, China can empower its local talent to lead global scientific discourse.

Traditional market and policy incentives often fail in ultra-rare diseases, as progress depends less on scale than on the ability to integrate data, expertise and patient communities across borders. The LNS community could serve as a good pilot case to illustrate how grassroots efforts, when coupled with scientific leadership and international expertise can generate research-ready infrastructure that rivals formal systems. Grassroots innovation, when substantively organized, can transcend structural limitations and reshape the landscape of ultra-rare disease research both in China and abroad.

3.3. Build the infrastructure of scalability

Just as the rapid expansion of electric vehicle (EV) industry required a national charging network, the rare diseases "innovation engine" requires a standardized data infrastructure. Implementing CHPO and ORPHACode at the system level is not a technical formality, but a strategic necessity. This standardized plumbing will ensure that the high-quality longitudinal data generated within China's population is interoperable, computable, and primed for global R&D investment.

Furthermore, building this infrastructure of scalability provides the empirical bedrock for sustainable healthcare financing. By rendering rare conditions visible within health care systems, policymakers can perform high-precision analysis of disease prevalence, direct and indirect treatment costs, and the real social economic burden on families and societies. This level of data granularity is the prerequisite for moving from speculative budgeting to evidence-based forecasting, enabling both social and commercial insurers to design risk-sharing models that are actuarially sound and socially equitable.

By investing in building the infrastructure for rare disease, China is not only addressing the needs of its own 20 million rare disease patients but is providing the world with a scalable model for collective scientific and social progress. The spotlight on rare diseases must be used to illuminate the structural path toward a truly universal healthcare ecosystem.

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Policy lessons regarding medical security for rare diseases in China: Insights from Zhejiang Province through the multiple streams framework

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SUMMARY: Rare diseases pose a persistent challenge to healthcare systems worldwide due to their low prevalence, high treatment costs, and rapid emergence of novel therapies. In China, while significant progress has been made through national rare disease lists and medical insurance negotiations, substantial medical security gaps remain at the subnational level. This Policy Forum examines the decade-long evolution of rare disease–specific medical security policies in Zhejiang Province (2015–2025) to draw broader lessons for designing sustainable and equitable coverage mechanisms under centralized insurance systems. Using the multiple streams framework (MSF) as an interpretive lens, this article puts forth three policy arguments. First, medical security for rare diseases cannot rely solely on basic medical insurance (BMI); instead, it requires institutional layering that combines insurance-based pooling, fiscal instruments, and social co-assistance. Second, in highly centralized governance contexts, policy entrepreneurship is predominantly state-embedded, with administrative agencies playing a decisive role in coupling problems, solutions, and political mandates. Third, policy innovation in relation to rare diseases is not a one-time event but an iterative process, in which each reform generates new problem definitions and policy windows. The Zhejiang experience demonstrates that under institutional constraints such as standardized benefit lists, local governments can achieve strategic innovation within the available institutional space by shifting their policy focus from reimbursing costs for "drugs on the Nationally Reimbursed Drug List (NRDL)" to targeted compensation for expenditures for drugs not on the NRDL. This pathway improves treatment affordability while maintaining fiscal sustainability, providing actionable insights for China and healthcare systems in other countries facing similar structural constraints.

Keywords: multiple streams framework, policy window, rare diseases, medical security, policy change, Zhejiang model

1. Introduction

Rare diseases, also known as orphan diseases, refer to illnesses with a very low incidence, small patient populations, and severe clinical manifestations. The definition of rare diseases varies across countries and regions due to differences in national contexts. In the United States, a rare disease is defined as affecting fewer than 200,000 individuals, or with a prevalence of less than 1 in 1,500; in the European Union, a prevalence below 1 in 2,000 is used as the threshold; in Japan, rare diseases are defined as affecting fewer than 50,000 individuals or with a prevalence of less than 1 in 2,500 (*1,2*). In China, the government defines and manages rare diseases through the publication of the first national Rare Disease List (121 conditions) and the Second national Rare Disease List (86 conditions) (*3,4*).

Rare diseases represent a major global public health challenge. Globally, more than 7,000 rare diseases have been identified, approximately 80% of which are caused by genetic factors, and nearly 70% manifest in childhood, cumulatively affecting around 300 million people worldwide (*5,6*). However, fewer than 10% currently have approved treatments or therapies (*7*). The diagnosis of rare diseases is often prolonged and complex, requiring multiple consultations and examinations, and treatment costs are typically high, placing a dual burden on patients of difficulty being diagnosed and expensive medications (*8,9*). In response to these issues, developed countries and regions such as the European Union, Japan, and the United States have successively introduced policies to promote the research and development of

orphan drugs and reduce costs through legislation, financial support, and market incentives while providing a high rate of reimbursement or special medical security funds for patients (*1,10,11*).

In China, there are nearly 20 million patients with rare diseases and over 200,000 new cases annually. At the national level, a series of institutional initiatives have been introduced to improve medical security for rare diseases (*12,13*). However, within the institutional framework of the National Basic Medical Insurance (NBMI) system, a degree of mismatch persists between its policy orientation of providing "basic, broad, and sustainable" coverage and the cost structure of orphan drugs, which are characterized by high unit prices and small patient populations. Considering the financial sustainability of the medical insurance fund, drugs with annual costs exceeding 300,000 RMB for reimbursement or 500,000 RMB for negotiation are typically excluded from Nationally Reimbursed Drug List (NRDL) (*7*). As a result, dozens of approved rare disease drugs remain outside the medical insurance reimbursement system, even though these high-cost medications often represent the only effective treatment option for some patients (*14*).

Given the limitations of the NBMI in covering rare disease expenditures, local policy innovation has become crucial to closing the coverage gap. Compared to national-level arrangements, local governments have greater flexibility to develop supplementary mechanisms based on fiscal capacity, population size, and the availability of medical resources. Since 2015, Zhejiang Province has led China in the establishment of a provincial medical security scheme for rare diseases, characterized by fiscal investment as guidance, medical insurance funds as the core financing source, and social assistance and charitable support as complementary components (*15*). This institutional arrangement has effectively alleviated limited treatment accessibility and the heavy financial burden faced by patients with rare diseases. An analysis of the decade-long evolution of Zhejiang's medical security policies for rare diseases from 2015 to 2025 can provide practical insights to optimize medical security mechanisms for rare diseases in China and healthcare systems in other countries facing similar structural constraints.

2. Analytical perspective: Interpreting policy change through the multiple streams framework (MSF)

The MSF, proposed by John W. Kingdon, is widely used to explain the mechanisms of policy change (*16*). According to this framework, the formation of public policy depends on three relatively independent yet potentially convergent streams: The problem stream, the policy stream, and the political stream. The MSF highlights the role of contextual and institutional factors in driving policy change, offering a conceptual lens to understand the internal logic through which health policies respond to evolving health challenges. It has been widely applied in health policy research and practice (*17-19*).

This article adopts MSF as its core analytical framework, which consists of three core components (Table 1). The problem stream refers to how social problems are identified, defined, and brought to public attention, driven by factors such as significant changes in indicators, focusing events, and feedback on existing policies. The policy stream involves advocacy and bargaining among policy community members (such as experts, bureaucrats, scholars, and interest groups) to promote their ideas or proposals, with policy proposals

Table 1. Core analytical framework based on the multiple streams framework

Stream Name	Stream Connotation	Driving Factors	Examples of Manifestations
Problem stream	Social problems perceived by decision-makers	Systematic indicators	Prevalence rates, cost data, *etc.*
		Focusing events	Extreme individual cases reported by the media
		Policy feedback	Criticism arising from inadequate coverage of existing policies
Policy stream	Various solutions proposed by the policy community	Policy proposals	Competition, combination, and optimization of various medical insurance, civil affairs, and fiscal policies
		Optimization & consolidation	Comprehensive evaluation and optimization of technical feasibility, value acceptability, and budget constraints
Political stream	The political environment independent of specific problems	Political forces	Strategic directions of national political, economic, and social development
		Interest groups	Institutional and behavioral adjustments of entities like medical insurance departments and public hospitals during reforms
		Public mood	Higher public expectations for people's well-being and healthcare

meeting certain criteria being more likely to gain traction. The political stream encompasses the political environment influencing the policy agenda, including political forces, government transitions, interest group activities, and public mood. When the three streams converge at a critical moment and are propelled by a policy entrepreneur (an individual or group with the resources and willingness to push a specific solution), policy change can be facilitated (*20*).

When this theory is applied to the context of Chinese governance, a notable feature is the localized reconstitution of the role of the policy entrepreneur. Unlike the conventional depiction of policy entrepreneurs as actors operating outside the institutional system, in China they are more commonly administrative agencies within the bureaucratic structure and their key decision-makers. They simultaneously perform multiple functions—including problem definition, policy design, and political coordination—and therefore have greater capacity for policy mobilization and implementation. In Zhejiang Province, relevant authorities leveraged bureaucratic authority and resource mobilization capacity to organically align the specific policy issue of medical security mechanisms for rare diseases with national strategies such as "targeted alleviation of poverty " and "common prosperity," thereby enhancing the political legitimacy and practical feasibility of institutional innovation and facilitating the opening of a policy window.

Medical security policies for rare diseases in Zhejiang were not developed overnight but progressed through three stages—a "special fiscal subsidy," a "special fund," and "multi-actor co-governance"—with each exhibiting distinct stage-specific characteristics. Each reform cycle alleviated existing problems while simultaneously exposing new institutional boundaries and financial pressures, thereby reshaping the problem stream and creating conditions for the opening of the next policy window (Figure 1).

3. Policies regarding medical security for rare diseases in Zhejiang Province

3.1. From fiscal subsidies to institutionalized risk pooling

Between 2015 and 2016, Zhejiang Province explored medical security for rare diseases institutionally, with policy formation reflecting the cumulative effect of the "problem stream." As high-cost orphan drugs successively came to market, the limitations of the existing basic medical insurance (BMI) system in addressing extremely high-cost individual situations became increasingly evident, leaving some patients' families facing substantial financial burdens. At the same time, sustained media coverage of "illness-induced poverty" among families affected by conditions such as Gaucher disease, amyotrophic lateral sclerosis (ALS), and phenylketonuria (PKU) further highlighted institutional shortcomings. Under the combined influence of these factors, rare diseases evolved from isolated clinical challenges into a public policy issue of broader social significance.

At the level of the "policy stream," the policy community—including experts from the medical insurance and healthcare sectors—began to explore solutions aimed at mitigating the financial risks associated with high-cost medications without undermining the

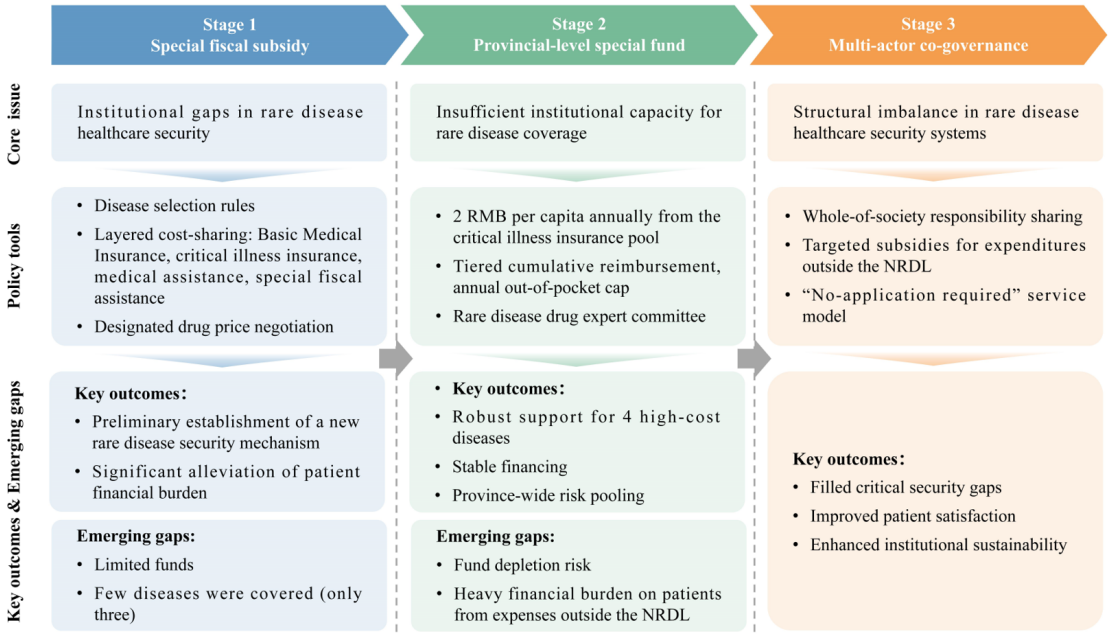

Figure 1. Policy evolution pathways of medical security for rare diseases in Zhejiang Province. *Abbreviation:* NRDL, Nationally Reimbursed Drug List.

foundational framework of the BMI system. Through iterative deliberation, a policy toolkit gradually took shape, centered on "special fiscal subsidies" and complemented by a "layered cost-sharing" mechanism.

In the "political stream," national strategies such as targeted alleviation of poverty and the development of a multi-tiered medical security system provided both institutional legitimacy and policy space. Zhejiang Province's tradition of piloting reforms and its relatively strong fiscal capacity further created favorable conditions for local policy innovation.

Through the interaction of the three streams, a policy window opened. In early 2015, four departments of Zhejiang Province—the Department of Human Resources and Social Security, the Department of Civil Affairs, the former Health and Family Planning Commission, and the Department of Finance—jointly issued the Notice on Enhancing Medical Security for Rare Diseases (Zhejiang Human Resources and Social Security Document No. 126 (2015)) (*21*), the Official Reply on Including Three Special Drugs for Rare Diseases, Including Cerezyme, in Reimbursement under Critical Illness Insurance (Zhejiang Human Resources and Social Security Letter No. 128 (2015)), and the Notice on Issues Concerning the Implementation of Medical Assistance (Special Assistance) for Rare Diseases (Zhejiang Civil Assistance Document No. 36 (2016)) (*22*). The policies were officially implemented across the province on January 1, 2016, marking the first step in exploring the establishment of a special medical security mechanism for rare diseases. With high-cost, case-specific drugs as an entry point, the policy established a "layered cost-sharing" model. After sequential reimbursement by BMI, critical illness insurance, and medical assistance, fiscal special subsidies were introduced to cover the remaining exceptionally high expenses. At the same time, targeted drug price negotiations significantly reduced the costs of treatments for Gaucher disease, PKU, and ALS.

In terms of implementation outcomes, the province treated a total of 365 patients suffering from the three rare diseases mentioned earlier between 2016 and 2018, incurring total drug expenses of 47.84 million RMB. Under the multi-tiered cost-sharing mechanism, BMI covered 2.89 million RMB (with riluzole for ALS included in the NRDL in 2017), critical illness insurance paid 19.67 million RMB, and special fiscal assistance contributed 22.92 million RMB. Together, these three mechanisms absorbed the vast majority of the financial risk, reducing the aggregate out-of-pocket burden for patients to 2.36 million RMB, with the average individual payment declining to approximately 6,400 RMB, thereby substantially alleviating the economic burden of high-cost medical care.

3.2. The emergence of provincial-level special funds

Following the publication of the first national list of Rare Diseases in 2018, rare diseases were formally recognized at the national level, and public concern over the issue of "having available treatments but lacking financial access" increased significantly. In the interim, the limitations of Zhejiang Province's earlier medical security mechanism—primarily reliant on special fiscal assistance—gradually became evident in terms of coverage and financial sustainability, generating notable policy feedback.

Against the backdrop of a continuously intensifying problem stream, the policy community, building on a systematic reflection of prior implementation experience, began to seek more stable and institutionalized solutions. This process led to the formulation of a scheme centered on a "provincial-level special fund."

The maturation of the "political stream" created a critical opportunity to improve medical security for rare diseases. In 2018, the establishment of the Zhejiang Provincial Healthcare Security Administration facilitated the integration of medical insurance management. In 2019, the central government explicitly called for local governments to explore mechanisms to ensure access to rare disease medications, thereby providing policy authorization for local innovation (*23*). Under the combined influence of top-level policy design and institutional restructuring, the problem, policy, and political streams converged once again, opening a new policy window.

In December 2019, the Zhejiang Provincial Healthcare Security Administration, in collaboration with the Provincial Department of Finance, the Health Commission, and the Department of Civil Affairs, jointly issued the Notice on Establishment of a Medical Security Mechanism for Drugs to Treat Rare Diseases in Zhejiang Province (*15*). This policy established the first provincially pooled special fund to cover drugs for rare diseases in China. A dedicated sub-account was created within the provincial medical insurance account, and it operated under separate accounting practices and independent management. Based on the number of participants in the BMI scheme, a fixed annual contribution of 2 RMB per capita was uniformly transferred from the critical illness insurance fund, thereby forming a stable and predictable financing source. In addition, a set of refined management mechanisms was introduced, including a tiered reimbursement system based on cumulative expenditures, an annual cap on individual out-of-pocket payments (set at 100,000 RMB per patient), and the involvement of an expert committee in decisions regarding drug inclusion and evaluation. These measures were designed to ensure both equity and financial sustainability. Moreover, medical assistance programs were implemented in parallel for eligible low-income patients; for those still experiencing financial hardship despite that assistance, additional support was provided by charitable organizations such as the provincial charity federation.

Since its implementation in 2020, fund coverage has gradually expanded and total expenditures have continued to increase (Table 2). With the growing number of patients and improvements in diagnostic capacity, however, potential operational pressures on the fund have also begun to emerge (Table 3). This indicates that while the system has effectively expanded risk pooling, it now faces new sustainability constraints, necessitating further optimization in areas such as dynamic adjustment of financing standards and drug price negotiation mechanisms.

3.3. Shifting from insurance-based coverage to multi-actor co-governance

In the problem stream, the National Healthcare Security Administration has continuously included rare disease medications in the NRDL, but a substantial number of patients still face a "coverage gap" due to the high costs of unlisted medications. With the ongoing emergence of new drugs and technologies, the financial burden on patients continues to rise. The existing special fund has limited capacity to absorb additional risks. There is thus an urgent need to explore new multi-tiered medical security mechanisms with broad societal participation.

In response, within the policy stream, the policy community began exploring multi-departmental approaches to medical security for rare diseases outside the scope of the NRDL. A mechanism of shared responsibility across society was developed, integrating diverse social resources. Specifically, out-of-pocket expenses for rare disease treatments not covered by the NRDL were covered by Zhoushan's multi-tiered subsidy, thereby creating additional space for local policy innovation within the existing national policy framework.

In the political stream, public expectations of "common prosperity" and improved social welfare provided normative support for the participation of social actors. At the same time, national and provincial policies promoting the development of philanthropy and voluntary donations to charity ("third distribution") offered institutional empowerment for local innovation. Acting as policy entrepreneurs, the Zhoushan Municipal Healthcare Security Administration and related departments seized the policy window by aligning the "multi-actor co-governance" scheme with the broader policy narrative of common prosperity, thereby facilitating rapid policy adoption.

In April 2025, the Zhoushan Municipal Healthcare Security Administration, together with the Zhoushan Civil Affairs Bureau and seven other departments, jointly issued the Notice on Establishing and Improving a (Trial) Multi-tiered Subsidy Mechanism for Rare Disease Medical Expenses, marking the successful convergence of the three streams (*24*). This mechanism establishes a tripartite linkage framework consisting of "social charity, departmental assistance, and special

Table 2. Zhejiang's special fund for rare diseases: Coverage by disease (units: 10,000 RMB, persons)

Disease	Drug	2020		2021		2022		2023		2024	
		Patients	Payment	Patients	Payment	Patients	Payment	Patients	Payment	Patients	Payment
Glycogen storage disease II	Myozyme	14	345.51	24	2,034.78	29	2,023.36	33	3,757.51	37	4,907.73
Fabry disease	Fabrazyme	6	197.44	17	954.29	29	1,118.85	46	2,392.17	56	3,168.79
Gaucher disease	Cerezyme	21	1,799.27	27	3,260.83	28	2,832.52	32	4,316.54	35	4,287.9
Phenylketonuria	Kuvan	15	32.01	23	59.92	18	22.22	–	–	–	–
Total		56	2,374.23	91	6,309.82	104	5,996.95	111	10,466.22	128	12,364.42

Table 3. Operational status of Zhejiang's special fund for rare diseases (units: 10,000 RMB)

Year	BMI Enrollment (units: 10,000 persons)	Fund Income	Patients Covered (units: persons)	Fund Expenditure	Fund Surplus	Cumulative Surplus
2020	5,054	10,108	56	2,374.23	7,733.77	7,733.77
2021	5,081	10,162	91	6,309.82	3,852.18	11,585.95
2022	5,577	11,154	104	5,996.95	5,157.05	16,743
2023	5,621	11,242	111	10,488.43	753.57	17,496.57
2024	5,713	11,858.4	128	12,364.42	-509.02	16,987.55

Abbreviation: BMI, Basic Medical Insurance.

fiscal support," with priority given to diseases that incur high out-of-pocket medical expenditures. Innovatively, it introduces a threshold of 50,000 RMB alongside a tiered sequence of resource interventions. Specifically, out-of-pocket expenses for rare disease treatments not on the NRDL are first partially reimbursed through "Zhouhuibao" (a form of commercial supplementary medical insurance). The portion exceeding 50,000 RMB is first covered through an initial round of assistance provided by temporary relief programs as well as by organizations such as the Federation of Trade Unions, the Disabled Persons' Federation, the Red Cross Society, and the Charity Federation in accordance with relevant policies. If the remaining individual burden after this first round still exceeds 50,000 RMB, a second round of support is provided by the special assistance fund for rare diseases, covering 30% of the excess, with an annual maximum subsidy of 100,000 RMB. Under this policy framework, commercial insurance providers progressively expand the range of rare disease drugs covered under "Zhouhuibao," thereby strengthening risk-sharing across multiple insurance schemes. In addition, this coordinated mechanism leverages the administrative hierarchy to break down data silos and it implements a "no-application-required" model of care. The medical security authority serves as a data hub, integrating medical expenditure information and regularly sharing it with relevant departments, enabling coordinated delivery of multi-tiered assistance and promoting a shift from a passive response to proactive governance.

Through this nine-department joint initiative, Zhoushan has expanded the scope of medical security from expenses covered by the NRDL to high-cost expenditures beyond the NRDL, effectively filling a critical institutional gap. The "no-application-required" model enhances patients' sense of accessibility while improving institutional sustainability. This transformation marks a shift in Zhejiang's medical security system for rare diseases from a government-led model toward a new stage of multi-actor collaborative governance.

4. Core policy arguments derived from the Zhejiang experience

4.1. Institutional layering is essential to medical security for rare diseases

Medical security for rare diseases cannot be effectively achieved through the mere expansion of BMI coverage. Rather, viable policy pathways typically entail the creation of a multi-tiered risk-sharing mechanism grounded in the logic of institutional layering (*25*). Zhejiang Province has progressively established a stratified medical security framework, with BMI as the foundational layer, critical illness insurance as an extension, and medical assistance as a safety net, complemented by special schemes for rare diseases and the participation of societal actors. Within this framework, BMI provides universal and routine coverage, critical illness insurance enhances reimbursement levels to mitigate catastrophic healthcare expenditures, and medical assistance provides a safety net for low-income populations. In addition, a special rare disease fund offers targeted financing for high-cost orphan drugs, while commercial supplementary insurance and charitable contributions further bridge the financing gap for medical expenses not covered by the NRDL. Through such a multi-layered institutional configuration, high-cost medical expenditures are effectively redistributed across different tiers of the system. This arrangement not only alleviates the systemic fiscal pressure on the BMI fund but also helps to enhance the stability and sustainability of medical security for rare diseases.

4.2. State-embedded policy entrepreneurship reshapes classic MSF assumptions

The Zhejiang case demonstrates that, under a highly centralized and administratively led governance structure, the operational logic of the MSF requires contextual adaptation. In the course of policy development, policy actors in Zhejiang strategically embedded the issue of medical security for rare diseases into the broader national policy narrative. Initially framed within the policy agenda of targeted alleviation of poverty and the prevention of illness-induced poverty, the issue was subsequently integrated into the overarching goals of "common prosperity" and the development of a multi-tiered medical security system. By aligning technical healthcare financing arrangements with national policy priorities, these actors facilitated the convergence of the problem, policy, and political streams, thereby creating critical conditions for the opening of policy windows.

This pattern—where core administrative agencies (*e.g.* the Healthcare Security Administration) function as "institutionally embedded policy entrepreneurs"—differs markedly from Western models that rely more heavily on external interest groups. It reduces the transaction costs of cross-sectoral coordination and highlights the capacity of administrative actors to proactively align political objectives with policy design (*26*). Such an approach constitutes a key driving force behind the effective implementation of complex healthcare policies.

4.3. Addressing "expenditures for drugs not on the NRDL" as a new frontier of policy innovation

Under the stringent state regulatory framework, local governments possess limited discretion over reimbursement for care covered "by the NRDL," hampering the provision of adequate security from high-cost medical expenditures. The practices in Zhoushan, Zhejiang Province, indicate that a critical entry point for policy innovation lies in dealing with high-cost expenditures for drugs not on the NRDL. By reconstructing the local governance network, this approach systematically integrates commercial supplementary medical insurance, temporary assistance from civil affairs, policy subsidies from organizations such as the Federation of Trade Unions, the Disabled Persons' Federation, the Red Cross Society, and the Charity Federation, and special subsidies for rare diseases. Together, these sectors collaboratively bear the exorbitant medical expenses not yet covered by the BMI. This model extends the focus of medical security from "drugs on the NRDL" to "drugs not on the NRDL," effectively bridging existing coverage gaps through a mechanism of multi-actor collaboration. It offers a replicable policy pathway for other regions seeking to manage medical expenditures outside the scope of the NRDL and to institutionally innovate approaches to medical security.

5. Policy implications for China and beyond

5.1. Designing sustainable rare disease funds under fiscal constraints

Against the backdrop of limited fiscal resources, establishing a provincial-level special fund for rare diseases is both feasible and stable, provided that it has an institutional financing mechanism. The experience of Zhejiang demonstrates that introducing a symbolic and minimal contribution within a broader pool of medical insurance funds—such as deducting a very small annual amount per capita (*e.g.* 2 RMB) from the critical illness insurance fund—enables the creation of a pooled fund of significant scale without imposing a noticeable burden on the public, thereby ensuring a stable source of financing for high-cost rare disease treatments. International experience likewise indicates that special funding mechanisms constitute an important policy instrument for addressing the high costs of rare disease treatment. Examples include Australia's Life Saving Drugs Program (LSDP), Japan's Nanbyo Medical Care Subsidy System, and Russia's High-Cost Nosologies Program. These systems all provide substantial medical security for patients with rare diseases through specific financial arrangements (*27,28*).

However, stable financing alone does not guarantee the long-term sustainability of such funds. With improvements in diagnostic capabilities and the continuous introduction of innovative therapies, related expenditures are likely to increase rapidly, placing persistent fiscal pressure on public healthcare systems (*29*). The sustainable operation of special funds therefore requires complementary institutional tools, such as systematic pharmaceutical price negotiations, health technology assessment (HTA), and dynamic management of reimbursement lists. Integrating clinical efficacy, cost-effectiveness, and payment decision-making enables the control of fiscal risks while prioritizing access to high-value therapies.

5.2. Balancing equity and efficiency for high-cost, low-prevalence conditions

One of the core challenges in rare disease policy lies in how to achieve a balance between equity and efficiency with limited public healthcare resources (*30*). Policymakers should carefully navigate the trade-off between "expanding the scope of disease coverage" and "providing patients with substantive financial protection."

In its institutional design, Zhejiang Province has introduced mechanisms such as caps on out-of-pocket expenditures and a tiered reimbursement structure with progressive rates (*31*), alongside multi-departmental, stratified subsidies for high-cost rare disease treatments that are not on the NRDL. These policy instruments offer valuable practical insights into addressing the equity–efficiency dilemma. By setting explicit ceilings on out-of-pocket payments and gradually increasing reimbursement ratios across expenditure brackets while simultaneously mobilizing multiple departments to provide targeted support for high-cost, out-of-pocket medical expenses, resources can be more effectively directed toward patients facing catastrophic health expenditures, thereby reflecting a clear principle of vertical equity. At the same time, to prevent declines in allocative efficiency, such payment policies typically require rigorous oversight by expert review committees or HTA bodies. These entities conduct comprehensive evaluations of the clinical efficacy and cost-effectiveness of drugs and treatment options prior to their inclusion within the support framework (*32*). Such mechanisms of institutional assessment not only safeguard patient interests but also help to maintain the operational

efficiency and fiscal sustainability of the medical security system.

5.3. Conditions for and limits of policy transferability across jurisdictions

The Zhejiang model offers significant empirical insights into the development of a national-level medical security framework for rare diseases. Moreover, the design of its diversified, multi-tiered security system echoes international policy principles regarding risk-sharing of medical expenses for rare diseases. Notably, the provincially pooled special fund and multi-departmental approach to medical security necessitate that local governments possess relatively robust fiscal capacity and substantial funding pools for BMI or critical illness insurance; otherwise, creating adequate risk-pooling capacity will be difficult. Additionally, the effective implementation of such policies hinges on a mature medical security system, highly institutionalized mechanisms of cross-sectoral collaboration, and the government's strong commitment to social equity. Despite these prerequisites and contextual limitations, Zhejiang Province's practical experience could still serve as an instructive policy blueprint for the creation of a robust medical security system for rare diseases.

6. Conclusion: Towards adaptive and multi-level management of rare disease care

Medical security for rare diseases should be conceptualized as a system of dynamically evolving policies. An analysis based on the MSF indicated that this system is continuously driven by the dual forces of advances in medical technology and shifting societal expectations, thereby requiring ongoing institutional adjustments in response. The evolution of medical security policies for rare diseases in Zhejiang Province exhibits distinct stage-based and adaptive characteristics. Institutional adjustments at each stage have not only responded to practical governance demands but have also laid a solid foundation for subsequent policies.

Within a highly centralized healthcare system, policymakers should maintain institutional flexibility and the capacity for policy innovation. When the NRDL cannot be rapidly expanded, policy innovation often needs to rely on supplementary institutional arrangements, such as the establishment of special funds or the exploration of mechanisms for multi-actor collaboration. The multi-departmental approach to medical security in Zhoushan, Zhejiang Province, has shifted the focus of coverage from reimbursing the cost of drugs on the NRDL to targeted compensation of expenses for drugs not on the NRDL. This reflects a form of strategic policy innovation in an existing institutional space and effectively bridges the gaps in the medical security system.

In the future, policy initiatives should focus on advancing higher-level risk pooling mechanisms and exploring the establishment of a national-level special fund for rare diseases in order to enhance medical security and promote regional equity. In addition, further steps should be taken to encourage the participation of societal actors, enabling supplementary mechanisms such as commercial insurance and charitable donations to produce a stable and coordinated paradigm within the medical security system for rare diseases (*33*). By continuously refining multi-actor collaboration and risk-sharing mechanisms, a more equitable and sustainable medical security system for rare diseases can be steadily created.

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Review

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Beyond malignancies: Clinical advancements of CAR T-cell in the treatment of autoimmune diseases

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SUMMARY: Chimeric antigen receptor (CAR) T-cell therapy targeting B cells has emerged as a breakthrough treatment for hematological malignancies and shows promising potential in autoimmune diseases. While selective targeting of B-cell activation and autoantibody production represents an innovative therapeutic approach in autoimmune conditions, clinical responses remain suboptimal in many patients due to incomplete B-cell depletion in tissues and limitations in identifying ideal target antigens. Over the past four years, autologous or allogeneic CAR T-cell therapy has demonstrated remarkable efficacy in autoimmune diseases, achieving rapid and sustained B-cell depletion alongside complete clinical and serological remission. This review examines the current landscape of B cell-targeting CAR T-cell therapy, its therapeutic applications in autoimmune disorders, ongoing translational research, and future developments.

Keywords: CAR T-cell therapy, autoimmune disease, immunotherapy

1. Introduction

Autoimmune diseases constitute a diverse spectrum of disorders characterized by disrupted immune tolerance. In these conditions, autoreactive T and B cells, together with autoantibodies, trigger organ damage through multiple effector pathways (*1*). The cornerstone of autoimmune disease management lies in modulating dysregulated T-cell and B-cell responses. Current standard therapeutic approaches aim to inhibit autoreactive immune cell-mediated tissue damage, primarily through the administration of glucocorticoids, nonsteroidal anti-inflammatory drugs, and immunosuppressive agents (including azathioprine, mycophenolate, and tacrolimus). However, these conventional treatments typically require indefinite administration and often result in significant adverse effects while providing suboptimal disease control (*2*).

The selective targeting of B-cell activation and autoantibody production has emerged as a promising therapeutic strategy in autoimmune diseases. Rituximab, a CD20-targeted monoclonal antibody, has been utilized off-label for various autoimmune conditions for approximately two decades (*3,4*). More recent developments include next-generation anti-CD20 and anti-CD19 antibodies, such as ocrelizumab, obinutuzumab, and inebilizumab, which demonstrate enhanced antibody-dependent cellular cytotoxicity and have shown efficacy in reducing disease activity while maintaining favorable safety profiles (*5-7*). Despite these advances, a substantial proportion of patients fail to achieve adequate symptomatic improvement, primarily due to incomplete B-cell depletion within tissue compartments and challenges in identifying optimal target antigens (*8,9*).

The development of therapeutic strategies enabling permanent discontinuation of immunosuppressive medications addresses a major unmet medical need. This review presents a comprehensive analysis of B cell-targeting chimeric antigen receptor (CAR) T-cell therapy and its applications in autoimmune disorders. We examine the rapidly evolving landscape of translational research in CAR T-cell therapies (Table 1, Figure 1), and explore future developments in this field.

2. Therapy principle of CAR T-cells

CARs represent sophisticated synthetic receptors comprising multiple functional domains from distinct origins. Their structure includes: *i*) An extracellular antigen recognition domain derived from antibodies, *ii*) A flexible hinge region, *iii*) A transmembrane domain,

Table 1. Clinical trials of CAR T-cell therapy for autoimmune diseases

Autoimmune disease (*Ref.*)	Number of patients	CAR T-cell target antigen(s)	T cell source	CAR T-cells duration	Safety	Outcomes	Period of drug-free
SLE (*20*)	1	CD19	autologous	7 weeks	no CRS/ICANS	improvement in laboratory parameters and clinical disease activity	no report
SLE (*21*)	5	CD19	autologous	30 days	grade 1 CRS: 3; no ICANS	improvement in laboratory parameters and clinical disease activity in all patients	median of 8 months
SLE (*22*)	8	CD19	autologous	40 days (received rituximab); 58 days (no rituximab)	grade 1 CRS: 5; no ICANS	improvement in laboratory parameters and clinical disease activity	up to 29 months
SLE (*23*)	8	CD19	autologous	up to 60 days	grade 1 CRS: 7; grade 3 CRS: 1; no ICANS	improvement in laboratory parameters and clinical disease activity in all patients	up to 365 days
SLE (*24*)	1	CD19	autologous	6 months	grade 1 CRS:1; no ICANS	improvement in laboratory parameters and clinical disease activity	8 months (plus hydroxychloroquine and low-dose glucocorticoids)
SLE (*26*)	15	BCMA/CD19	autologous	exceeding 28 days	grade 1 CRS: 13; ICANS:1	improvement in laboratory parameters and clinical disease activity in 12 patients	up to 1134 days
SLE (*57*)	4	CD19	allogeneic	180 days	grade 1 CRS: 4; no ICANS or GVHD	improvement in laboratory parameters and clinical disease activity in all patients	during the 6-month follow-up period, 1 patient achieved a drug-free status
SLE (*58*)	3	CD19	allogeneic	Within 6–12 months	no CRS/ICANS/GVHD	improvement in laboratory parameters and clinical disease activity in all patients	patient 1 withdrew the study; 12 months (patient 2 plus prednisone for 6 months; patient 3 plus prednisone continuously
SLE (*71*)	5	CD19	*In Vivo*	within 2–3 days	grade 1 and 2 CRS: 3; no ICANS	improvement in laboratory parameters and clinical disease activity	no
ASS (*27*)	1	CD19	autologous	within 50 days	grade 1 CRS: 1; no ICANS	improvement in laboratory parameters and clinical disease activity	up to 180 days
ASS (*28*)	1	CD19	autologous	within 30 days	grade 1 CRS: 1; grade 1 ICANS	improvement in laboratory parameters and clinical disease activity	up to 150 days
ASS (*29*)	1	CD19	autologous	within 149 days	grade 1 CRS: 1; no ICANS	improvement in laboratory parameters and clinical disease activity	8 months (plus mycophenolate and nintedanib)

Abbreviations: SLE, systemic lupus erythematosus; ASS, antisynthetase syndrome; IMNM, immune-mediated necrotizing myopathy; NMOSD, neuromyelitis optica spectrum disorder.

Table 1. Clinical trials of CAR T-cell therapy for autoimmune diseases (continued)

Autoimmune disease (*Ref.*)	Number of patients	CAR T-cell target antigen(s)	T cell source	CAR T-cells duration	Safety	Outcomes	Period of drug-free
IMNM (*31*)	1	BCMA	autologous	within 2months	grade 1 CRS: 1; no ICANS	improvement in laboratory parameters and clinical disease activity	18 months
Systemic sclerosis (*32*)	1	CD19	autologous	11months	grade 1 CRS:1; no ICANS	improvement in laboratory parameters and clinical disease activity	11 month (plus mycophenolate and nintedanib)
Systemic sclerosis (*22,33*)	4	CD19	autologous	40 days (received rituximab); 58 days (no rituximab)	grade 1 CRS:3 no ICANS	improvement in laboratory parameters and clinical disease activity	up to 6 month
Systemic sclerosis (*56*)	2	CD19	allogeneic	6 months	no CRS; no ICANS; no GVHD	improvement in laboratory parameters and clinical disease activity in all patients	6 months
Generalised myasthenia gravis (*34*)	9	BCMA	autologous	no report	no CRS no ICANS	improvement in laboratory parameters and clinical disease activity in all patients	up to 9 months (most continued receiving corticosteroids)
Generalised myasthenia gravis (*35*)	2	BCMA	autologous	patient1:3 months patient2:6 months	grade 1 CRS: 1 no ICANS	improvement in laboratory parameters and clinical disease activity in all patients	18 months
Generalised myasthenia gravis (*36*)	1	CD19	autologous	still detectable after 62d	no CRS; no ICANS; no GVHD	improvement in laboratory parameters and clinical disease activity	62 days (plus low-dose glucocorticoids)
Myasthenia gravis / Lambert-Eaton syndrome (*37*)	2	CD19	autologous	154 and 94 days	patient 1: grade 1 CRS, grade 1 ICANS; patient 2: grade 2 CRS, no ICANS	improvement in laboratory parameters and clinical disease activity in all patients	up to 7 months
Generalised myasthenia gravis (*38*)	18	bispecific BCMA/ CD19	autologous	within 28days	grade 1 CRS: 7; ICANS:1	improvement in laboratory parameters and clinical disease activity in 17 patients	On day 180, 15 participants discontinued their glucocorticoid
NMOSD (*39*)	12	BCMA	autologous	6 months	all patients had grade 1 or 2 CRS; No ICANS	improvement in clinical disease activity	At a median 5.5-month follow-up, 11 patients attained drug-free remission
Multiple sclerosis (*41*)	2	CD19	autologous	Patient 1: remained detectable on day 100 patient 2: may detect at days 20	Patient 1: grade 1 CRS, no ICANS; Patient 2: no CRS, no ICANS	patient 1: improvement in clinical disease activity patient 2: neurological symptoms were stable	patient 1: up to 100days patient 2: last follow-up 28days
Progressive multiple sclerosis (*42*)	5	BCMA	autologous	continued detection over the subsequent 3 months	grade 1 CRS: 4; ICANS: no report	improvement in laboratory parameters and clinical disease activity in all patients	up to 9 months

Abbreviations: SLE, systemic lupus erythematosus; ASS, antisynthetase syndrome; IMNM, immune-mediated necrotizing myopathy; NMOSD, neuromyelitis optica spectrum disorder.

Table 1. Clinical trials of CAR T-cell therapy for autoimmune diseases (continued)

Autoimmune disease (*Ref.*)	Number of patients	CAR T-cell target antigen(s)	T cell source	CAR T-cells duration	Safety	Outcomes	Period of drug-free
CIDP (*43*)	2	BCMA	autologous	6 months	grade 1 CRS: 2; ICANS: no report	improvement in laboratory parameters and clinical disease activity in all patient	patient 1: up to 12 months, relapse following COVID-19 infection patient 2: up to 24 months

Abbreviations: SLE, systemic lupus erythematosus; ASS, antisynthetase syndrome; IMNM, immune-mediated necrotizing myopathy; NMOSD, neuromyelitis optica spectrum disorder.

and *iv*) An intracellular activation domain derived from T cells (Figure 2).

The antigen-binding domain, typically constructed as a single-chain variable fragment, facilitates MHC-independent target antigen recognition. The hinge region and transmembrane domain serve as a structural bridge, connecting the extracellular antigen-binding component to the intracellular signaling machinery. The intracellular domain incorporates T-cell receptor (TCR) components essential for initiating T-cell activation upon antigen engagement (*10,11*).

Second-generation and later CAR designs incorporate one or two co-stimulatory domains (predominantly CD28 and/or 4-1BB) alongside the activation domain, enhancing T-cell activation, proliferation, and survival capabilities. Through genetic engineering, CAR-encoding DNA is integrated into T cells, generating CAR T-cells capable of antigen recognition, activation, and target cell elimination upon host infusion (*12*). Current clinical research focuses primarily on CARs targeting CD19 or B-cell maturation antigen (BCMA) expressed on B-cell surfaces (*13,14*).

3. Clinical implementation of CAR T-cell therapy

The therapeutic protocol for CAR T-cell treatment involves utilizing autologous T cells and requires preliminary lymphodepletion chemotherapy (*15*). This preparative regimen, typically employing cyclophosphamide and fludarabine, creates an optimal microenvironment for CAR T-cell proliferation and activation. The manufacturing process encompasses: *i*) Leukopheresis to collect sufficient functional lymphocytes, *ii*) T-cell modification using viral vectors, and *iii*) *In vitro* expansion under stringent quality control measures (Figure 3).

CAR T-cell therapy has demonstrated remarkable efficacy in B-cell malignancies, including B-cell acute lymphoblastic leukemia and large B-cell lymphoma (*16,17*). Notably, in refractory and relapsed disease settings, CAR T-cells have shown the potential to induce sustained and potentially curative responses, highlighting their therapeutic promise (*18*).

3.1. CAR T-cell therapy in systemic immune-mediated disease

3.1.1. Systemic lupus erythematosus (SLE)

SLE is a severe autoimmune condition predominantly affecting young women and has historically shown limited response to conventional B-cell depleting antibody therapies. Nevertheless, it has emerged as the autoimmune disease with the most prolific and advanced CAR T-cell research. Preclinical studies by Jin *et al.* demonstrated that anti-CD19 CAR T-cell therapy effectively eliminated circulating CD19+ B cells in

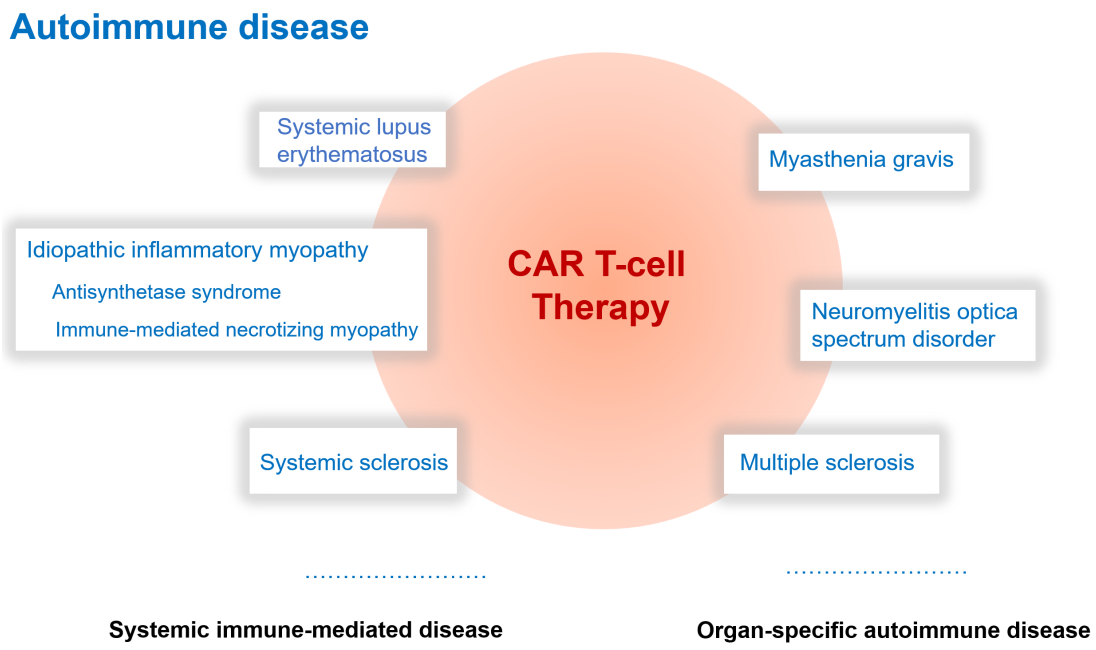

Figure 1. The therapeutic spectrum of CAR T-cells treatment in autoimmune disease.

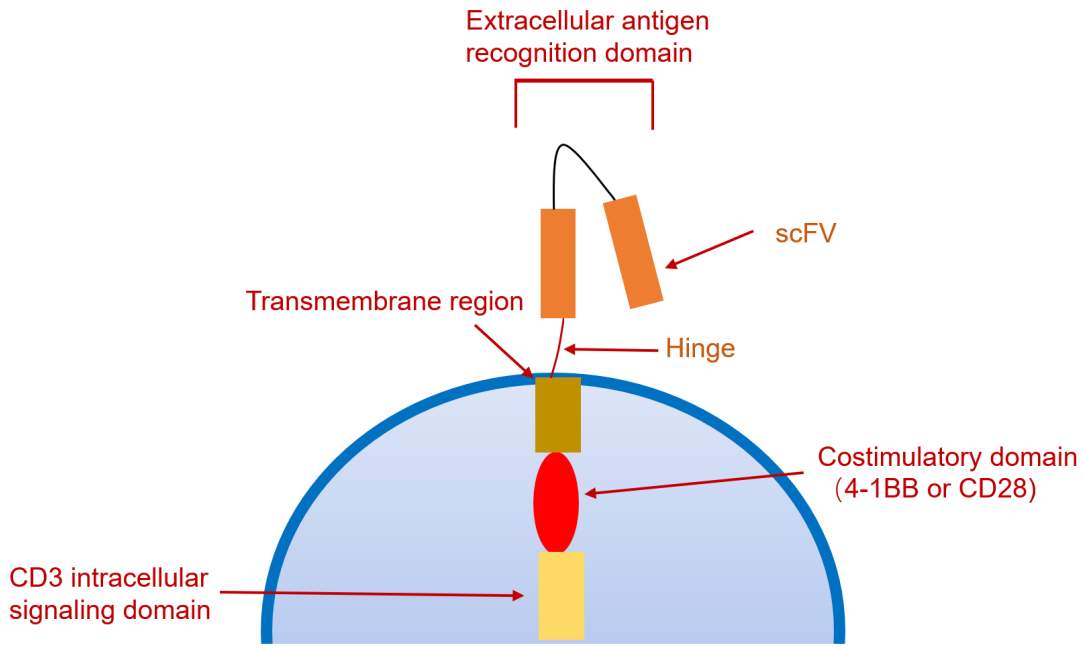

Figure 2. Schematic representation of the CAR T structure. The CAR contains a single-chain variable fragment (scFv), a transmembrane region, an intracytoplasmic costimulatory domain (usually 4-1BB or CD28 in 2nd-generation constructs), and a CD3 intracellular signaling domain.

murine SLE models, resulting in improved survival rates and attenuated manifestations of skin lesions and glomerulonephritis (*19*). These findings also suggested potential prevenative applications of CAR T-cell therapy in SLE.

A breakthrough in clinical application occurred in 2021 when Mougiakakos *et al.* reported the first case of CD19-targeted CAR T-cell therapy in autoimmune disease: a 21-year-old woman with refractory SLE. The therapy demonstrated robust *in vivo* expansion of CAR T-cells followed by a characteristic decline, with persistent detection of circulating CAR T-cells for seven weeks. Notably, the patient experienced no adverse events such as cytokine release syndrome (CRS), neurotoxicity, or prolonged cytopenia, while maintaining sustained B-cell depletion. Within five weeks, double-stranded DNA autoantibody levels decreased significantly, accompanied by clinical remission

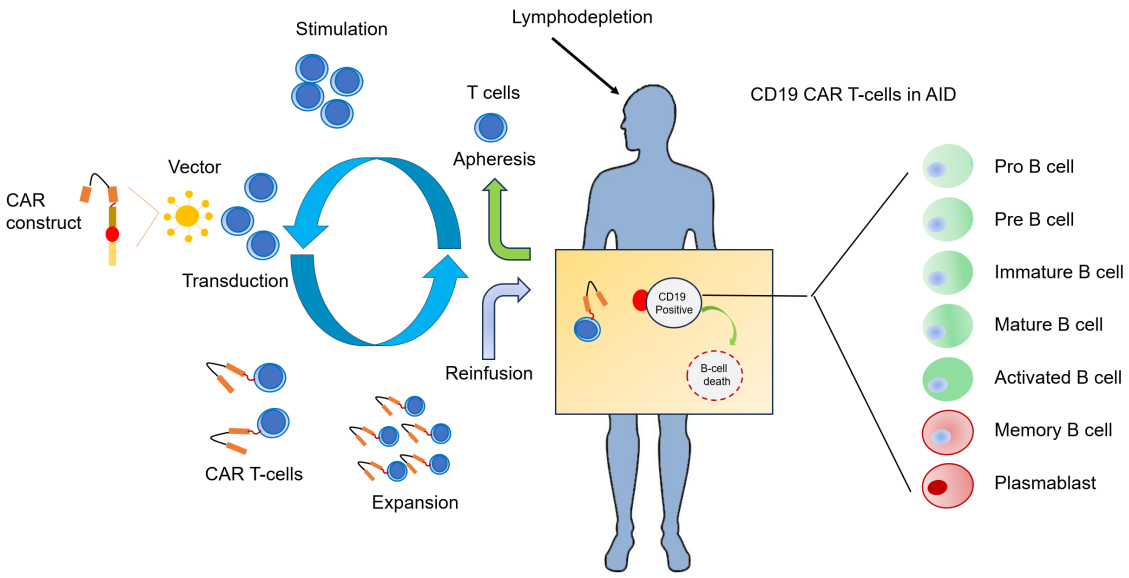

Figure 3. Illustration of autologous CAR T-cells treatment. T cells are collected from the patients' peripheral blood by apheresis. Next, T cells are genetically modified to include a CAR and finally expanded to obtain millions of CAR T-cells. After lymphodepleting chemotherapy, CAR T-cells are reinfused into the patients. Anti-CD19 CAR T-cells, for example, recognise CD19 expressed at various stages of the B-cell lineage, become activated, and destroy the target cell. *Abbreviations*: AID, autoimmune disease. CAR, chimeric antigen receptor.

evidenced by improved proteinuria and SLE Disease Activity Index scores. The rapid reduction in dsDNA autoantibodies suggested CD19-expressing plasmablasts as their primary source (*20*).

Building on these initial successes, subsequent studies have evaluated the safety and clinical efficacy of CD19-targeted CAR T-cell therapy in patients with treatment-resistant or moderate-to-severe SLE. Despite variations in dosing regimens and follow-up durations (up to 29 months), the findings collectively confirm the therapy's transformative potential. Most patients achieved either disease remission or a low disease activity state, accompanied by normalized serologic parameters, while long-term safety was characterized by only mild infections. These results position CAR T-cell therapy as a groundbreaking advancement for refractory SLE, particularly for severe clinical phenotypes including lupus nephritis and immune thrombocytopenia (*21-24*). Furthermore, its efficacy in penetrating sanctuary sites may be key to its success in complex manifestations such as neuropsychiatric lupus (*25*).

Feng *et al.* found that peripheral $CD19^+$ B cells and bone marrow $CD19^-BCMA^+$ long-lived plasma cells (LLPCs) are dominant autoantibody sources, indicating that successful CAR T-cell therapy for SLE must target both cell populations. Indeed, dual anti-CD19/anti-BCMA CAR T-cell therapy has demonstrated good safety and promising efficacy in treatment-refractory SLE. Multi-omic analyses confirmed the elimination of autoreactive $CD19^+BCMA^+$ clones, along with reconstitution of naïve B cells and downregulation of pathogenic immune signatures—findings that point to improved immune homeostasis. Longitudinal monitoring of three patients for one year revealed sustained eradication of pathogenic clones, hinting at a potential cure (*26*).

3.1.2. Idiopathic inflammatory myopathy: Antisynthetase syndrome (ASS)

Müller *et al.* documented remarkable therapeutic success with CD19 CAR T-cell therapy in ASS. By day 180 post-administration, the patient demonstrated near-complete recovery of muscle strength and endurance, accompanied by significant improvements in biochemical markers and imaging studies (*27*). Extended observations from other studies confirmed that patients maintained major clinical responses without the need for glucocorticoids or other immunosuppressive agents for up to 12 months (*28,29*).

Müller *et al.* demonstrated that BCMA CAR T-cell therapy can restore drug-free remission after relapse of ASS after the first CD19 CAR T-cell treatment. This case highlights the challenges in CAR T-cell reinfusion, underscores the potential of alternative targets and therapeutic products, and suggests that plasma cell depletion may enhance therapeutic outcomes in treatment-refractory patients (*30*).

3.1.3. Immune-mediated necrotizing myopathy (IMNM)

Qin *et al.* reported significant therapeutic success with BCMA CAR T-cell therapy in IMNM, documenting improved limb strength by month three and near-normal neurological function at nine months. Clinical and radiological improvements persisted beyond 18 months without additional immunomodulatory intervention. The study revealed comprehensive immune system

modulation, demonstrated through longitudinal single-cell RNA analysis and detailed receptor sequencing. Notable findings included specific CD8+ CAR T-cell characteristics, featuring enhanced NK-like phenotype patterns and distinct cell death tendencies compared to malignancy applications (*31*).

3.1.4. Systemic sclerosis

Third-generation CD19 CAR T-cell combination therapy demonstrated significant efficacy in systemic sclerosis, as reported by Merkt *et al.* (*32*). Treatment resulted in improved skin fibrosis and lung function, with dramatic regression visible on imaging studies. Eleven-month follow-up confirmed sustained improvement through normalized inflammatory markers (CRP and hsTNT) and declining autoantibody levels. In a cohort of four patients, marked reductions in global disease and skin activity were observed six months post-treatment, enabling complete discontinuation of glucocorticoids and other immunosuppressive medications (*22,33*).

3.2. CAR T-cell therapy in organ-specific autoimmune disease

3.2.1. Myasthenia gravis

Granit *et al.* demonstrated significant therapeutic potential of BCMA-directed mRNA CAR-T cell therapy in generalized myasthenia gravis, with symptom improvement emerging after 5–8 weeks and persisting up to 12 months. This approach notably eliminated the requirement for lymphodepletion chemotherapy while avoiding common complications such as CRS, neurotoxicity, and hematological toxicities (*34*). Tian *et al.* demonstrated that proliferating cytotoxic-like $CD8^+$ T cell clones were identified as primary effectors in autoimmunity, whereas pre-infusion cytotoxic/proliferation impairment and profound mitochondrial dysfunction in $CD8^+$ T cells—along with subsequent generation of defective CAR T-cell products—may explain patient-specific therapeutic outcomes (*35*). Additional studies demonstrated that CD19 CAR T-cell infusion improved muscle strength, correlating with improved antibody profiles (*36,37*). Dual-target CAR T-cell (*e.g.*, BCMA-CD19) showed promise in Zhang *et al.*'s cohort, where refractory generalized MG patients achieved remission, suggesting broader antigen targeting may reduce relapse risk (*38*).

3.2.2. Neuromyelitis optica spectrum disorder (NMOSD)

Qin *et al*.'s research revealed promising outcomes for BCMA CAR T-cell therapy in relapsed/refractory AQP4-IgG seropositive NMOSD patients. During a median 5.5-month follow-up, all eleven patients maintained relapse-free status with improved disability measures and quality-of-life outcomes, accompanied by declining serum AQP-4 antibody levels. Mechanistic studies identified proliferating cytotoxic-like CD8+ CAR T-cell clones as primary autoimmunity effectors. The enhanced chemotactic properties of anti-BCMA CAR T-cells facilitated blood-CSF barrier crossing, enabling effective elimination of CSF plasmablasts and plasma cells while suppressing neuroinflammation. Notably, CD44-expressing early memory phenotype correlated with sustained CAR T-cell persistence (*39,40*).

3.2.3. Multiple sclerosis (MS)

Fischbach *et al.* reported pioneering treatment of progressive MS using fully human CD19 CAR T-cell therapy (KYV-101) in two patients. The therapy demonstrated favorable safety profiles with evidence of CAR T-cell presence and expansion in cerebrospinal fluid, notably without neurotoxicity. The observed intrathecal antibody reduction, coupled with CAR T-cell expansion, suggested effective targeting of CNS CD19+ cells (*41*). Qin *et al.* demonstrated that anti-BCMA CAR-T cells could not only enter CNS but also reduce oligoclonal bands (OCBs) and kappa free light chains (KFLC), leading to significant functional improvement in the progressive multiple sclerosis (PMS) cohort, with follow-up of up to 9 months. Notably, CAR T-cells in the cerebrospinal fluid (CSF) exhibited a delayed peak and longer persistence compared with those in peripheral blood and bone marrow. Critically, TSPO-PET imaging revealed that this clinical improvement was likely mediated by alleviation of microglia-mediated neuroinflammation (*42*).

3.2.4. Chronic inflammatory demyelinating polyneuropathy

Dong *et al.* reported two patients had no severe adverse events and achieved drug-free remission within 6 months post–CAR T-cell therapy. One patient experienced relapse 12 months post-infusion following severe COVID-19 infection, and the other patient had achieved sustained symptom remission for 24 months post-infusion. Disease relapse coincided with pathogenic B cell reactivation and recurrence of axon/myelin-targeting autoantibodies or pathogenic peptides, while B cell metabolic reprogramming featuring hyperglycolysis constituted a mechanistic driver of relapse (*43*).

4. CAR T-cell toxicity in autoimmune diseases

CAR T-cell therapies are associated with significant adverse events, including CRS, immune effector cell-associated neurotoxicity syndrome (ICANS), and hemophagocytic lymphohistiocytosis, all of which present complex clinical management challenges (*44*). CRS manifests as an acute systemic inflammatory syndrome characterized by sepsis-like symptoms,

including fever and hypotension. The underlying mechanism involves activated CAR T-cells interacting with myeloid cells, leading to substantial cytokine release. The standard therapeutic approach includes tocilizumab (anti-interleukin-6) administration and steroid therapy (*45*).

ICANS typically develops within days to weeks following CAR T-cell administration. While its precise mechanisms remain incompletely understood, current evidence suggests that CAR T-cells secrete pro-inflammatory cytokines into the circulation, leading to blood-brain barrier disruption. This disruption results in cytokine accumulation within the central nervous system and subsequent activation of resident microglial cells (*46*). Initial manifestations include dysgraphia, word-finding difficulties, tremor, cognitive impairment, and fatigue, necessitating consistent monitoring. More severe cases may present with epileptic seizures, increased intracranial pressure, and potentially, coma (*47*). Treatment protocols typically involve dexamethasone administration, with high-dose methylprednisolone reserved for grade 4 ICANS (*48*). Cytopenia represents another significant adverse effect, attributed to either haematotoxic lymphodepletion or underlying immunological processes (*49*). Extended cytopenia particularly warrants attention due to increased susceptibility to infectious complications.

However, a notable distinction exists between cancer and autoimmune disease applications of CAR T-cell therapy. A meta-analysis indicates that CRS occurs in approximately 55.3% of patients, with about 18.5% being severe (*50*). Additionally, while incidence of ICANS ranges from 2% to 64% (severe: 0–50%) (*51*), two Phase I trials reported hemophagocytic lymphohistiocytosis in 32.7% and 35.6% of patients, respectively—a complication with a mortality rate that can reach 80% (*52*). Patients with autoimmune diseases generally demonstrate superior tolerability, experiencing either no or mild manifestations of CRS or ICANS (approximately 61% and 3%, respectively) (Table 1). This markedly improved safety profile may be attributed to the substantially lower antigen burden present in autoimmune conditions compared to B-cell malignancies (*39*). This differential toxicity profile highlights the potential advantages of CAR T-cell therapy in autoimmune disease applications, though continued vigilance and monitoring remain essential components of clinical management.

5. Future in CAR

5.1. Current limitations and allogeneic approaches

Hundreds of studies involving CAR T-cell therapy for autoimmune diseases are registered on *ClinicalTrials.gov*, predominantly in the United States and China, with BCMA and CD19 being the main targets. However, to date, FDA-approved CAR T-cell therapies remain exclusively autologous, involving complex multistep processes. This approach presents significant challenges, including manufacturing and transit delays, elevated costs, and dependence on patient T-cell fitness, collectively limiting therapeutic accessibility (*53*). Several challenging stages—including scale-up, cell source selection, gene delivery, purification, storage, and quality control—can compromise the quality of CAR immune cells and increase cost per dose. Therefore, it is critical to select an appropriate manufacturing strategy (*e.g.*, centralized, point-of-care, next-day, or *in vivo* generation) and to integrate innovations like novel gene transfer methods, alternative cell sources, automation, and artificial intelligence to overcome these bottlenecks and ensure success (*54*).

Allogeneic or "off-the-shelf" CAR T-cells derived from healthy donors offer several advantages: immediate availability of cryopreserved products, standardized production, opportunities for multiple modifications, potential for redosing or combining CAR T-cells targeting different antigens, and reduced costs. However, these cells risk triggering life-threatening graft-versus-host disease and may face rapid host immune elimination. Recent advances in gene editing, particularly TRAC and/or B2M knockout to reduce TCR or MHC class I expression, show promise in addressing these challenges (*55,56*). Wang *et al.* demonstrated the first successful application of off-the-shelf allogeneic CD19-targeted CAR T-cell in treating one relapsing SRP-IMNM case and two relapsing diffuse cutaneous systemic sclerosis cases. The engineered cells persisted beyond three months, achieving complete B-cell depletion within two weeks. Six-month follow-up revealed deep remission without significant adverse events, evidenced by improved clinical response indices and reversed inflammation and fibrosis (*56*). Recently, Yang *et al.* reports the first clinical application of allogeneic anti CD19 CAR T-cell therapy in patients with refractory SLE, demonstrating significant clinical remission and a favorable safety profile. No patients developed immune ICANS or GVHD during treatment (*57*). Wang *et al.* also got favorable results with the allogeneic CD19-targeted CAR T-cell therapy (*58*).

5.2. CAR T-cell innovation

Chimeric autoantibody receptor (CAAR) T cell technology represents a significant advancement, potentially enabling selective elimination of pathogenic B cells while preserving healthy B cells. Oh *et al.* developed a MuSK-CAAR system comprising the MuSK autoantigen linked to CD137-CD3ζ signaling domains, demonstrating specific cytotoxicity against B cells expressing anti-MuSK surface autoantibodies (*59*). In an MG mouse model, MuSK-CAART reduced anti-MuSK IgG without decreasing B cells or total

IgG levels, reflecting MuSK-specific B cell depletion. Specific off-target interactions of MuSK-CAART were not identified *in vivo*, in primary human cell screens or by high-throughput human membrane proteome array. This technology has progressed to phase 1 clinical trials for MuSK autoantibody-positive MG treatment (*59*).

Recent developments include DNA-CAART cells specifically targeting anti-dsDNA autoantibody-expressing B cells, showing promising results in lupus nephritis treatment (*60*). Similarly, DSG3-CAART has demonstrated efficacy in mucosal pemphigus vulgaris, with successful preclinical studies enabling first-in-human trials (*61*). Additional applications are being explored in NMDAR encephalitis (*62*) and experimental autoimmune encephalomyelitis (*63*).

5.3. Alternative cell therapy approaches

CAR-NK cells present distinct advantages over CAR T-cells, offering enhanced tumor-specific targeting and cytotoxicity through co-stimulatory molecules like NKG2D and CD244. These cells demonstrate reduced adverse effects and lower production costs, though challenges persist regarding persistence and transduction efficiency (*64*). Gao *et al.* firstly showed that allogeneic CD19-targeted CAR NK cells were tolerable, with minimal treatment-related adverse events that have burdened other effective immunotherapies, and showed encouraging preliminary efficacy in patients with relapsed or refractory SLE who had been systematically pretreated (*65*). iPSC-derived CD19/BCMA dual-targeting CAR NK cells also demonstrated its treatment effect in systemic sclerosis (*66*).

Regulatory T cells (Tregs) represent another promising approach, functioning through direct cellular interactions and immunosuppressive cytokine production (*67*). CD19-CAR Tregs have demonstrated efficacy in suppressing antibody production and B-cell differentiation *via* TGF-β-dependent mechanisms, with reduced GvHD risk compared to conventional CAR T-cells (*68*). In SLE models, Fox19CAR-Tregs have shown ability to restrict autoantibody generation and restore immune system composition without significant toxicity (*69*).

In vivo CAR T-cell engineering aims to generate CAR T-cells directly within the patient's body. This approach seeks to overcome the limitations of conventional *ex vivo* manufacturing—such as its labour-intensive processes and limited production capacity—by eliminating need for complex external cell processing and logistics. It also holds the potential to enhance clinical outcomes. Driven by recent advances in virology, RNA therapeutics, and nanotechnology, the field is undergoing a radical transformation. The current strategy employs targeted delivery systems, including lentiviral vectors and lipid nanoparticles, to introduce CAR-encoding genetic material into the body's endogenous T cells (*70*). In their preliminary study, Wang *et al.* found that cell-targeted LNP technology can successfully generate functionally active CD19 CAR T-cells *in vivo* in patients with SLE. These CD19 CAR T-cells were capable of depleting B cells, modulating disease-associated autoantibodies, and reducing disease activity. The treatment was associated with only low-grade CRS and no other major toxic effects (*71*).

6. Conclusions

CAR T-cell therapy signifies a pivotal paradigm shift from chronic immunosuppression toward a potential "one-time curative" strategy in autoimmune diseases. To fully realize this transformative potential, rigorous long-term immune monitoring and expansive multicenter trials are essential to confirm durable efficacy and safety.

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Review

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The skin as a sentinel organ for neurodegeneration: An underrecognized target for dementia prevention

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SUMMARY: Dementia prevention increasingly requires attention to modifiable systemic inflammatory stressors. In older adults, bullous pemphigoid (BP), herpes zoster (HZ), psoriasis, atopic dermatitis (AD), rosacea, prurigo nodularis (PN), and chronic pruritus are not merely disorders limited to the skin; they may signal or amplify neuroimmune vulnerability. Observational studies link BP with dementia and Alzheimer's disease, HZ with incident dementia and vascular cognitive injury, and psoriasis, AD, rosacea, or PN with smaller but biologically plausible cognitive risks. The proposed skin-brain axis integrates cytokine spillover, endothelial activation, blood-brain barrier dysfunction, BP180/BP230 autoantigen sharing, varicella-zoster virus neurotropism and vasculopathy, barrier failure, dysbiosis, itching-induced fragmented sleep, and medication or frailty-related cognitive toxicity. Clinically, cognitive impairment also worsens skin surveillance, hygiene, topical adherence, and recognition of pain, itching, infection, or blistering. Although causality and dementia prevention remain unproven, the evidence justifies proactive dermatological care in older adults and greater cognitive vigilance in older patients with severe inflammatory or pruritic dermatoses. Recombinant zoster vaccination, prompt antiviral therapy, steroid-sparing BP strategies, modern anti-inflammatory treatment for AD, psoriasis, and PN, and systematic attention to sleep, itching, caregiver capacity, and the medication burden are practical, low-regret steps while prospective brain-relevant trials are developed. This translational framework highlights mechanisms clinicians can now interrupt and endpoints investigators can soon measure. We propose that the skin should be recognized as a sentinel organ for neurodegeneration and that dermatological disease represents a potentially modifiable contributor to cognitive decline.

Keywords: dementia, skin-brain axis, bullous pemphigoid, herpes zoster, psoriasis, atopic dermatitis, rosacea, prurigo nodularis

1. Introduction

Population aging has made dementia a defining public-health and geriatric-care challenge. The World Health Organization estimates that the number of adults age 60 years and older will increase from 1.0 billion in 2020 to 1.4 billion in 2030 and 2.1 billion in 2050, while the population age 80 years or older is projected to triple to 426 million over the same period (*1,2*). Dementia is expanding in parallel: an estimated 57 million people were living with dementia worldwide in 2021, more than 60% of whom were living in low- and middle-income countries, and Global Burden of Disease forecasting suggests that this number may reach 152.8 million by 2050 (*3,4*). These trends have shifted dementia prevention away from a narrow focus on late-stage neurodegeneration toward cumulative, modifiable stresses across a person's life course. In addition to vascular, metabolic, sensory, and lifestyle risks, prevention frameworks increasingly need to account for peripheral inflammation, infection, sleep disruption, medication toxicity, frailty, and other systemic stressors that may erode cognitive reserve before dementia is clinically established.

The skin is a distinctive entry point into this broader prevention framework because it is visible, accessible, immune-active, and continuously exposed to environmental, microbial, inflammatory, vascular, and neural signals. Aging skin is characterized by impaired barrier repair, xerosis, dysregulated immunity, sensory dysfunction, vascular fragility, and slower wound healing, while cognitive impairment reduces the ability to recognize itching, pain, infection, blistering, adverse effects of medication, or early skin breakdown and it

limits adherence to topical regimens (*5-7*). However, the skin should be considered not only a vulnerable target in dementia care, but also a potential sentinel organ for dementia-related biology. Chronic inflammatory, infectious, autoimmune, and pruritic skin diseases may reveal systemic immune activation, neurovascular stress, fragmented sleep, pain, itching, and frailty-related vulnerability in ways that are directly observable in routine dermatological practice.

This review focuses on inflammatory, autoimmune, infectious, and pruritic dermatoses with emerging dementia-related signals, including bullous pemphigoid (BP), herpes zoster (HZ), psoriasis, atopic dermatitis (AD), rosacea, prurigo nodularis (PN), and chronic pruritus. The strength and directionality of evidence differ substantially across these conditions. BP and HZ currently provide the most distinctive disease-specific signals: BP because of its strong association with dementia and biologically plausible BP180/BP230-related neurocutaneous autoimmunity, and HZ because varicella-zoster virus neurotropism, vasculopathy, antiviral treatment, and zoster vaccination create a temporally discrete and potentially preventable neurocutaneous model. In contrast, psoriasis, AD, rosacea, PN, and chronic pruritus offer more modest, heterogeneous, or hypothesis-generating evidence, although their links with systemic inflammation, itching, sleep loss, a mood disturbance, vascular comorbidity, and the treatment burden remain clinically important.

We have organized the evidence into three clinically testable axes linking skin disease and cognitive vulnerability: neuroinflammation, neurovascular injury, and neurofunctional disruption. The neuroinflammatory axis integrates cytokine spillover, endothelial activation, blood-brain barrier vulnerability, microglial and astrocytic priming, and BP-related autoantigen sharing. The neurovascular axis emphasizes HZ/varicella-zoster virus (VZV)-related vasculopathy, endothelial injury, thrombosis, ischemic burden, and vascular cognitive impairment. The neurofunctional axis captures itching, pain, fragmented sleep, sedating or anticholinergic medication exposure, corticosteroid toxicity, infection, frailty, delirium risk, and caregiver-dependent treatment failure. This framework does not assume that treating a skin disease prevents dementia. Rather, it proposes that a dermatological disease can provide visible, modifiable, and research-ready signals through which dermatologists, geriatricians, neurologists, and primary-care clinicians can identify cognitive vulnerability earlier, they can reduce low-regret contributors to brain stress, and they can design prospective studies with brain-related endpoints.

2. Why this issue deserves attention

Dementia is a dominant challenge of population aging, and current prevention frameworks emphasize management of cumulative vascular, inflammatory, sensory, sleep, and lifestyle risks (*8,9*). At the same time, inflammatory and pruritic dermatoses are common in later life, frequently undertreated in frail patients, and often dismissed as problems of comfort or appearance. This separation is increasingly untenable. A skin-brain axis model proposes bidirectional communication: chronic cutaneous inflammation may contribute to systemic and central neuroimmune activation, whereas cognitive decline impairs barrier care, scratching control, hygiene, treatment adherence, and timely reporting of early blistering, pain, infection, or itching (*10*).

3. Clinical and interventional signals linking skin disease and cognition

The strongest dermatological signal currently comes from BP, a prototypic inflammatory blistering disorder of late life. A systematic review and meta-analysis found that BP is associated with adverse cognitive outcomes, and observational studies have repeatedly reported increased antecedent dementia in BP cohorts (*11,12*). Mechanistic plausibility is strengthened by evidence that BP180-related autoimmunity may intersect with neuronal tissue, with higher BP180 autoantibody levels reported in patients with Alzheimer's disease and distinct central nervous system (CNS)-related epitope recognition patterns described in neurodegenerative disease (*13,14*). Given that BP also causes severe itching, skin breakdown, sleep disruption, infection risk, and corticosteroid exposure, it is a plausible amplifier of cognitive vulnerability in patients who are already frail. Table 1 summarizes the major clinicopathologic associations.

Beyond epidemiologic overlap, the BP–dementia signal is biologically unusual because BP180/collagen XVII and BP230/dystonin have neuronal isoforms. In Alzheimer's disease, higher serum BP180 autoantibody levels correlate with more severe dementia, and the epitopes recognized in Alzheimer's disease or multiple sclerosis differ from those typically seen in cutaneous BP, suggesting epitope-specific neurocutaneous immunity rather than simple bystander seropositivity (*15,16*). This pattern is consistent with a bidirectional model in which neurodegeneration may expose neural BP antigens and prime autoimmunity, while systemic autoantibody and complement activation sustain a frailty-promoting inflammatory state.

HZ provides a second compelling example. Population-based studies suggest that incident HZ, and particularly when the central nervous system is involved, is associated with a higher risk of subsequent dementia, while antiviral treatment may attenuate this association (*17,18*). Even more provocative are recent vaccine studies showing that zoster vaccination is associated with a lower incidence or delayed diagnosis

Table 1. Associations between skin diseases and cognitive impairment

Skin disease	Associated cognitive outcome(s)	Representative evidence	Practical message
BP	All-cause dementia; Alzheimer's disease; broader neurologic comorbidity	Systematic review/meta-analysis and multiple cohort/case-control studies support an association; BP180-related autoimmunity provides biologic plausibility.	Use cognitive screening and delirium-risk review before systemic corticosteroids; align steroid-sparing strategy, topical feasibility, itching control, infection prevention, and caregiver training.
HZ	Incident dementia; vascular cognitive impairment; higher concern after CNS involvement	Population-based cohorts link HZ with subsequent dementia, while antiviral therapy and zoster vaccination are associated with lower risk.	Treat HZ as a sentinel neurocutaneous event when ophthalmic, CNS-involved, or severe; prioritize vaccination, prompt antivirals, pain/sleep control, and follow-up for delirium or executive decline.
Psoriasis	All-cause dementia; Alzheimer's disease; possible cognitive impairment	Systematic reviews/meta-analyses suggest a modest excess risk, although some studies are heterogeneous or null.	Treat psoriasis as a systemic inflammatory disease and address cardiovascular, mood, and lifestyle comorbidities.
AD	All-cause dementia; neurocognitive burden related to sleep loss, itching, and inflammation	Recent meta-analysis suggests a modest association, but causal inference remains uncertain; symptom burden is substantial.	Use nocturnal itching and fragmented sleep as cognitive biomarkers; track caregiver-reported sleep, simplify topical regimens, and treat inflammation early.
Rosacea	All-cause dementia; Alzheimer's disease	A nationwide Danish cohort found increased risk of dementia and especially Alzheimer's disease; a 2024 commentary highlighted rosacea as an underappreciated dementia-associated dermatosis.	Ask older patients with persistent inflammatory rosacea about memory symptoms, sleep, and medication burden; treat rosacea as a chronic inflammatory disorder rather than a cosmetic condition.
PN/chronic prurigo	Measured cognitive impairment; severe daytime dysfunction; sleep-related cognitive burden	Inpatient data documented cognitive impairment in PN, and phase 2/3 studies confirm profound itching and sleep disturbance as treatable disease domains.	Quantify nocturnal scratching and sleep disruption with diaries or actigraphy when possible; use targeted itching control as a brain-relevant intervention.
Chronic pruritus/xerosis in older adults	Sleep disruption, inattention, low mood, daytime dysfunction; may worsen apparent cognition	High symptom burden and reduced quality of life are consistently documented, especially in older adults.	Perform medication reconciliation, xerosis repair, itching control, and sleep-risk review before escalating sedating or anticholinergic drugs.

Abbreviations: BP, bullous pemphigoid; HZ, herpes zoster; CNS, central nervous system; AD, atopic dermatitis; PN, prurigo nodularis.

of dementia in older adults (*19-21*). These findings do not indicate that recombinant zoster vaccine is a dementia treatment, but they do reinforce the broader principle that prevention of dermatological disease may have neurological relevance. Current immunization recommendations already support 2-dose recombinant zoster vaccination in adults age ≥ 50 years and in immunocompromised adults age ≥ 19 years (*22,23*).

The mechanistic bridge is also stronger in HZ than in most inflammatory dermatoses because VZV is neurotropic, infects vascular endothelium, and activates inflammasome and amyloid-related pathways. Clinically, complicated HZ should therefore be considered a sentinel neurocutaneous event rather than an isolated rash, and particularly in older adults with delirium, gait decline, or new executive dysfunction.

The association between psoriasis and dementia appears more modest and heterogeneous, and yet the direction of the evidence is generally consistent with a systemic inflammatory link. Systematic reviews and meta-analyses suggest a small excess dementia risk in psoriasis, supported by a nationwide cohort study showing increased risk of Alzheimer's disease (*24-26*). Likewise, a recent meta-analysis found that AD was associated with all-cause dementia in longitudinal cohorts, although Mendelian randomization did not confirm a clear causal genetic effect (*27*). Importantly, both psoriasis and AD are now regarded as multisystem inflammatory diseases with important comorbidity implications, and both can produce chronic pruritus, fatigue, poor sleep, anxiety, depression, and reduced physical activity—factors that may worsen cognition even before formal dementia is diagnosed (*28-37*).

The dermatological spectrum is probably broader than these four entities. In a Danish nationwide cohort, rosacea was associated with increased dementia and especially Alzheimer's disease risk, with higher estimates in patients diagnosed in specialist settings (*38,39*). Prurigo nodularis also deserves attention: measurable cognitive impairment has been documented in inpatients, and the disorder couples intense IL-31-induced itching to repeated nocturnal arousal, anxiety, and compulsive

scratching (*40-42*). Even when frank dementia is absent, these states can worsen executive function, medication adherence, and day–night behavioral stability in older adults.

4. How a skin-brain inflammatory axis may operate

4.1. Neuroinflammation

The first axis places chronic cutaneous inflammation in direct conversation with the aging brain. Psoriasis, AD, BP, rosacea, and chronic prurigo can export IL-1β, IL-6, TNF-α, IL-17A/F, IL-23, IL-4, IL-13, IL-31, TSLP, and IL-33 into systemic circulation, where endothelial activation and blood-brain barrier (BBB) vulnerability can amplify microglial and astrocytic responses (*10,28,30,34,43*). BP adds a disease-specific autoimmune trigger: neuronal isoforms of BP180/collagen XVII and BP230/dystonin make epitope spreading a plausible route by which neurodegeneration and cutaneous autoimmunity reinforce each other. This neuroinflammatory axis therefore integrates the former cytokine, BBB, microglial, barrier, dysbiosis, and BP autoantigen mechanisms into one measurable pathway (Table 2, Figure 1). Among the three axes, this is the strongest and most biologically coherent pathway: associations noted at the cohort level provide moderate epidemiologic support, the inflammation-BBB-neuroinflammation sequence is broadly accepted, and data emerging from an atopic dermatitis model implicate IL-17 in BBB disruption, neuroinflammation, and cognitive dysfunction (*28,30*). Nevertheless, these lines of evidence should not be read as direct proof that skin inflammation causes dementia.

4.2. Neurovascular injury

The second axis emphasizes vascular injury, with HZ/VZV reactivation as the clearest dermatological trigger. VZV can infect neural and vascular tissue, activate IL-6 production through TLR2-dependent NF-κB signaling, trigger NLRP3 inflammasome assembly with IL-1β processing, and create amyloidogenic cellular and plasma environments (*44-47*). Clinically, ophthalmic or CNS-involved zoster can converge on endothelial inflammation, vasculitis, thrombosis, white-matter ischemic injury, delirium, gait decline, and vascular cognitive impairment. Psoriasis and rosacea may contribute to the same axis through chronic endothelial activation and microvascular dysfunction, but HZ supplies the most specific and preventable neurovascular model (*17-21,24-28,38,39*). Compared to axis 1, this pathway is supported by strong general evidence that peripheral inflammation can degrade BBB integrity, but direct evidence that cutaneous disease itself causes neurovascular cognitive injury remains limited. The genetic or pathway overlap between psoriasis, AD, Alzheimer's disease, and Parkinson's disease is suggestive rather than definitive, and the vascular-inflammation model is biologically plausible but still largely inferential. For HZ/VZV, the zoster-brain vasculopathy-cognition chain is clinically important

Table 2. Three-axis mechanisms linking skin disease and cognitive impairment

Mechanism	Dermatological examples	Molecular / clinical detail	Potential brain-level consequence	Interpretation
Axis 1: Neuroinflammation	Psoriasis, AD, BP, rosacea, PN/chronic prurigo	Cutaneous IL-1β, IL-6, TNF-α, IL-17/23, IL-4/13, IL-31, TSLP, and IL-33 can prime endothelium and BBB vulnerability; BP180/BP230 epitope spreading adds a disease-specific autoimmune bridge.	BBB dysfunction, microglial and astrocytic priming, cytokine amplification, reduced cognitive reserve	Unifies cytokines, BBB, microglia, barrier failure, dysbiosis, and BP autoantigen sharing into one testable pathway (Evidence level: strongest but still indirect).
Axis 2: Neurovascular injury	HZ/VZV reactivation; psoriasis and rosacea endothelial activation	VZV neurotropism, endothelial infection, vasculitis, thrombosis, ischemia, TLR2/NF-κB signaling, NLRP3 inflammasome activation, and amyloidogenic stress.	Vascular cognitive impairment, white-matter injury, delirium, gait decline, dementia acceleration	Most specific preventable bridge; supports vaccination, urgent antivirals, and neurovascular follow-up after complicated HZ (Evidence level: moderate/inferential; direct evidence limited).
Axis 3: Neurofunctional disruption	AD, PN, BP, chronic pruritus/xerosis	IL-31/TSLP sensory circuits, nocturnal itching, scratching, pain, fragmented sleep, sedating or anticholinergic drugs, systemic corticosteroids, infection, and frailty.	Attention and memory fluctuation, sleep-related cognitive burden, delirium vulnerability, functional decline	Most dermatology-specific clinical axis; nocturnal itching and actigraphy can become cognitive-risk indicators (Evidence level: clinically strong but indirect functional pathway).

Abbreviations: BP, bullous pemphigoid; HZ, herpes zoster; CNS, central nervous system; AD, atopic dermatitis; PN, prurigo nodularis; VZV, varicella-zoster virus.

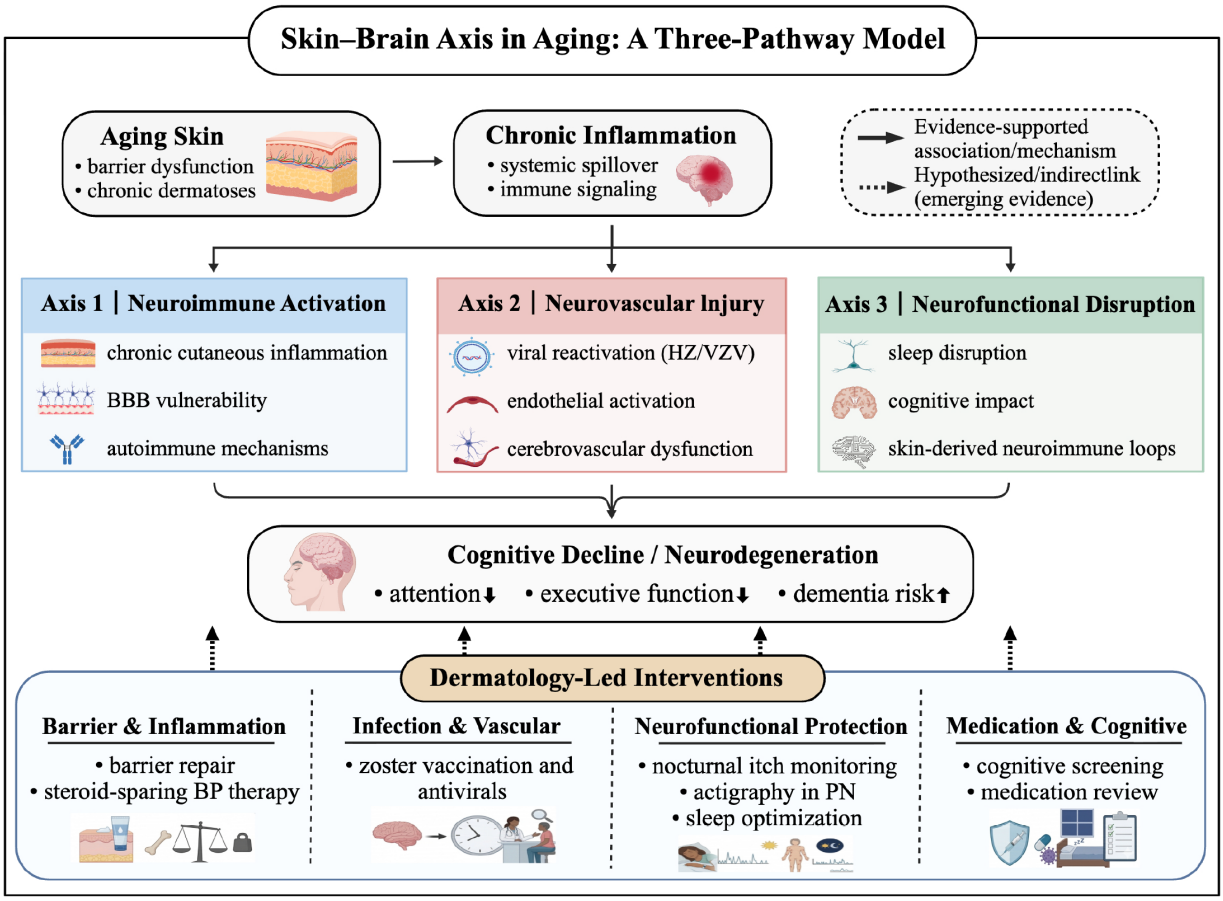

Figure 1. Three-axis skin-brain framework for dermatological control as a dementia-modifying strategy. Aging skin can function as a sentinel organ for neurodegeneration through Axis 1, neuroinflammation (cytokines, BBB vulnerability, microglia, and BP180/BP230-related autoimmunity); Axis 2, neurovascular injury (VZV, endothelial activation, vasculopathy, thrombosis, ischemia, and amyloidogenic stress); and Axis 3, neurofunctional disruption (itching, pain, fragmented sleep, medication toxicity, frailty, and delirium). Dermatology-led interventions--barrier repair, steroid-sparing BP therapy, cognitive screening before corticosteroids, zoster vaccination and antivirals, monitoring of nocturnal itching in AD, actigraphy in PN, sleep optimization, and a medication review--represent practical points at which clinicians can interrupt the pathway. Converging evidence suggests that these axes link cutaneous disease to brain vulnerability, although causality remains to be established. *Abbreviations*: BP, bullous pemphigoid; HZ, herpes zoster; PN, prurigo nodularis; BBB, blood-brain barrier; VZV, varicella-zoster virus.

but remains based on a handful of clinical observations rather than systematic causal evidence.

4.3. Neurofunctional disruption

The third axis depicts how skin disease degrades brain function even when structural neurodegeneration in not yet evident. Nocturnal itching, pain, burning, dysesthesia, scratching, and anxiety repeatedly fragment sleep, reduce slow-wave sleep, impair daytime attention, and disrupt circadian and autonomic stress responses. In AD and PN, IL-31-, TSLP-, periostin-, and IL-33-linked sensory-neuroimmune loops make itching both a symptom and a quantifiable brain-related mediator. In BP and chronic pruritus, sedating antihistamines, anticholinergics, opioids, systemic corticosteroids, infection, and frailty can compound chronic vulnerability with reversible confusion (*15,34,35,48*). This axis is especially dermatology-specific because itching intensity, nocturnal scratching, topical feasibility, actigraphy, and sleep response are directly visible and modifiable in skin clinics. The clinical evidence is convincing but mechanistically indirect: skin disease can reliably induce itching, pain, and sleep fragmentation, and sleep disturbance is a well-established contributor to cognitive decline, whereas evidence that this pathway directly causes structural neurodegeneration remains limited. Accordingly, axis 3 is best defined as a functional and behavioral route to cognitive vulnerability rather than a direct neurodegeneration mechanism.

5. Emerging interventional evidence: From dermatology trials to brain-related endpoints

A clearer evidence hierarchy helps preserve scientific caution without weakening the central message (Table 3). The strongest dementia-related signals currently come from zoster vaccine natural experiments and matched cohort analyses, followed by disease-specific epidemiology with biological specificity, mechanistic

Table 3. Evidence hierarchy for dermatological control as a dementia-modifying strategy

Evidence tier	Evidence type	Representative examples	Brain-relevant inference	Dermatology-specific action
1	Quasi-experimental prevention signal	Live, recombinant, and AS01-adjuvanted zoster vaccine analyses	A visible skin-preventive intervention may alter dementia timing or diagnosis-free survival.	Make zoster vaccination review routine in dermatology and geriatric skin visits.
2	Disease-specific epidemiology plus biological specificity	BP with dementia and BP180/BP230 neurocutaneous autoimmunity; complicated HZ with cognitive outcomes	Certain dermatoses behave as sentinel organs for brain vulnerability rather than nonspecific comorbidities.	Use BP and complicated HZ as triggers for cognitive screening, delirium-risk review, and caregiver planning.
3	Mechanistic and experimental support	Cytokine-BBB-microglia signaling; VZV inflammasome and amyloidogenic signaling; endothelial activation	The three axes are biologically testable with inflammatory, vascular, imaging, sleep, and neurocognitive endpoints (The relative confidence differs by axis: Axis 1 is the strongest mechanistic pathway, Axis 2 is plausible but more speculative, and Axis 3 is clinically robust but functionally indirect).	Embed mechanistic sampling and cognitive outcomes into dermatology cohorts and trials.
4	Dermatology RCTs targeting brain-relevant mediators	BLISTER in BP; dupilumab in AD and PN; nemolizumab in PN; vascular imaging trials in psoriasis	Treatments already modify steroid burden, itching, sleep, scratching, or vascular inflammation--the mediators most likely to affect cognition.	Choose therapies with attention to sleep, itching, delirium, medication toxicity, and frailty rather than skin scores alone.
5	Clinic-level sentinel monitoring	Nocturnal itching in AD, actigraphy in PN, steroid decisions in BP, ocular/CNS HZ follow-up	Dermatology can identify risk earlier than memory clinics because the relevant signals are visible, symptomatic, and longitudinal.	Track nocturnal itching, scratching, topical feasibility, caregiver capacity, and medication burden as cognitive-risk indicators.

Abbreviations: BP, bullous pemphigoid; HZ, herpes zoster; CNS, central nervous system; AD, atopic dermatitis; PN, prurigo nodularis; BBB, blood-brain barrier; VZV, varicella-zoster virus; RCTs, randomized controlled trials.

studies, and dermatology trials that improve brain-related mediators such as itching, sleep, steroid burden, and vascular inflammation. This ladder supports a practical translation: dermatological control should be evaluated not only by with skin clearance but also with delirium, sleep, cognitive fluctuations, gait, caregiver burden, medication toxicity, and biomarker endpoints. With regard to BP, the BLISTER trial showed that doxycycline was safer than prednisolone over 52 weeks as an initial strategy, a clinically meaningful finding for frail older adults at risk of delirium, infection, and steroid myopathy (*48*). With regard to AD, dupilumab produced rapid and sustained improvement in sleep across five randomized trials (*49*). With regard toa1 PN, dupilumab and nemolizumab alleviated itching and improved sleep within days to weeks (*41,42*). Psoriasis provides a useful cautionary note: vascular imaging endpoints in biologic trials have been more difficult to shift than cutaneous scores, indicating that brain-related pathways may need to be observed longer or measured using more specific biomarkers (*50*) (Table 4).

6. What should clinicians do now?

The key message is practical rather than speculative. Older adults and cognitively impaired patients should receive better care to prevent skin disease and be treated earlier, not only because skin disorders are distressing, but because uncontrolled cutaneous inflammation may contribute to broader neurologic vulnerability. For BP, guideline-concordant anti-inflammatory treatment, itching control, infection prevention, wound care, and steroid stewardship are essential (*15*). For HZ, vaccination, prompt antiviral treatment, and a closer neurological follow-up after a complicated infection are reasonable low-regret measures (*17-23*). For psoriasis and AD, clinicians should actively suppress inflammation, restore the barrier, address sleep and mood, simplify regimens, and avoid chronic systemic corticosteroids where modern guideline-supported options exist (*27,31-34,49*). These actions are summarized in Table 5.

For rosacea and chronic prurigo, clinicians should also think beyond appearance scores. Refractory burning, flushing, facial dysesthesia, or nocturnal pruritus may signal broader neurovascular or neuroimmune dysregulation, warranting explicit assessment of sleep quality, mood, subjective cognitive change, and caregiver burden. Across all older patients, medication reconciliation should specifically flag first-generation antihistamines, benzodiazepines, anticholinergic co-prescriptions, and repeated corticosteroid bursts.

Table 4. Interventional and experimental evidence relevant to the skin-brain axis

Intervention/ condition	Design/population	Brain-relevant endpoint	Main results	Interpretation
Live zoster vaccine	Natural experiment in Wales; older adults eligible by birth-date cutoff	Incident dementia over 7 years	Vaccination associated with 20% relative reduction in new dementia diagnoses.	Best current quasi-experimental evidence that a dermatological preventive intervention may alter dementia risk (*20*).
Recombinant zoster vaccine (Shingrix)	Matched EHR-based natural experiment comparing recombinant *vs.* live vaccine	Time lived without dementia diagnosis	Recombinant vaccine associated with 17% longer diagnosis-free time, equivalent to 164 additional days without dementia diagnosis.	Supports a clinically meaningful vaccine signal and motivates trials focused on mechanism and causality (*19*).
Doxycycline-first strategy in BP	Pragmatic non-inferiority RCT; 253 analyzable BP patients, mean age 77.7 years	Severe/life-threatening/ fatal treatment-related events at 52 weeks	Short-term blister control was lower than prednisolone, but long-term severe adverse events were much lower with doxycycline (18.2% *vs* 36.3%).	Not a dementia trial, but highly relevant because steroid toxicity and frailty can worsen cognition in older BP patients (*48*).
Dupilumab in AD	Five randomized, double-blind, placebo-controlled trials, pooled N=2,632	Sleep loss and sleep disturbance	Sleep improved rapidly and durably, with significant separation from placebo beginning in week 1-2.	Provides interventional support for the itching-sleep-cognition pathway (*49*).
Dupilumab in PN	Two randomized phase 3 trials (PRIME/PRIME2)	Worst itching NRS and skin lesion response	Both trials met primary and key secondary endpoints, with a marked reduction in itching and alleviation of lesions.	Demonstrates that one of the most cognitively burdensome itching disorders is now targetable with modern therapy (*41*).
Nemolizumab in PN	Phase 2 randomized trial/ post hoc sleep analysis	Sleep disturbance and scratching during sleep	Improvement in sleep disturbance emerged within days; actigraphy showed reduced scratching during sleep.	Particularly relevant to cognitive vulnerability induced by chronic nocturnal arousal (*42*).
Secukinumab in psoriasis (VIP-S)	Randomized placebo-controlled trial, $n = 91$	Aortic vascular inflammation by FDG-PET/CT	Cutaneous improvement was achieved, but short-term vascular imaging improvement was neutral.	Important negative/neutral comparator showing that brain-relevant systemic endpoints may not normalize as quickly as skin scores (*50*).

Abbreviations: BP, bullous pemphigoid; AD, atopic dermatitis; PN, prurigo nodularis.

Being mindful of the converse view is important. Patients with mild cognitive impairment or dementia are less able to report itching, adhere to topical regimens, recognize secondary infection, or tolerate burdensome full-body treatment plans. Dermatologists should therefore ask about memory impairment, missed medications, falls, nighttime agitation, and caregiver capacity when evaluating older patients with severe inflammatory dermatoses. Geriatricians and neurologists should add a routine skin inspection, xerosis care, itching screening, and a vaccination review to dementia care. A skin-limited model of care is no longer adequate for this population.

A practical research-ready workflow would include: baseline cognitive screening in older patients with BP, HZ, severe AD, severe psoriasis, rosacea with a substantial inflammatory burden, or chronic prurigo; structured recording of nocturnal itching and sleep loss; and longitudinal tracking of steroid exposure, vaccination status, falls, delirium, and caregiver-reported functional changes. These measures are simple enough for clinical use and could rapidly generate pragmatic data.

7. Conclusion

Healthy skin and healthy cognition should not be siloed. Current evidence does not prove that treating skin disease will prevent dementia, but it does support a biologically coherent and clinically actionable hypothesis: chronic skin inflammation, barrier dysfunction, viral reactivation, and itching-related physiological stress may all feed a skin-brain inflammatory axis. Accordingly, older adults and people with cognitive impairment should receive more proactive dermatological care, while older patients with severe skin disease need to be closely monitored for cognitive decline. An integrated approach is already justified on clinical grounds, and future prospective studies should determine how well it can protect the brain. The next generation of studies should pair dermatological interventions with brain-related endpoints—cognitive trajectory, delirium, actigraphy, endothelial biomarkers, neurofilament light, MRI white-matter burden, and pragmatic vaccination or steroid-sparing trials in older adults. Writings on this topic are most persuasive when they are honest about causality

Table 5. Guideline-informed clinical actions at the skin-brain interface

Condition/ setting	Skin-focused action	Cognition-focused action	Guideline/consensus anchor	Key caveat
BP	Use guideline-concordant anti-inflammatory treatment, wound care, infection prevention, itching control, and steroid-sparing strategies; make cognitive status part of the treatment choice before systemic corticosteroids.	Document baseline cognition, delirium risk, falls, sleep disruption, caregiver ability to apply topical therapy, and steroid toxicity risk before starting systemic treatment.	EADV BP guideline	The key dermatology decision is not only which drug controls blisters, but which regimen is least likely to destabilize cognition in a frail patient.
HZ prevention in older adults	Administer 2-dose recombinant zoster vaccine to eligible adults; review vaccination status routinely.	Integrate vaccine review into memory-clinic, geriatric, and dermatology visits.	ACIP/CDC recommendations	Vaccination is not yet a proven dementia-prevention therapy despite encouraging observational data.
Acute HZ	Promptly start antivirals and monitor for ocular or CNS complications.	Watch for delirium, pain-related insomnia, and functional decline after infection.	Population-based cohort evidence plus standard HZ care principles	Neurologic risk appears highest with complicated or CNS-involved disease.
Psoriasis	Suppress systemic inflammation and optimize long-term disease control; assess metabolic and vascular comorbidities.	Screen for depression, sleep problems, vascular risk, and subjective cognitive complaints.	AAD-NPF psoriasis comorbidity guideline	The dementia signal is modest and heterogeneous; avoid overstating causality.
AD	Prioritize moisturization, barrier repair, topical anti-inflammatory therapy, and modern systemic options when indicated; avoid chronic systemic corticosteroids.	Treat nocturnal itching as a cognitive biomarker: track sleep diaries, caregiver reports, nighttime scratching, daytime attention, and regimen complexity.	AAD adult AD guidelines	Cognitive benefit is not yet proven, but itching and sleep are measurable, treatment-responsive mediators that dermatologists can monitor.
Rosacea	Treat by phenotype, suppress papulopustular inflammation, and control flushing/ocular disease using guideline-based therapy.	Ask about subjective cognitive change, migraine-like symptoms, sleep quality, and medication burden in older adults with persistent inflammatory disease.	S2K rosacea guideline	Direct intervention data on cognition are absent; action is currently based on epidemiologic and mechanistic plausibility.
PN/chronic prurigo	Use stepwise chronic-prurigo management and consider modern targeted therapy when disease is severe or sleep-disruptive; quantify scratching burden when possible.	Track nocturnal itching, concentration, mood, caregiver-reported day-night function, and actigraphy-derived scratching/sleep metrics when feasible.	PN guideline/expert guidance	Actigraphy can turn a skin symptom into a cognitive-risk signal and a trial endpoint, but implementation standards are still emerging.
Cross-cutting older adult/ dementia care	Perform a routine skin inspection, xerosis care, itching screening, wound surveillance, and medication reconciliation.	Classify patients by the three axes--neuroinflammation, neurovascular injury, and neurofunctional disruption--and flag first-generation antihistamines, benzodiazepines, anticholinergics, opioids, and repeated steroid bursts.	WHO dementia risk-reduction guidance and geriatric best practice	Only dermatology routinely observes the visible triggers--barrier failure, blistering, zoster, itching behavior, scratch injury, and topical feasibility--that make this prevention pathway actionable.

Abbreviations: BP, bullous pemphigoid; HZ, herpes zoster; CNS, central nervous system; AD, atopic dermatitis; PN, prurigo nodularis.

and yet forward-thinking enough to envision where the field should go next.

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Mini-Review

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A neurologist's guide to VEXAS syndrome: Differentiating somatic autoinflammation from autoimmune mimics

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SUMMARY: This review characterizes VEXAS syndrome (Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic) as a prototype of adult-onset autoinflammation that challenges traditional autoimmune paradigms. Driven by constitutive activation of innate myeloid cells *via* Ubiquitin-Like Modifier Activating Enzyme 1 (UBA1) mutations, VEXAS affects the nervous system in approximately 6–10% of cases. We identify the peripheral nervous system as the primary target (70%), typically manifesting as refractory axonal polyneuropathy, while central involvement may present as neutrophilic meningoencephalitis. Crucially, we highlight the "hematologic paradox"—hyperinflammation co-occurring with macrocytic anemia rather than thrombocytosis—as the key biomarker distinguishing VEXAS from vasculitic mimics, necessitating early genetic sequencing for targeted clone suppression.

Keywords: VEXAS syndrome, UBA1, neuroinflammation

1. Introduction

Adult-onset neuroinflammation is framed through the lens of autoimmunity, where a breach in adaptive immune tolerance leads to T-cell or antibody-mediated attacks against specific neural antigens. VEXAS (Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic) syndrome challenges this established paradigm. It represents a distinct category of autoinflammatory disease driven not by antigen recognition, but by the constitutive, innate activation of myeloid cells due to somatic mutation (*1,2*).

The discovery of somatic mosaicism confirmed that acquired mutations may drive this adult-onset disease, which may exhibit with neurological symptoms that mimic traditional inflammatory disorders (*3*). Neurologists may misdiagnose VEXAS as 'atypical vasculitis' and initiate lymphocyte–depleting therapies that are mechanistically ineffective against an innate myeloid clone.

Given the rarity of typical diagnostic clues in neurological presentations, VEXAS remains critically underdiagnosed (*1*). This mini-review addresses the need to provide neurologists with a specific diagnostic framework in order to identify these patients (*4*). Rather than an exhaustive systematic analysis, this article provides a focused conceptual synthesis and clinical perspective. By defining the specific clinical and hematological signatures of this UBA1–driven disease, we propose a stepwise diagnostic algorithm to distinguish neuro VEXAS syndrome from its autoimmune and rheumatological mimics (*5*).

2. Scope of the review

This mini–review synthesizes literature published between January 2020 and December 2025, coinciding with the initial description of VEXAS syndrome. To ensure clinical relevance, we prioritized the analysis of primary data from large, multi–center retrospective cohorts and mechanistic studies over isolated case reports. The thematic scope focuses on defining neurological phenotypes, genotype-phenotype correlations, and treatment outcomes. Emphasis was placed on studies elucidating the "hematological paradox" and the distinction between clonal inflammation and classical autoimmunity. The final synthesis integrates these findings to establish a practical diagnostic framework for the practicing neurologist.

3. Genetic abnormalities and pathophysiological mechanism

The primary molecular mechanism underlying VEXAS

syndrome is a disruption in the ubiquitin-proteasome system. This dysfunction stems from the Ubiquitin-Like Modifier Activating Enzyme 1 (UBA1) gene, which is responsible for producing the E1 enzyme—a critical component in flagging aberrant proteins for elimination (*2*). Somatic mutations in VEXAS are predominantly restricted to codon 41 (p.Met41). These mutations specifically disrupt the production of the cytoplasmic variant, UBA1b, but leave the nuclear variant, UBA1a, unaffected (*1*). This isoform causes a severe impairment of cytoplasmic ubiquitination capacity, leading to the accumulation of pathogenic protein aggregates, while DNA repair and other nuclear functions remain relatively intact (*6,7*).

Consequently, this proteostatic dysfunction triggers an active maladaptive stress response. The accumulation of ubiquitination-deficient proteins triggers the Unfolded Protein Response (UPR), a conserved stress pathway intended to restore homeostasis (*8*). In myeloid cells, however, this stress response results in constitutive, antigen-independent activation of the NLRP3 inflammasome. Unlike autoimmune responses which require specific antigen recognition, VEXAS myeloid clones are intrinsically driven to a hyper-inflammatory state solely by proteostatic stress. Consequently, these macrophages exhibit sustained, constitutive activation, explaining why therapies targeting antigen presentation are ineffective (*9*). As a result, a hyper-inflammatory phenotype characterized by the dysregulated secretion of IL–1β, IL-6, and tumour necrosis factor–alpha (TNFα), drives systemic manifestations and neuroinflammation, in the absence of infection or other triggers (*10,11*) (Figure1).

On a cellular level, the UBA1 mutation exerts a differential effect across cell lines. Lymphocytes are highly sensitive to ubiquitin deficiency; they cannot sustain the metabolic stress of the UPR and undergo rapid apoptosis, resulting in the profound lymphopenia seen in more than 90% of patients (*12*). Conversely, myeloid cells are resistant to this apoptotic signal. Adaptive responses lead to sequestering defective proteins into cytoplasmic vacuoles, thus entering a state of senescent hyperinflammation (*13*). The precise mechanism by which UBA1–mutated clones breach the blood-brain barrier (BBB) is not yet fully understood (*14*). Contemporary evidence suggests that CNS involvement is not exclusively attributed to cytokine-induced endothelial activation; an active cellular (mainly neutrophilic) invasion analogous to the syndrome's cutaneous lesions (neutrophilic dermatosis) constitutes an additional contributor (*15,16*). Moreover, UBA1-mutated neutrophils exhibit delayed apoptosis and prolonged survival that sustain their accumulation in tissues (*1,13*). Histopathological analysis of skin tissues frequently reveals perivascular infiltrates of mature neutrophils admixed with $CD163^{+}$ myeloid precursors (*15*). We hypothesize that a similar 'neuro-neutrophilic' mechanism may drive the CNS pathology, where long-lived myeloid clones cross the BBB, resulting in neutrophilic pleocytosis and parenchymal damage distinct from the lymphocytic inflammation seen in autoimmune CNS disorders (*17,18*).

While the loss of the UBA1b isoform is the unifying mechanism, the clinical trajectory is heavily influenced by the specific amino acid substitution at codon 41. Current literature stratifies risk based on the specific amino acid substitution (*1,6*). The p.Met41Val (Valine) variant drives the most aggressive hematologic

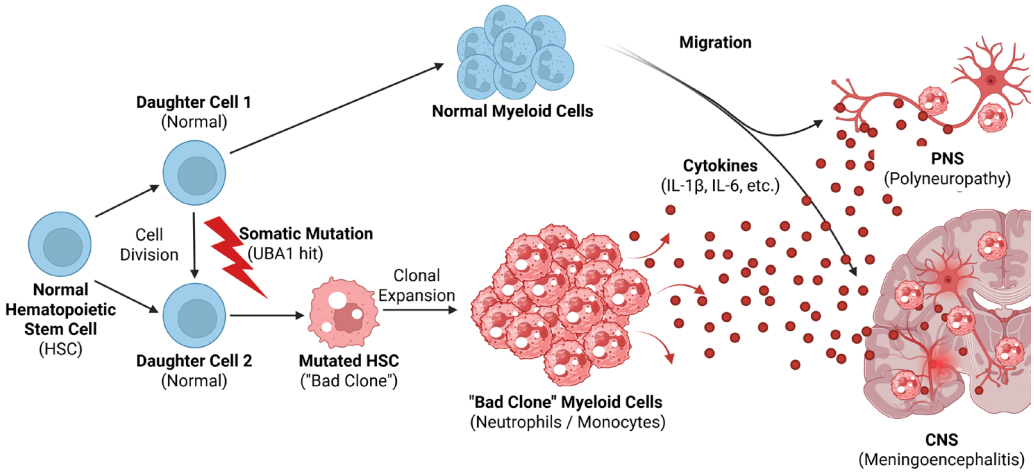

Figure 1. Pathogenesis of Somatic Mosaicism in Neuro–VEXAS. Schematic illustration of the pathogenic clonal expansion. A single hematopoietic stem cell (HSC) acquires a somatic UBA1 mutation, leading to the expansion of inflammatory myeloid cells (neutrophils and monocytes, red). These pathogenic clones hyper–secrete proinflammatory cytokines (*e.g.*, IL–1β, IL–6) and migrate into neural tissue. The diagram illustrates the dual impact on the nervous system: invasion of the Central Nervous System (CNS) resulting in meningoencephalitis, and infiltration of the Peripheral Nervous System (PNS) causing the prevalent vasculitic polyneuropathy. *Note*: This figure was created using BioRender.com. *Abbreviations*: CNS, Central Nervous System; HSC, Hematopoietic Stem Cell; IL, Interleukin; PNS, Peripheral Nervous System; UBA1, Ubiquitin–like modifier activating enzyme 1.

phenotype, correlating with transfusion dependence and significantly reduced overall survival (5–year survival ~50%) (*6,19*). Consequently, Valine positivity serves as a critical prognostic marker for early mortality, necessitating aggressive hematologic intervention (*e.g.*, transplantation). However, no data currently confirm that Valine carriers are at higher risk for neurological manifestations (*20*). In contrast, the p.Met41Leu (Leucine) and p.Met41Thr (Threonine) variants are associated with superior survival but are strongly linked to cutaneous neutrophilic dermatosis (Sweet Syndrome) (*19*). Nevertheless, caution is needed to avoid mistaking the 'mild' mortality profile of Leucine for a lack of neuro-inflammatory risk; these patients may remain prone to tissue infiltration despite preserved marrow function.

In summary, the specific UBA1 mutations dictate a unique pathophysiology where intrinsic myeloid activation drives both systemic hyperinflammation and simultaneous bone marrow stress. This sets the biological foundation for the 'hematologic paradox', establishing a direct causal link between the somatic clonal expansion in the marrow and the subsequent aggressive infiltration of the central and peripheral nervous systems.

4. Neurological manifestations of VEXAS syndrome

Diagnosing VEXAS syndrome depends on identifying a hallmark triad of symptoms that allows distinction from systemic autoimmune disorders and vasculitides. A male adult with neurologic defects and refractory macrocytosis, chondritis, and an abnormal bone marrow biopsy is a classic case for a VEXAS diagnosis. The patient typically presents with refractory macrocytosis (MCV > 100 fL) which may be thought to result from myelodysplastic syndromes (MDS), which is different than the normocytic anemia typical in cases of chronic disease seen in patients with autoimmune diseases such as systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA) (*15*). Inflammation of the auricular and nasal cartilage (chondritis) occurs in 50-60% of patients, presenting as saddle-nose deformity that can mimic relapsing polychondritis (*6*). Bone marrow biopsy reveals vacuolization of myeloid and erythroid precursor cells, the characteristic sign of the disease often underreported by pathologists unless specifically prompted (*1,19*).

Neurological evaluation frequently reveals involvement of the peripheral nervous system (PNS), affecting approximately 70% of patients with neurological manifestations (*20*). The pathologic process occurs due to a neutrophilic vasculitis of the vasa nervorum; thus, there is an ischemic damage to the nerves. This will produce clinical symptoms that resemble those found in Polyarteritis Nodosa (PAN), or ANCA–associated vasculitis. These symptoms are those of a length dependent, axonal sensorimotor polyneuropathy (*ie*: progressively distal weakness, and progressive distal sensory loss). While this is the classic presentation for these patients, a significant proportion of patients present with a mononeuritis multiplex (*17,21*).

With regards to cranial neuropathies, the facial and vestibulocochlear nerves are preferentially affected. Cranial involvement is often contiguous to chondritis; inflammation of the ear cartilage or nasal structures extends locally to entrap or inflame adjacent nerves. Consequently, the sudden onset of facial palsy or sensorineural hearing loss in a middle–aged man or older with presumed Relapsing Polychondritis (RP) should prompt screening for UBA1 mutations (*22*). Notably, unlike Guillain–Barré syndrome or chronic demyelinating distal polyneuropathy, neuropathy in VEXAS is primarily axonal and is often refractory to intravenous immunoglobulin. Treatment necessitates suppression of the myeloid clone (*23*).

CNS manifestations are present in approximately 10–30% of cases and although less frequent than PNS involvement, they are commonly severe and indicative of advanced disease stage (*6,19,20*). Unlike the lymphocyte–predominant type of inflammation seen in paraneoplastic syndromes or autoimmune encephalitis, VEXAS produces a neutrophilic meningoencephalitis. The patients usually begin by presenting with symptoms of a subacute decline in cognition and/or mental status and also develop seizures. Lumbar punctures performed on these patients will often show evidence of neutrophilic pleocytosis as well as increased levels of cerebrospinal fluid (CSF) protein and normal levels of glucose; this allows for distinguishing from those encephalitides that are caused by viruses or autoimmunity, where the pleocytosis is characterized by an elevation in the number of lymphocytes (*18,24*).

Rarely, VEXAS syndrome may present pseudotumoral CNS involvement; however, evidence for this phenotype is currently limited to isolated case reports, and clinicians should interpret this association with caution. A recent study reported an individual with significant central nervous system (CNS) lesions that demonstrated ring enhancement and were producing mass effect. The clinical presentation of this case of tumefactive demyelination mimicked that of high-grade glioma and primary CNS lymphoma on initial imaging studies; therefore, a brain biopsy was performed to rule out neoplastic glial cells and confirm the presence of neutrophils instead of lymphocytes (*25*). Neurological symptoms of the disease can also involve the orbits; and thus cause orbital myositis, or dacryoadenitis. The patient develops double vision (diplopia), swelling of the eye (proptosis) and paralysis of one or more of the eye muscles (ophthalmoplegia), and this can mimic the symptoms of IgG4–Related Disease or Tolosa–Hunt Syndrome, especially in the case of the RP phenotype (*19*). In addition, the patient could have various other symptoms such as focal brain stem dysfunction; these include ataxia, multidirectional nystagmus and cranial neuropathy of one or more cranial nerves, which is due

to neutrophilic rhombencephalitis, either isolated or associated with an episode of meningitis (*20*).

Cerebrovascular consequences of the autoinflammatory syndrome may be equally devastating (*26*). Inflammation and activation of the coagulation cascade, anemia and anti–phospholipid antibodies may predispose to thrombosis (*27*). Moreover, the senescent, hyper–inflammatory myeloid clones may infiltrate cerebral vessels, leading to localized vessel wall inflammation and constriction mediated by hyperactive neutrophils, resulting in encephalopathic changes or lacunar events (*28*). While true CNS vasculitis affecting large or small vessels is uncommon compared to PNS involvement, it constitutes a documented phenotype of the syndrome, specifically identified in vasculitis-focused cohorts (*23*). Stroke in VEXAS patients is usually attributed to lacunar infarcts, and the syndrome is associated with cerebral small vessel disease (*29*). Cerebral venous thrombosis has been reported in a minority of VEXAS cases (*30*), though this is currently based on single case observations rather than large cohort data.

Magnetic resonance imaging (MRI) findings are nonspecific and highly variable, displaying T2/FLAIR hyperintensities in the periventricular white matter and brainstem which represent sites of active neutrophilic invasion (*14,31*). The imaging technique 18F–fluorodeoxyglucose (FDG)–PET/CT has emerged as the superior modality for visualizing sites of active inflammation (*32*). Intense, symmetric tracer uptake in the ear and nose cartilage is typical for the disease. Patchy vascular uptake is also frequently demonstrated (*19*). FDG–PET evaluation has been suggested for patients with unexplained encephalopathy and a negative MRI evaluation in search of subclinical systemic inflammation that may lead to VEXAS diagnosis (*16*).

Ultimately, whether manifesting as meningoencephalitis, cranial neuropathy, or axonal polyneuropathy, these neurological deficits are direct extensions of the underlying myeloid clonality. Therefore, diagnostic suspicion must be immediately elevated when severe neuro-inflammatory syndromes are paradoxically coupled with macrocytosis or progressive cytopenias, rather than the reactive thrombocytosis typical of classical autoimmune mimics.

5. Differential diagnosis and mimics

VEXAS syndrome patients are frequently misdiagnosed as people with a primary rheumatologic disorder. A major driver of this misdiagnosis is that these patients often fulfill the classification criteria for Polyarteritis Nodosa (PAN), RP or Giant Cell Arteritis (*6,14,19*). In addition, VEXAS patients frequently exhibit non-pathogenic autoantibodies, such as anti-nuclear antibodies and lupus anticoagulant, leading to misdiagnoses such as SLE or primary antiphospholipid syndrome in the setting of stroke. However, these serologies often represent a dysregulated immune milieu rather than a primary autoimmune diathesis (*27*). Additionally, approximately 50% of patients will meet criteria for MDS during the disease course (*33*). Unexplained neurological deterioration may serve as the primary catalyst for genetic investigation, ultimately unmasking the somatic mutation in cases that otherwise lack classic diagnostic triggers (*25*).

One of the most significant clinical characteristics that distinguish VEXAS from other autoimmune vasculitis syndromes is that systemic inflammation and bone marrow failure occur together. Typical systemic vasculitides (like PAN or GCA) have a reaction to the systemic inflammation of the bone marrow causing it to produce an acute phase response and thus thrombocytosis and leukocytosis will result. In contrast, VEXAS is defined by a fundamental uncoupling of the inflammatory response: the somatic mutation drives profound systemic inflammation (elevated CRP/ferritin) while simultaneously impairing hematopoiesis, resulting in progressive bone marrow failure (cytopenias) rather than the reactive thrombocytosis seen in classic vasculitis (*34*). The pattern of hyper-inflammation paired with marrow failure is a reliable distinguishing feature. In a patient diagnosed with refractory PAN and exhibiting macrocytic anemia and/or thrombocytopenia, the diagnosis warrants re-evaluation for the possibility of a UBA1-driven myeloid neoplasia (*35*).

VEXAS diagnosis and differentiation from other emerging somatic syndromes is particularly difficult in the setting of negative UBA1 testing. While VEXAS typically follows a chronic course, somatic NLRC4 mutations present as a hyperacute, IL–18–driven 'cytokine storm' with fulminant Macrophage Activation Syndrome (*36*). Conversely, somatic NLRP3 mosaicism mirrors VEXAS chronicity but manifests as aseptic meningitis and sensorineural hearing loss without the characteristic macrocytosis; these low-level clones often require Next-Generation Sequencing (NGS) for detection (*37*). Finally, phenotypes indistinguishable from VEXAS may stem from somatic mutations in OTULIN or SHARPIN. These disorders share the somatic clonal ubiquitin–defect mechanism and neurological overlaps, representing the essential next step in the diagnostic algorithm for the 'UBA1–negative' patient (*38,39*).

To prevent delayed diagnosis and the futile use of broad immunosuppression, clinicians must consider VEXAS syndrome earlier in the diagnostic process. A high index of suspicion for UBA1 mutations is required when adult-onset neuroinflammation presents with specific "red flags". Common misdiagnoses—such as unclassifiable systemic vasculitis (particularly mimicking PAN or GCA), atypical autoimmune encephalitis, or idiopathic myelitis—should be critically re-evaluated if they occur in a male patient over 50 years of age who is refractory to standard therapy (*40*). The most definitive early red flag prompting immediate genetic sequencing

is the presence of unexplained cytopenias—specifically macrocytic anemia or thrombocytopenia—occurring concurrently with systemic inflammation, sharply contrasting with the reactive thrombocytosis expected in classical autoimmune disorders (*33*).

Considering the existence of numerous potential mimics and the paucity of UBA–1 genetic testing in clinical practice, an appraisal of diagnostic algorithms for adult-onset vasculitis and neurological manifestations may help guide clinical practice. While neuroimaging is frequently nonspecific, it remains essential for excluding structural mimics (*e.g.*, malignancy). In patients presenting with neurological symptoms indicating vasculitic process of the PNS or CNS and concomitant hematologic abnormalities (notably macrocytic anemia and thrombocytopenia), bone marrow aspiration and biopsy should be considered in the diagnostic approach, in concert with vascular imaging and electrophysiological evaluation (Figure 2) (*40*).

6. Management implications

It must be emphasized that current therapeutic strategies for VEXAS syndrome are provisional and based entirely on retrospective cohorts and case series, as no randomized controlled trials (RCTs) have yet been published. The therapeutic strategy for VEXAS requires a careful trade–off between controlling disease activity and minimizing the toxicity of immunosuppression. While high-dose corticosteroids (0.5–1 mg/kg) typically yield rapid improvement in neurological symptoms, this initial success is rarely durable. A defining feature of the syndrome is severe steroid dependency; attempts to taper the dosage below 15–20 mg/day almost always precipitate a relapse (*19,41*).

With regards to steroid sparing agents, in the case of VEXAS, Janus kinase (JAK) inhibitors have emerged as superior treatment options to TNF and IL–1 blockade. JAK inhibitors act by suppressing the JAK–STAT pathway, thereby severing downstream signaling of IL–6 and type I/II interferons. This mechanism is very effective at reducing the cytokine peak and the hyperinflammatory state that the aberrant myeloid clone

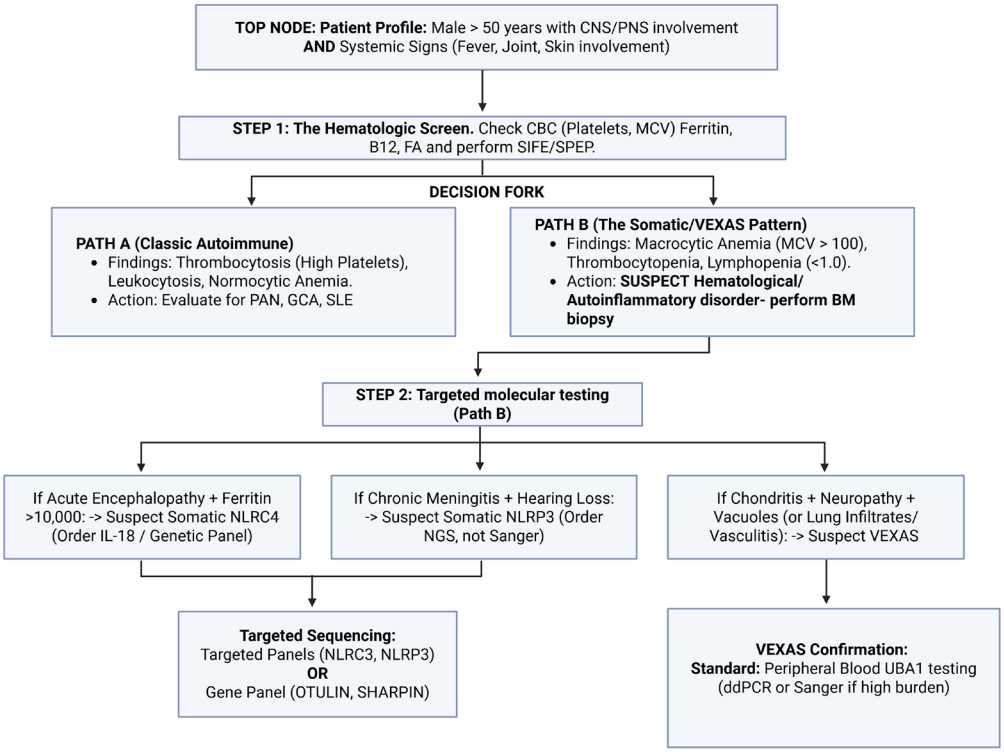

Figure 2. Proposed Diagnostic Algorithm for Suspicion of Somatic Autoinflammation with Neurological manifestations. This flowchart illustrates a stepwise approach for evaluating adult males (> 50 years) with undefined neuroinflammation. The algorithm centres on the "Hematologic Screen" (Step 1) as the primary discriminator between autoimmune mimics (Path A) and somatic clonal disorders (Path B). Path A (Autoimmune) is suggested by reactive thrombocytosis and leukocytosis, while Path B (Somatic/VEXAS) is identified by the "hematologic paradox" of systemic inflammation coexisting with signs of marrow failure (macrocytic anemia, thrombocytopenia). Step 2 directs specific molecular testing based on distinct phenotypic clusters: acute encephalopathy with extreme hyperferritinemia (NLRC4), chronic meningitis with sensorineural hearing loss (NLRP3), or the classic VEXAS triad (UBA1). *Note*: This figure was created using BioRender.com. *Abbreviations*: BM, Bone marrow; CBC, Complete blood count; CNS, Central nervous system; ddPCR, Droplet digital polymerase chain reaction; FA, Folic acid; GCA, Giant cell arteritis; IL, Interleukin; MCV, Mean corpuscular volume; NGS, Next–generation sequencing; NLRC3, NLR family CARD domain containing 3; NLRC4, NLR family CARD domain containing 4; NLRP3, NLR family pyrin domain containing 3; OTULIN, OTU deubiquitinase with linear linkage specificity; PAN, Polyarteritis nodosa; PNS, Peripheral nervous system; SHARPIN, SHANK–associated RH domain interactor; SIFE, Serum immunofixation electrophoresis; SLE, Systemic lupus erythematosus; SPEP, Serum protein electrophoresis; UBA1, Ubiquitin–like modifier activating enzyme 1.

has caused, yet it does not eliminate the underlying clonal proliferation (*42*). Studies have demonstrated that the JAK1/2 inhibitor Ruxolitinib results in superior response rates compared to TNF and IL–1 inhibitors, serving as the steroid-sparing treatment of choice (*33,42*). Systemic symptoms (fever, chondritis) typically resolve within weeks of JAK inhibition, however, established axonal polyneuropathy may show limited reversibility, reflecting permanent axonal loss rather than active inflammation (*23*). Therefore, while robust retrospective cohort data establish JAK inhibitors as highly effective for symptom control, they are not disease–modifying; they suppress proinflammatory signal transduction pathways but fail to eradicate the underlying UBA1–mutated clone (*43*). Currently, based on small cohort experiences, allogeneic hematopoietic stem cell transplantation remains the only truly disease–modifying and potentially curative option for patients with high–risk genotypes (*p*.Met41Val) or transfusion dependence (*13*). In the long term, neurological outcomes are intrinsically linked to the successful management of the underlying hematologic disorder. Rapid diagnosis and the immediate deployment of targeted therapies are essential strategies to optimize clinical response and prevent the morbidity caused by chronic steroid exposure (*41,42*).

7. Limitations

The retrospective nature of existing cohorts currently limits our understanding of neuro-VEXAS. Most data are derived from hematology referral centers, potentially introducing a reporting bias in cases of milder neurological deficits (*19,20*). Furthermore, true mutation prevalence in the group of seronegative CNS vasculitis remains unknown, as UBA1 sequencing testing is uncommon in these cases and not yet a standard practice (*3*). Long–term longitudinal data of VEXAS patients, especially regarding neurological symptoms and related disability, and their outcomes following treatment are currently lacking (*42*). Finally, the diagnostic algorithm proposed herein is derived from retrospective phenotypic patterns. Its clinical utility requires validation in prospective studies, particularly in tertiary centers with a sufficient volume of VEXAS cases, to establish its value in real-world neurological practice.

8. Conclusions

VEXAS syndrome has redefined the landscape of adult–onset neuroinflammation, exposing somatic clonal evolution as a driver of disease distinct from classical autoimmunity. By recognizing its distinct haematological features, clinicians may bypass futile empiric immunosuppression and prioritize high–yield molecular testing. Ultimately, the shift from treating 'atypical autoimmunity' to targeting innate clonal drivers may enable prevention of irreversible neurological injury in people with VEXAS syndrome.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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Original Article

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Understanding the disease burden and unmet needs of patients with primary immunodeficiency in China: A quantitative study

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SUMMARY: To quantitatively describe the disease burden and living status of patients with primary immunodeficiency (PID) in China, a descriptive, nationwide cross-sectional survey was conducted in September 2024 *via* a patient organization, yielding 435 valid responses. Among respondents, 82% were male and 77% were pediatric; antibody deficiencies were the most common category (63%), with X-linked agammaglobulinemia (49%) being the most frequent self-reported subtype. The mean diagnostic delay was 3 years, with 45.2% waiting over 1 year and 78.6% experiencing prior misdiagnosis or missed diagnosis. Although 82% received immunoglobulin therapy, only 7% reported being relatively healthy without complications. Health-related quality of life (HRQoL) utility values, measured *via* EQ-5D instruments, were 0.87 for children and 0.84 for adults, appearing lower than reference population norms. Educational disruption affected 25.1% of pediatric patients, while 27% of adult patients were unemployed and 47.1% required frequent sick leave. Caregiving demands were extensive, with 53.4% of pediatric patients requiring dedicated care, resulting in 51.5% of their primary caregivers resigning from their jobs. In conclusion, PID imposes substantial medical, psychological, and socioeconomic burdens in China. These descriptive findings highlight an urgent need for earlier diagnosis, improved therapeutic access, and integrated societal support systems for education, employment, and caregiving.

Keywords: rare diseases, primary immunodeficiency, quality of life, care burden

1. Introduction

Primary immunodeficiency (PID) is a group of disorders caused by genetic mutations that disrupt the development or function of immune organs, immune-active cells, and immune molecules such as immunoglobulins, cytokines, complement, and cell surface proteins (*1*). These defects result in impaired immune function, though the severity of disease can vary considerably among patients. With a compromised immune system, individuals with PID are unable to mount effective defenses against bacterial, viral, or fungal infections. Consequently, they are prone to recurrent infections and may also develop complications involving multiple systems, including the respiratory, hematological, gastrointestinal, integumentary (skin and mucosa), and endocrine systems.

Due to classifications of disease groups being updated frequently, there is still no unified international standard for estimating the prevalence of PID or its newly reclassified counterpart, inborn errors of immunity (IEI). According to several registry-based prevalence reports published in Europe, the prevalence of PID in Europe was approximately 5 cases per 100,000 population (*2-4*). More recent studies, however, suggest that the prevalence of IEI may be around 1 in 1,000, likely due to the inclusion of additional disease entities in updated classifications (*5*). In China, no epidemiological studies on PID have yet been conducted, and therefore no specific data on its incidence or prevalence are available. Nonetheless, among patients currently diagnosed, the more common subtypes include severe combined immunodeficiency (SCID), X-linked agammaglobulinemia (XLA), X-linked hyper-IgM syndrome (XHIM), chronic granulomatous disease (CGD), Wiskott-Aldrich syndrome (WAS), common variable immunodeficiency (CVID), and activated PI3K delta syndrome (APDS).

Currently, PID has been included in the second Chinese national list of rare diseases (No. 66), but the lack of systematic data presents a major obstacle to effective healthcare planning and policy formulation.

In addition, research on PID in China has primarily focused on clinical aspects, while studies addressing patients' quality of life remain relatively limited. As a result, there is a significant knowledge gap regarding the social and psychological impacts of PID on patients'

living status in China.

To address this gap, the current study was designed as a descriptive, cross-sectional, questionnaire-based survey. It aims to describe the demographic characteristics of the patient population, clinical subtypes, healthcare/diagnosis and treatment experiences, quality of life, social participation, as well as caregiving burdens. The expected objectives are as follows: *i*) to describe the demographic characteristics of the surveyed PID patients in China, including age and gender distribution; and *ii*) to report the current status of these PID patients and their families in terms of diagnosis and treatment, medication, disease burden, and quality of life.

2. Methods

The project employed a quantitative research design by incorporating quantitative patient surveys to comprehensively gather data and capture the current circumstances and needs of patients with PID.

2.1. Study design and participants

The current study employed a descriptive, cross-sectional, questionnaire-based survey design using convenience sampling to assess the healthcare/diagnosis experience, quality of life, social participation, and caregiving burden among PID patients and their caregivers in China.

The current study was conducted in strict accordance with ethical standards. As this was an anonymous, non-interventional online survey, formal ethical approval from a medical institutional review board was not applicable/obtained. However, the study was conducted in strict adherence to the ethical principles of the Declaration of Helsinki regarding the protection of human subjects. Prior to completing the questionnaire, all participants were informed of the study sponsor, the objectives of the survey, the intended use of the data, and the measures implemented to ensure data confidentiality and security. Submission of the completed questionnaire was regarded as provision of informed consent to participate and acknowledgment that the data would be used solely for the purposes of this research.

The inclusion criteria for this study were: *i*) patients formally diagnosed with PID or their primary caregivers; and *ii*) residing in China. The exclusion criteria were: *i*) refusal to provide informed consent; *ii*) duplicate submissions from the same IP address or user; and *iii*) questionnaires with largely incomplete or logically implausible responses.

2.2. Data collection and questionnaire development

An online questionnaire survey was conducted in September 2024, with patient recruitment facilitated through the patient organization PID Care China. Given this recruitment strategy, a convenience sample of patients heavily engaged with advocacy networks was obtained. A total of 448 questionnaires were collected, of which 435 were valid. No valid responses were obtained from Tianjin Municipality, Hainan Province, Qinghai Province, Tibet Autonomous Region, Ningxia Hui Autonomous Region, or the Hong Kong, Macao, and Taiwan regions.

The survey instrument consisted of two parts: a standardized, internationally validated tool for measuring quality of life (EQ-5D), and a self-developed questionnaire designed by the research team to capture specific socio-clinical parameters. The development of the self-designed items was formulated based on a comprehensive literature review and tailored specifically to the context of PID in China. To ensure content validity and clinical relevance, the initial draft of the questionnaire underwent expert review by clinical immunologists and leaders from the patient advocacy group (PID Care China). Revisions were made based on their feedback to ensure the terminology was patient-friendly and clinically accurate before national distribution. The collected data were automatically recorded *via* the Jinshuju platform and analyzed using statistical software.

The survey was organized into five major domains:

i) Demographics and clinical profile

This domain collected information on age, gender, geographic distribution and clinical profile.

ii) Diagnosis/healthcare and treatment experience

Items in this section collected detailed information on multiple aspects of patients' medical journeys. Specifically, it captured the initial reasons for seeking medical consultation, the interval between symptom onset and confirmed diagnosis, and experiences of misdiagnosis or missed diagnosis. It also examined the geographic distribution of diagnosis, including whether patients were diagnosed locally or needed to travel to other cities or provinces, as well as the medical departments where diagnoses were ultimately confirmed. In addition, this section assessed current treatment modalities, together with patients' prognosis under existing treatment regimens.

iii) Health-related quality of life (HRQoL)

HRQoL was measured using the EuroQol five-dimension instrument (EQ-5D), a widely applied, standardized, self-reported measure of health status suitable for diverse patient populations and diseases. The EQ-5D evaluates quality of life across five dimensions: mobility, usual activities, self-care, pain/discomfort, and

anxiety/depression, with each dimension represented by a single item.

For pediatric patients, the EQ-5D-Y-3L (youth version) was employed, in which each dimension is rated on three levels: no problems, moderate problems, or extreme problems.

For adult patients, the EQ-5D-5L was employed, with each dimension rated on five levels: no problems, some problems, moderate problems, severe problems, or extreme problems.

Respondents indicated the statement that best described the patient's health status. In addition, the EQ-5D includes the EQ Visual Analogue Scale (EQ-VAS), which captures the respondent's perception of the patient's overall health on the day of survey completion.

For adult respondents, HRQoL scores (EQ-5D-5L utility values) were calculated and compared with Chinese population norms. For pediatric patients, due to the complete absence of Chinese EQ-5D-Y normative data, Japanese adolescent EQ-5D-Y health utility norms were used as a reference. Japan and China share geographic and broad cultural proximities, making the Japanese value set a reasonable proxy for East Asian populations. However, this comparison was undertaken with caution, emphasizing overall descriptive trends rather than direct numerical equivalence.

iv) Social participation

For minors, participation was evaluated based on school attendance status (regular attendance, temporary suspension, or permanent discontinuation) and the number of school days missed. For adults, employment status was categorized as unemployed, part-time or flexible employment, full-time employment, agricultural work, or retired. Additional indicators included limitations in physical health affecting employability, restrictions in social participation due to health conditions, and the frequency of health-related absences in work.

v) Caregiving burdens

This domain examined the need for caregiving among patients of different age groups, the frequency of care required, the identity of the primary caregiver, and the caregiver's employment status. It further assessed the degree to which caregiving responsibilities disrupted employment, the reasons for such disruption, and the number of workdays missed due to caregiving duties.

2.3. Statistical analysis

Data were analyzed using R studio. In alignment with the descriptive nature of the study design, all statistical analyses were strictly descriptive. Continuous variables were presented as means, and categorical variables were summarized using frequencies and percentages. No inferential statistical tests (*e.g.*, hypothesis testing or *p*-value calculations) were performed, as the study aimed solely to describe the current landscape of disease burden rather than to test comparative or causal relationships between variables.

3. Results

3.1. Participant demographics

The majority of PID patients participating in this survey were male (82%), with females accounting for 18%. Pediatric patients constituted 77% of the respondents, while adult patients (≥ 18 years) comprised 23%. Approximately 47% were under 10 years of age, 35% were between 10–19 years, 11% were between 20–29 years, 6% were between 30–39 years, and only 1% were aged 40 years or above. Patients originated from 28 provinces, autonomous regions, and municipalities across China, with the largest proportions from Guangdong, Henan, and Shandong Provinces.

3.2. Clinical profile

In this study, patients' PID conditions were classified into the following major groups: antibody deficiencies (63%), combined immunodeficiencies (14%), combined immunodeficiencies with syndromic features (6%), defects of innate immunity (6%), autoinflammatory disorders (3%), diseases of immune dysregulation (2%), phagocytic defects (2%), bone marrow failure syndromes of monogenic origin (0.5%), phenocopies of PID (0.5%), and cases with uncertain diagnosis (3%). Patients or their caregivers self-reported the disease category according to the patients' diagnosis.

With regard to specific PID subtypes (Table 1), the most participants were diagnosed with X-linked agammaglobulinemia (XLA), representing approximately 49% of the total sample. Other relatively common subtypes included combined immunodeficiency (CID, 7%), severe combined immunodeficiency (SCID, 6%), and common variable immunodeficiency (CVID, 5%).

3.3. Diagnosis/healthcare experience

3.3.1. Symptoms at first medical consultation

Patients presented with a diverse range of initial symptoms (Figure 1A). The most frequently reported reasons for the first medical consultation were recurrent upper respiratory tract infections (48.5%), persistent fever (42.6%), and severe respiratory problems (31.1%). These leading reasons were similarly distributed across both pediatric and adult groups (Figure 1B).

3.3.2. Time to diagnosis and misdiagnosis

Table 1. Distribution of specific PID subtypes

Disease Types	Number of Patients Participated	Number of Participating Patients	Proportion
X-Linked Agammaglobulinemia/XLA	212		49%
Combined Immunodeficiency/CID	31		7%
Severe Combined Immunodeficiency/SCID	26		6%
Common Variable Immunodeficiency/CVID	23		5%
PIK3CD Mutation (GOF)/APDS	15		3%
Hiper-IgE Syndrome/HIES	14		3%
Mendelian Susceptibility To Mycobacterial Diseases/MSMD	9		2%
Chronic Granulomatous Disease	8		2%
Other	8		2%
Inflammasome-Associated Autoinflammatory Diseases	7		2%
Inherited thrombocytopenia With Immunodeficiency	7		2%
NFKB2 Deficiency	6		1%
Invasive Fungal Infections	6		1%
EBV-Susceptible lymphoproliferative Disease	4		1%
Other Combined Immunodeficiency Syndromes	4		1%
PIK3R1 Deficiency	3		1%
Familial Hemophagocytic Lymphohistiocytosis	3		1%
Severe Viral Susceptibility Disorders	3		1%

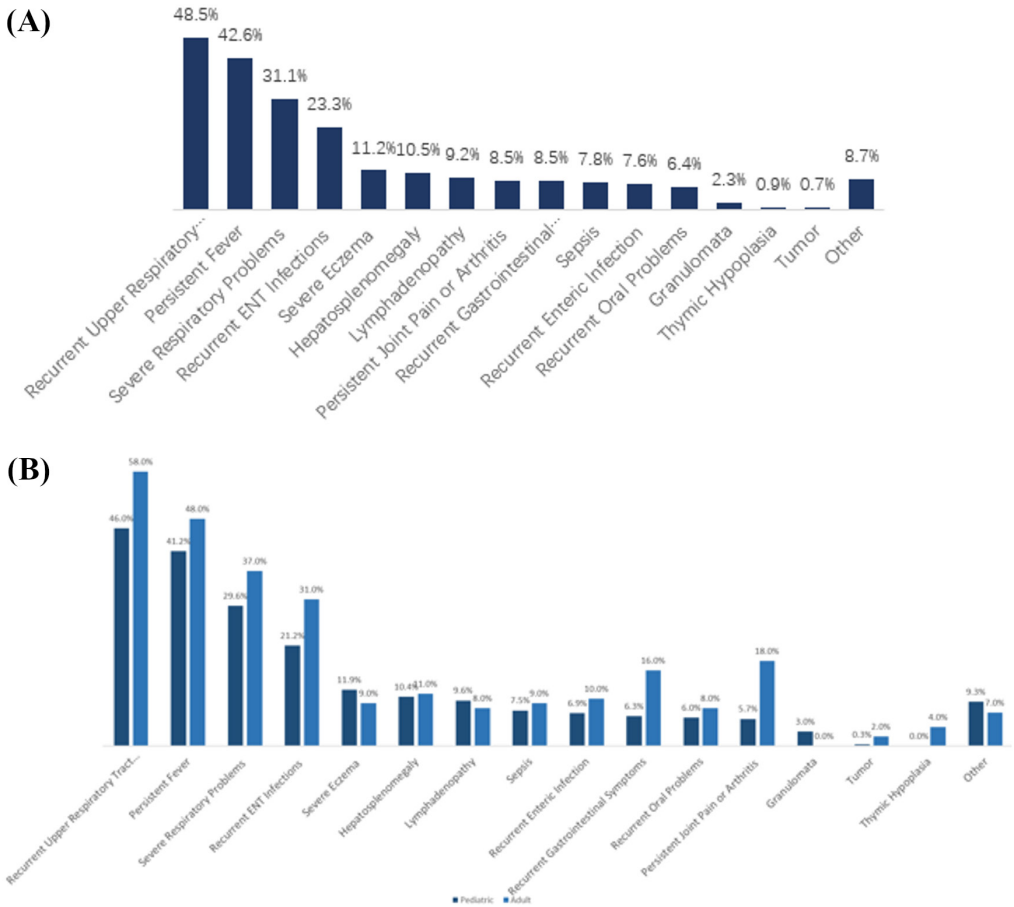

Figure 1. (A) Distributions of initial symptoms and (B) Symptoms grouped by age.

The mean interval from symptom onset to confirmed diagnosis was three years. Overall, 45.2% of patients required more than one year, and 11.6% experienced diagnostic delays exceeding five years (Figure 2A). Descriptive comparisons indicated that pediatric patients were diagnosed within one year more frequently than adults (58.0% *vs*. 41.9%) (Figure 2B). A high proportion of patients (78.6%) reported experiencing misdiagnosis or missed diagnosis (Figure 2C), with 66.0% reporting that physicians provided only symptomatic treatment without establishing a clear diagnosis. These patterns were largely consistent across age groups (Figure 2D).

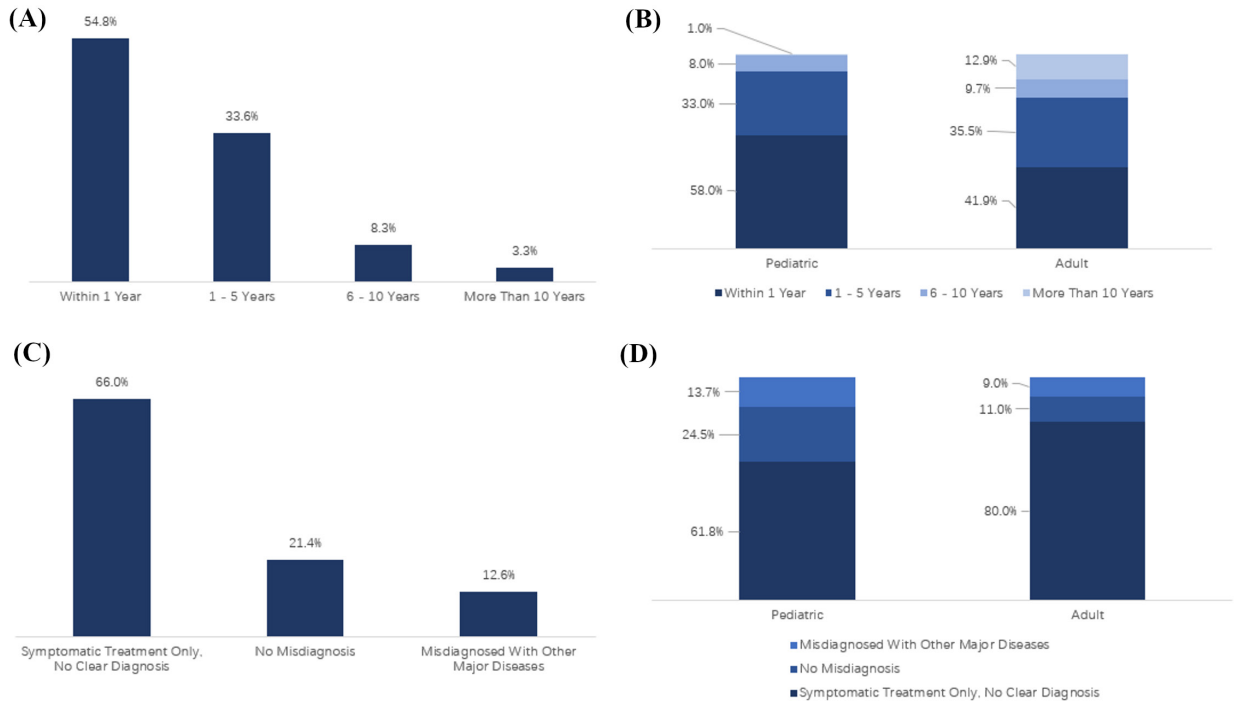

Figure 2. (A) Overall distribution of time-to-diagnosis; (B) Time-to-diagnosis grouped by age; (C) overall misdiagnosis of patients; and (D) Misdiagnosis grouped by age.

3.3.3. Geographic distribution of diagnosis

The survey showed a high proportion of patients required travelling for their diagnosis, with 64.8% unable to obtain a confirmed diagnosis locally. Around 46.0% of the participants were diagnosed outside their home province. The leading locations for confirmed diagnosis were Shanghai (21.6%), Beijing (15.6%), Guangdong (12.0%), and Chongqing (11.3%).

3.3.4. Departments of diagnosis

Due to the heterogeneity of initial symptoms, patients received their diagnoses across various clinical specialties. Overall, 56.1% of patients were diagnosed in immunology departments, whereas 12.4% were diagnosed in respiratory department, 11.5% in pediatrics, 7.6% in hematology departments, 2.8% in infectious diseases departments and 2.8% in critical care departments.

3.3.5. Treatment modalities and prognosis

Most patients received immunoglobulin replacement therapy (82%) and other pharmacological therapies (83%) as their primary treatment, while 17% underwent hematopoietic stem cell transplantation. Despite ongoing treatment, only 7% of survey participants reported being relatively healthy with no complications (Figure 3). Approximately 56% experienced persistent symptoms such as recurrent colds or chronic rhinitis, and 48% experienced bronchitis or pneumonia.

3.4. HRQoL

3.4.1. Pediatric patients

Among pediatric patients, the most frequently reported problems on the EQ-5D-Y-3L were pain/discomfort and depression/anxiety (Figure 4A). The mean EQ-VAS score was 66.5. According to the Chinese EQ-5D-Y-3L value set, the mean health utility value was 0.87 (*6*). Based on a comprehensive literature search of PubMed, CNKI, and Wanfang databases (up to September 2024) using the terms "EQ-5D-Y" and "China" or "Chinese adolescents", no published studies were identified that summarize EQ-5D-Y population norms for healthy Chinese adolescents. Therefore, Japanese adolescent health utility norms (ranging from 0.911 to 0.942) were utilized as a descriptive proxy (*7*).

3.4.2. Adult patients

Among adult patients, the most frequently reported problems on the EQ-5D-5L were anxiety/depression and pain/discomfort (Figure 4B). The mean VAS score was 65.9, appearing lower than the Chinese population norm of 87.1 (*6*). Based on the Chinese EQ-5D-5L value set (*8*), the mean health utility value of adult PID patients was 0.84, appearing lower than the reported Chinese population norm of approximately 0.95 (*9*).

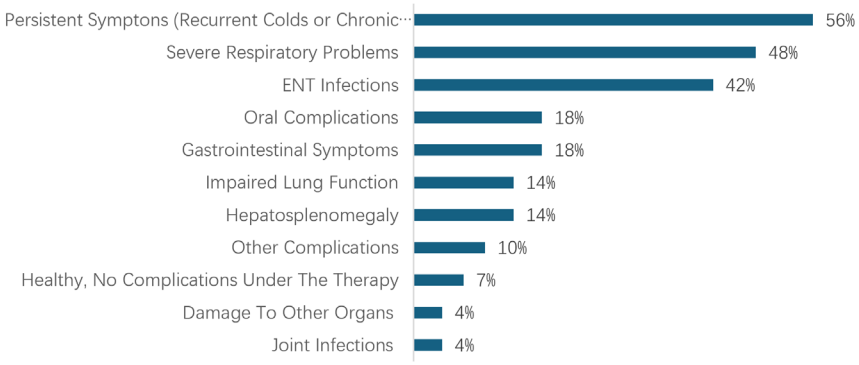

Figure 3. Patient prognosis under current treatment, symptoms and complications.

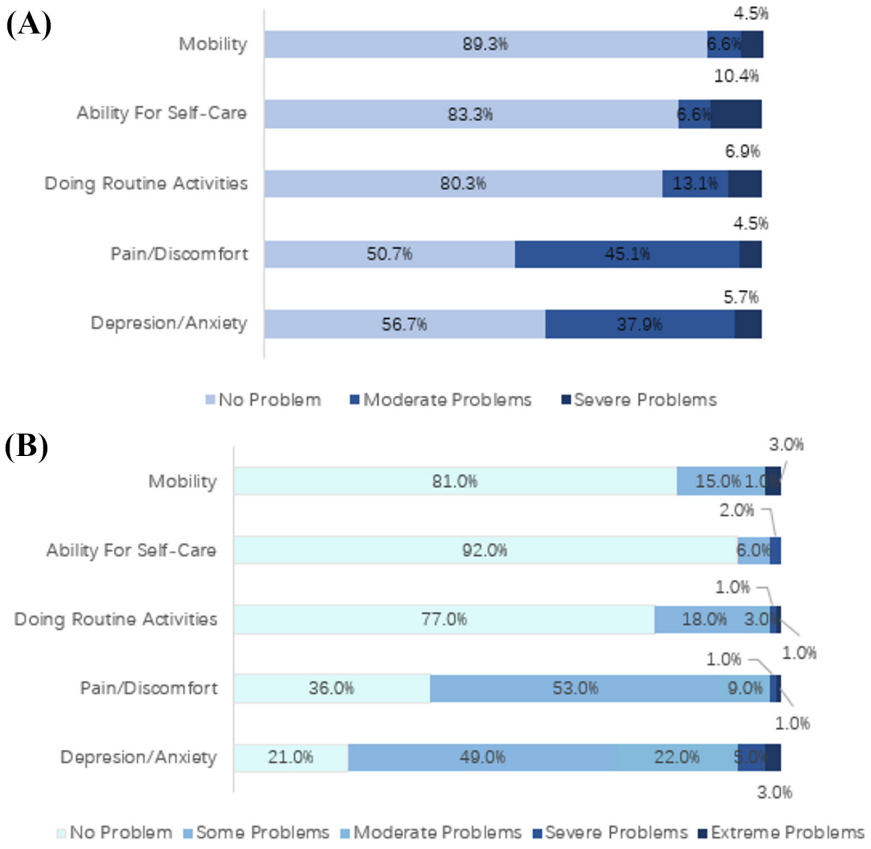

Figure 4. (A) HRQoL of pediatric patients and (B) HRQoL of adult patients. *Abbreviation*: HRQoL, health-related quality of life.

3.5. Impact of PID on education in pediatric patients

Among pediatric patients, 74.9% were able to continue their education without major disruption, while 25.1% experienced varying degrees of impact. Specifically, 11.9% discontinued their education, 11.6% were temporarily suspended, and 1.5% transferred to special schools.

Beyond attendance status, the disease exerted substantial impacts through frequent school absences and discrimination (Figure 5A), with 37.3% of pediatric participants missing 6 or more days of school per month (Figure 5B).

Among adult patients, 38% were enrolled as students, while 27% were unemployed or between jobs. Only 35% were engaged in full-time (26%) or part-time employment (9%).

Employed adults reported substantial work-related challenges, including frequent sick leave (47.1%), reduced job competitiveness (41.4%), and restricted occupational choices (38.6%) (Figure 6A). Among employed adults, 100% reported missing at least 1–5 days of work per month due to PID (Figure 6B).

3.6. Caregiving burdens

Caregiving support was required for 53.4% of pediatric patients and 21.0% of adult patients. Parents served as

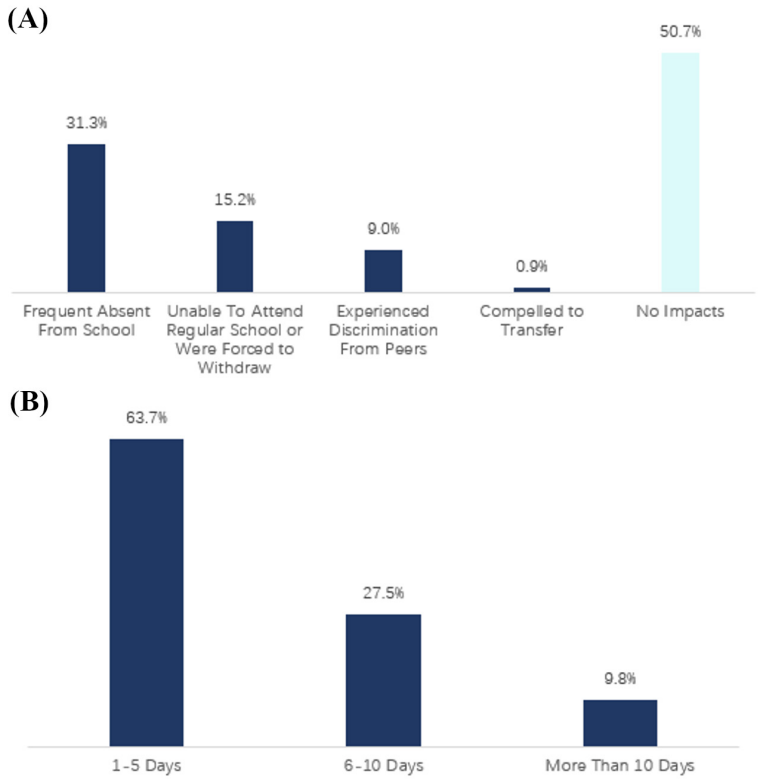

Figure 5. (A) Impact of PID on education of pediatric patients and (B) Absence per month of pediatric patients due to PID. *Abbreviation*: PID, primary immunodeficiency.

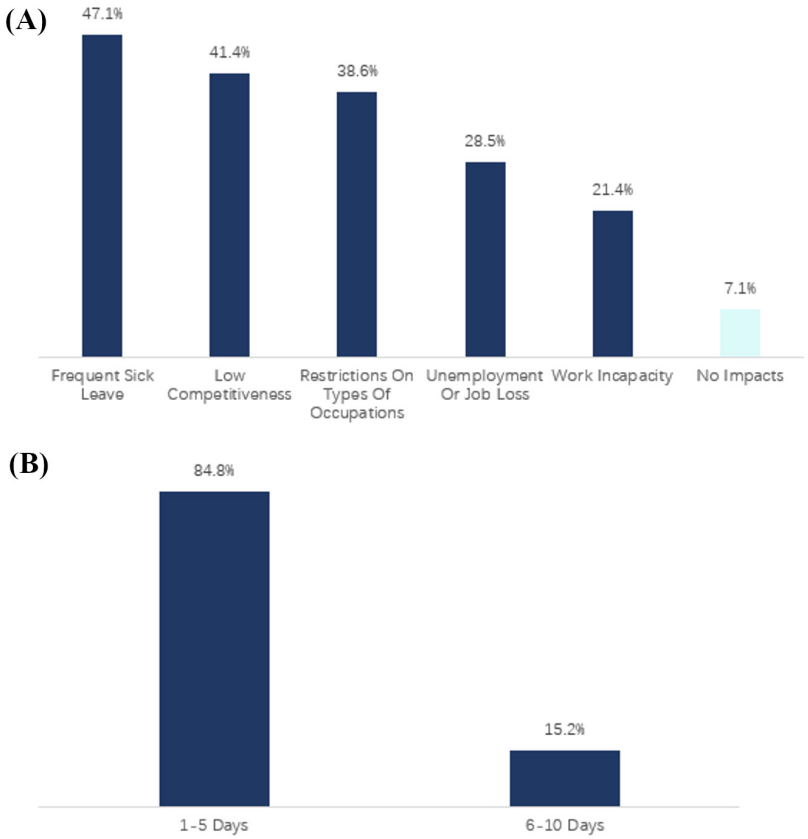

Figure 6. (A) Impact of PID on employment of adult patients and (B) Days of absence of adult patients per month due to PID. *Abbreviation*: PID, primary immunodeficiency.

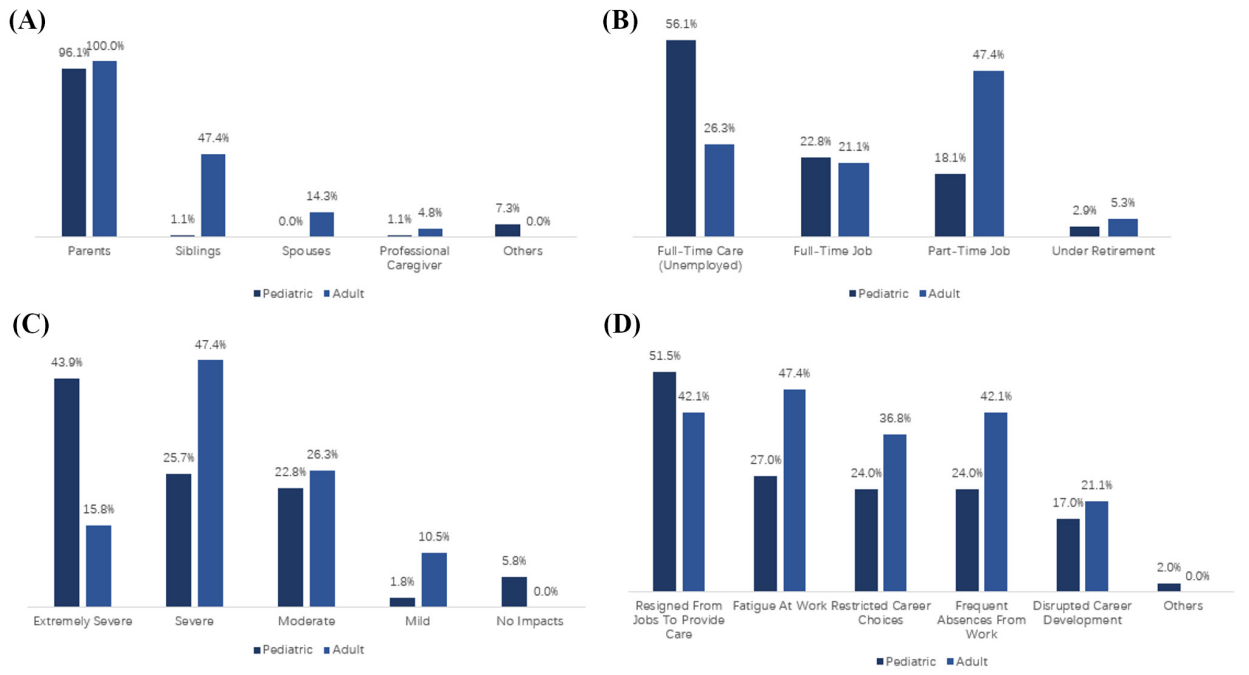

Figure 7. (A) Caregiver identity of different age groups; (B) Employment status of caregivers of different age groups; (C) The severity of impact of PID on employment of caregivers grouped by age; and (D) The impact of PID on employment of caregivers grouped by age.

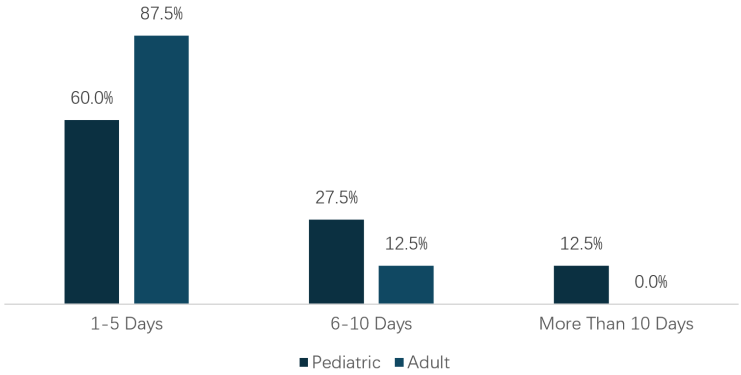

Figure 8. Days of absence of caregivers grouped by age.

the primary caregivers for nearly all pediatric (96.1%) and adult (100%) patients requiring care (Figure 7A).

Among those needing care, 36.9% of pediatric patients and 4.8% of adult patients needed full-time caregiving; 42.5% of pediatric patients and 28.5% of adult patients needed care for most of the day and 20.5% of pediatric patients and 66.7% of adult patients occasionally needed care.

Caregiving burden has shown to impact the employment status of primary caregivers, where 56.1% of pediatric patient caregivers and 26.3% adult patient caregivers were unemployed and providing full-time care (Figure 7B). Specifically, 51.5% of pediatric patient caregivers and 42.1% of adult patient caregivers had resigned from their jobs entirely to provide care (Figure 7D). Only 5.8% of pediatric patient caregivers reported no impact on their employment due to caregiving needs (Figure 7C).

High rates of absenteeism were also reported among employed caregivers, particularly those caring for pediatric patients (Figure 8).

4. Discussion

Based on a comprehensive literature search of PubMed, CNKI, and Wanfang databases (up to September 2024) using terms such as "primary immunodeficiency," "disease burden", and "China", the current study provides one of the first comprehensive descriptive quantitative assessments of the disease burden and unmet needs of patients with PID in China. The findings highlight profound challenges across diagnosis, treatment, quality of life, education, employment, and caregiving, underscoring the urgent need for integrated medical and

social support systems.

A major finding is the delay in diagnosis. On average, patients required three years from symptom onset to confirmed diagnosis, with nearly half (45.2%) waiting more than one year and 11.6% experiencing delays of over five years. Furthermore, 78.6% of patients reported misdiagnosis or missed diagnosis, with many initially receiving only symptomatic treatment. These data reveal critical gaps in early detection and clinical awareness. Expanding physician training in immunology, improving access to specialized diagnostic tests, and promoting the establishment of regional referral networks are crucial steps to reduce diagnostic delays and improve patient outcomes.

HRQoL results further underscores the heavy disease burden. Both pediatric and adult patients reported considerable emotional and physical distress. Average EQ-VAS scores for both pediatric (66.5) and adult patients (65.9) appeared numerically lower than population norms. Similarly, utility values (0.87 in children; 0.84 in adults) were lower than those of the general Chinese population and appeared lower than reported values for certain other chronic diseases in previous literature. These results indicate that the heavy burden of the disease and the restrictions it imposes, underscoring the need for interventions that address not only the physical health of patients with PID but also their psychological well-being and social integration. Establishing patient support networks, providing targeted mental health resources, and advancing policies that improve the socio-economic conditions of patients and their families should be regarded as integral components of a comprehensive care strategy.

The societal impact of PID is equally pronounced. Among pediatric patients, one in four reported disruptions of education, including school suspension, dropout, or transfer to special schools. Even those who remained in mainstream education frequently missed classes. Among adults, frequent sick leave, reduced job competitiveness, and occupational limitations were widespread. These findings reflect the significant constraints PID imposes on educational attainment and employment stability, ultimately restricting social participation and future opportunities. Policies that facilitate school and workplace support (*e.g.*, flexible attendance, remote working), could substantially improve the social integration of PID patients.

The burden extends beyond patients to their families. For caregivers, particularly of pediatric patients, the impact of caregiving burden on their career was severe. Frequent absences, reduced career development, and loss of income were widespread. These findings indicate the need for targeted caregiver support programs, including financial assistance, respite care services, and flexible workplace policies that accommodate caregiving responsibilities.

The current study has several important limitations. First, as a cross-sectional survey, the study is fundamentally descriptive and cannot establish causal relationships between PID and the reported socio-economic or quality-of-life outcomes. Second, the study lacks a healthy control or comparator group, limiting the ability to make definitive inferential comparisons. Third, participant recruitment was facilitated through a patient organization (PID Care China), resulting in a convenience sample. This approach introduces selection bias, as it may preferentially include patients and families with higher disease awareness, stronger social support, or greater engagement with advocacy groups, thereby limiting the nationwide generalizability of the findings. Fourth, all data, including PID diagnosis and specific subtype classifications, were collected *via* self-reported questionnaires. Without verification through medical records, this raises concerns about potential misclassification (particularly at the subtype level), recall bias, and reporting inaccuracies, which may not be able to fully capture the nuanced experiences of PID patients and their families. Finally, the lack of Chinese normative data for EQ-5D-Y required reliance on Japanese reference values, which may limit direct comparability due to cross-country methodological and cultural differences. Future research should integrate qualitative methods, such as patient and caregiver interviews, to better capture lived experiences, and utilize clinical registry data to verify medical parameters.

In conclusion, this study highlights the multifaceted disease burden of PID in China, spanning medical, psychological, educational, occupational, and caregiving dimensions. Addressing these challenges requires a holistic approach that goes beyond clinical management to include social support systems and policy-driven initiatives. Efforts to shorten diagnostic delays, expand access to advanced therapies, strengthen mental health and educational support, and protect caregiver employment rights are urgently needed. Such measures will not only improve clinical outcomes but also promote the long-term well-being and social inclusion of PID patients and their families.

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Original Article

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Surgical treatment and prognosis of type II congenital extrahepatic portosystemic shunts: A single-center experience of 31 cases

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SUMMARY: Congenital extrahepatic portosystemic shunts (CEPS) are rare congenital vascular malformations characterized by an abnormal communication between the hepatic portal venous system and the systemic venous system. Type II CEPS preserves partial portal venous blood flow and can usually be treated with conventional surgery rather than solely relying on liver transplantation. To determine the optimal surgical methods and complication management strategies for type II CEPS patients, we retrospectively analyzed 31 predominantly adult patients with type II CEPS, documenting their surgical approaches and the occurrence of postoperative complications. Five surgical approaches were employed: 11 patients underwent shunt occlusion with 5 cases of complications; 5 patients underwent splenic vessels ligation with 2 cases of complications; 5 patients underwent shunt occlusion combined with splenic artery ligation with 4 cases of complications; 8 patients underwent shunt occlusion combined with distal splenorenal shunt with 3 cases of complications; and 2 patients with lower extremity edema underwent inferior vena cava shunt bypass surgery, with no significant complications observed. In conclusion, surgery centering on the shunt occlusion demonstrates promising therapeutic value and remains the mainstay in the treatment of type II CEPS. Meanwhile, postoperative complications remain a concern, necessitating long-term monitoring and management.

Keywords: congenital extrahepatic portosystemic shunts, portal vein, surgical treatment, prognosis, complication

1. Introduction

Congenital extrahepatic portosystemic shunts (CEPS), also known as Abernethy malformation, is a congenital vascular malformation characterized by an abnormal communication between the extrahepatic portal venous system and the systemic venous system. CEPS has a low global incidence, with fewer than 400 cases reported in the relevant literature to date. CEPS is classified into two types based on the presence or absence of intrahepatic portal venous blood flow (*1,2*). Type I CEPS is characterized by the complete absence of portal venous blood flow to the liver, while type II CEPS is characterized by partial preservation of portal venous blood flow to the liver (*3,4*). To confirm the classification of CEPS patients, balloon occlusion testing is required for those screened by routine imaging examinations to determine the presence of intrahepatic portal venous branches (*5*). For patients diagnosed with type II CEPS, due to the presence of intrahepatic portal venous branches, favorable therapeutic outcomes can usually be achieved through shunt ligation alone (*6*).

Previous findings have documented that some type II CEPS patients may present with severe complications, including hepatic encephalopathy (HE), gastrointestinal bleeding (GIB), pulmonary arterial hypertension (PaHT), and hepatopulmonary syndrome (*7-10*). Some patients with type II CEPS may develop hepatic nodules. Although most are benign, malignant transformation remains possible (*11*). For patients with such severe complications, surgical treatment can alleviate symptoms and slow disease progression to a certain extent. For asymptomatic patients, prophylactic surgical treatment can prevent such severe complications (*12*).

Currently, shunt occlusion remains the primary surgical approach for managing type II CEPS patients, including shunt ligation and endovascular embolization (*13*). Most previous studies have confirmed that shunt occlusion yields favorable recovery outcomes in pediatric-dominant patient populations, but there is a scarcity of literature documenting treatment approaches for adult-dominant populations (*8,10*). This study

aims to summarize our single-center experience with individualized surgical management, focusing on decision-making principles, perioperative outcomes, complication patterns, and long-term follow-up.

2. Patients and Methods

2.1. Study subjects

A total of 31 patients with type II CEPS who were hospitalized in the Department of Hepatobiliary and Pancreatic Surgery at the Chinese People's Liberation Army General Hospital from January 2011 to December 2024 were enrolled in this study. The inclusion criterion was that all patients were confirmed as type II CEPS by balloon occlusion testing, which demonstrated preserved intrahepatic portal venous flow. Patients with type I CEPS (absence of intrahepatic portal perfusion) were excluded.

2.2. Preoperative evaluation and diagnostic confirmation

All patients underwent comprehensive preoperative imaging assessments, including abdominal computed tomography (CT), magnetic resonance imaging (MRI), and/or ultrasonography (US). These examinations served to delineate shunt anatomy and classify shunts according to the Blanc system (*14*), which encompassed categories such as extrahepatic portosystemic shunt (EHPS), end to side like portocaval shunt (ESPC), side to side like portocaval shunt (SSPC), portohepatic shunt (PH), and persistent ductus venosus (PDV). Anatomical variants within this classification, including extrahepatic portorenal (EHPR), extrahepatic porto iliac/caval (EHPC), end to side like portorenal (ESPR), side to side like portorenal (SSPR), and side to side like portoatrial (SSPA), were also documented. In addition, imaging was used to evaluate severity of portal hypertension and to identify associated complications, such as hepatic nodules or gastroesophageal varices.

Laboratory investigations included measurements of liver function parameters (alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, albumin, prothrombin time (PT)), blood ammonia levels, and indocyanine green retention 15 min (ICG R15) to evaluate hepatic reserve and operative risk.

Definitive classification of CEPS was established *via* balloon occlusion angiography. Temporary occlusion of the shunt allowed assessment of intrahepatic portal vein patency and portal pressure dynamics, thereby distinguishing type II (partial portal flow preserved) from type I shunts.

2.3. Selection of surgical approaches

Surgical strategy was individualized according to preoperative shunt anatomy, portal hemodynamics, and major clinical manifestations. Preoperative imaging was used to evaluate shunt type, diameter, length, and anatomical relationship to the portal venous system, while intraoperative portal pressure measurement and ultrasonography were used to assess the hemodynamic tolerance of shunt occlusion and to guide final operative strategy. The main clinical considerations included portal hypertension, variceal bleeding risk, hyperammonemia, and lower-extremity symptoms related to abnormal venous drainage. Based on these factors, patients were assigned to one of five surgical approaches (Figure 1).

Shunt occlusion was selected for patients in whom direct interruption of the shunt was considered technically feasible and hemodynamically tolerable. Two options were used. Surgical ligation was preferred in patients with thick or short shunts, or in those requiring additional open surgical procedures. In these patients, absence of obvious congestion in the small intestine and colon after occlusion was used as an intraoperative indicator of acceptable portal venous outflow and tolerable portal pressure elevation. Endovascular embolization was considered in patients with relatively small shunts or in those who were unable to tolerate general anesthesia. After embolization, portal pressure was reassessed to ensure that it did not exceed 25 cmH_2O.

Splenic vessels ligation (ligation of splenic artery and vein) was used mainly in patients with splenic vein–left renal vein shunts accompanied by a splenic vein steal phenomenon identified by intraoperative ultrasonography.

Shunt occlusion combined with splenic artery ligation was considered in patients in whom direct shunt occlusion alone was judged likely to cause excessive postoperative portal hypertension. In these cases, splenic artery ligation was used to reduce portal inflow and improve hemodynamic tolerance after shunt restriction.

Shunt occlusion combined with distal splenorenal shunt (DSRS) or side-to-side anastomosis between the splenic vein and the inferior vena cava (IVC) was reserved for patients with severe portal hypertension suggested by clinical or imaging findings, or with marked varices along the lesser curvature of the stomach and a substantial risk of bleeding identified during intraoperative exploration. In patients with splenic vein shunts, splenic vessels ligation (*i.e.*, shunt occlusion) was performed first, followed by splenorenal shunting. In patients with other shunt types, such as portorenal or gastrorenal shunts, splenic vessels ligation and splenorenal shunting were performed first, followed by shunt occlusion.

IVC shunt bypass surgery was selected for patients with portoiliac shunts who presented with claudication and significant lower-extremity edema. In these patients, an artificial bypass from the shunt to the IVC was created to restore venous return and relieve venous congestion.

Intraoperative changes in portal pressure before and after temporary or definitive shunt occlusion

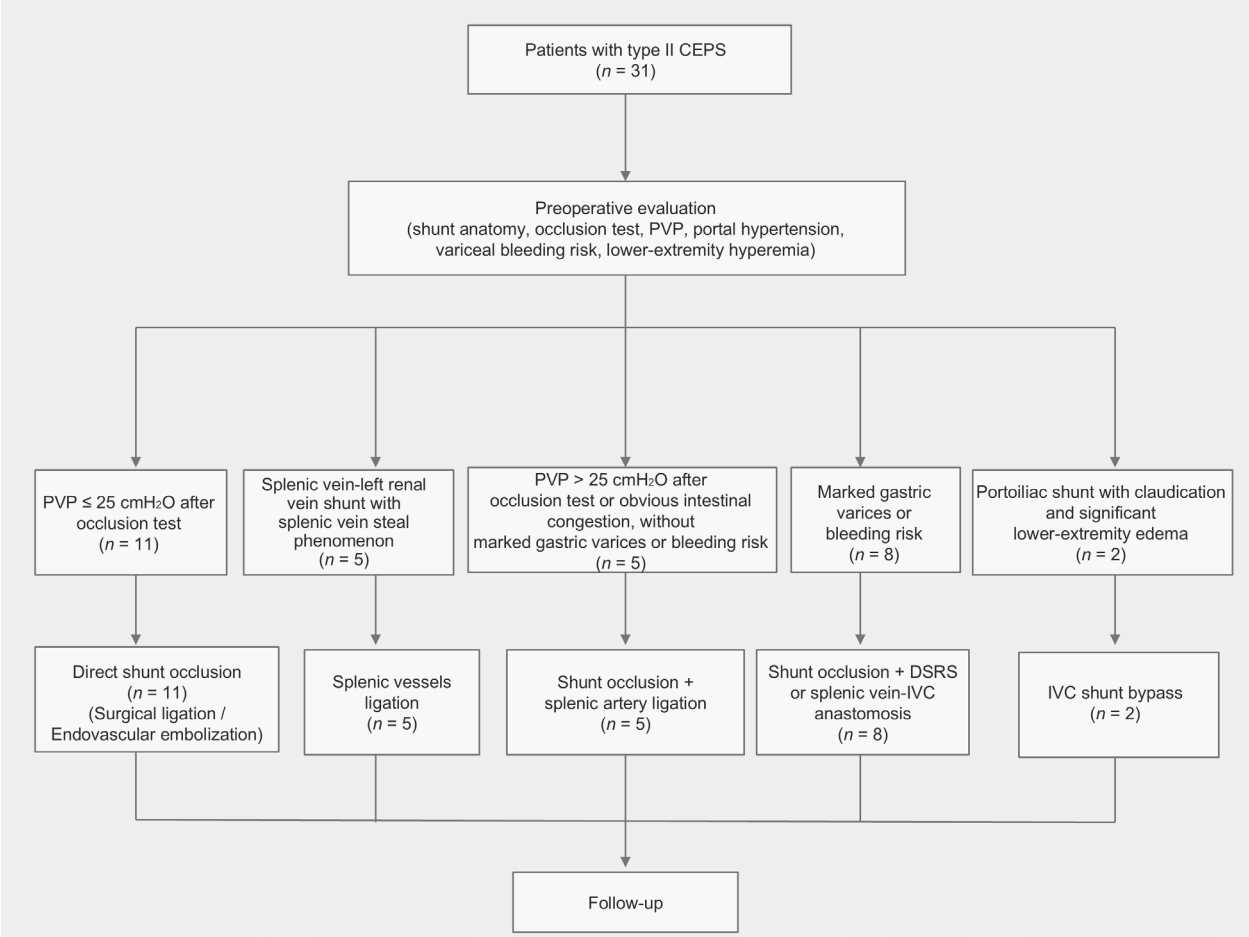

Figure 1. Surgical decision-making flowchart. *Abbreviations*: CEPS, congenital extrahepatic portosystemic shunt; PVP, portal venous pressure; DSRS, distal splenorenal shunt; IVC: inferior vena cava.

were recorded in all applicable patients. Blood flow direction and velocity were monitored by intraoperative ultrasonography to confirm the hemodynamic effect of the procedure. Postoperatively, imaging re-evaluation and laboratory testing were performed to assess recovery and detect complications.

2.4. Study follow-up

Postoperative evaluation included serial imaging (CT/US) and laboratory tests to assess restoration of hepatopetal portal flow, changes in liver volume, and the development of complications, such as thrombosis, recurrent shunts, or variceal progression. Symptom recurrence or new complications prompted further diagnostic work-up and tailored management. Follow-up data were collected until December 2024.

2.5. Statistical methods

SPSS 26.0 software was used to analyze data for each group. Measurement data conforming to normal distribution were expressed as mean ± standard deviation ($\bar{x} \pm s$) and compared using *t*-test; measurement data not conforming to normal distribution were expressed as median and interquartile range (IQR) M_d (P25, P75) and compared using the rank sum test. A p value < 0.05 was considered statistically significant. Given the small sample sizes in several subgroups, all statistical analyses were considered exploratory. No adjustment for multiple comparisons was performed because of the descriptive nature of the study.

2.6. Ethical approval

This study was approved by the Ethics Committee of Human Experimentation of the PLA General Hospital (No.S2018-013-01). All patients or their parents (for patients younger than 18 years) signed informed consent forms prior to inclusion in the study. This study was conducted in accordance with the Declaration of Helsinki.

3. Results

3.1. Baseline characteristics of patients

A total of 31 patients were enrolled in this study, including 13 males (42%). The median age at diagnosis was 39 years (range: 2–71 years). The follow-up cutoff

date was December 2024, and detailed baseline data are shown in Table 1.

Among the 31 enrolled patients, six were diagnosed incidentally during physical examination. The main symptoms at admission of the remaining patients were as follows: HE (n = 9, 29%), hyperammonemia (n = 20, 65%), PaHT (n = 4, 13%), hepatic nodules (n = 19, 61%), GIB (n = 7, 23%), abdominal pain (n = 4, 13%), dyspnea (n = 2, 6%), left lower extremity claudication (n = 2, 6%), and hemoptysis (n = 1, 3%). All patients were confirmed as type II CEPS by balloon dilation-occlusion testing. Anatomical types of shunts in all patients were classified according to the 4-category congenital portosystemic shunts (CPS) model proposed by Blanc, and information such as type II CEPS complications and specific surgical approaches is summarized in Table 2.

Among the 20 patients diagnosed with hyperammonemia, the mean blood ammonia level was 69.47 ± 21.60 μmol/L. Nine of these patients had HE before treatment, with a mean blood ammonia level of 81.92 ± 22.67 μmol/L. Lower extremity claudication was caused by a portoiliac shunt. Among the hepatic nodules, 7 were focal nodular hyperplasia (FNH), 8 were cirrhotic nodules (CN), and non-specific hepatic nodules (NSHN) were found in 8 patients on pathological examination.

Liver function test indicators of patients were as follows: the median aspartate aminotransferase (AST) was 24 U/L (IQR: 21.6–41.2), with abnormalities (≥ 40 U/L) in 9 patients. The median alanine aminotransferase (ALT) was 18.2 U/L (IQR: 14.1–26), with abnormalities (≥ 40 U/L) in 3 patients. The median total bilirubin was 21.9 μmol/L (IQR: 13.6–36.9), with abnormalities (> 21 umol/L) in 17 patients. The mean albumin level was 33 ± 5.63 g/L, with abnormalities (< 35 g/L) in 16 patients. Blood ammonia was measured in 30 patients, with a mean value of 54.33 ± 28.17 μmol/L (normal range: 0–32 μmol/L), and 20 patients had abnormalities. Preoperative ICG-R15 was measured in 21 patients, with a mean value of 33.60 ± 14.46%. PT was measured in all patients, with a mean value of 17.36 ± 2.44 s, and abnormalities (> 15 s) were observed in 28 patients

3.2. Treatment approaches and perioperative complication management

Thirty-one patients with type II CEPS underwent surgical intervention, including shunt occlusion (n = 11, 35.5%), splenic vessels ligation (n = 5, 16.1%), shunt occlusion combined with splenic artery ligation (n = 5, 16.1%), shunt occlusion combined with DSRS (n = 8, 25.8%), and IVC shunt bypass (n = 2, 6.4%). A descriptive summary of perioperative outcomes across the five surgical strategies is provided in Table 3. Overall, blood ammonia levels and ICG-R15 decreased significantly after surgery (p = 0.001 and p = 0.04), while portal pressure and liver volume increased significantly (p = 0.008 and p < 0.001, respectively). In contrast, no significant postoperative changes were observed in spleen volume (and p = 0.923). Detailed hemodynamic and volumetric data are presented in Table 4.

Table 1. Baseline Characteristics (n = 31)

Characteristics	*n*	%
Sex (Male)	13	42
Hepatic encephalopathy	9	29
Incidental finding on examination	6	19
Gastrointestinal bleeding	7	23
Abdominal pain	4	13
Dyspnea	2	6
Left lower limb claudication	2	6
Hemoptysis	1	3

A total of eleven patients received shunt occlusion, including six who underwent surgical ligation and five who underwent endovascular embolization. After treatment, blood ammonia levels decreased from 73.40 ± 22.72 μmol/L to 36.2 ± 20.67 μmol/L, and ICG-R15 decreased from 33.95 ± 19.68% to 21.16 ± 14.47%. Portal pressure increased from 11.45 ± 6.18 cmH_2O to 16.4 ± 4.39 cmH_2O. Liver volume increased from 734.61 ± 227.08 cm^3 to 864.22 ± 247.04 cm^3, whereas spleen volume showed only a limited change (333.475 ± 242.84 cm^3 *vs.* 363.89 ± 243.16 cm^3). When the surgical ligation and endovascular embolization subgroups were descriptively compared, changes in blood ammonia level, liver volume, and spleen volume appeared broadly comparable, although these subgroup observations should be interpreted with caution given the limited sample size.

Of the five patients who underwent splenic vessels ligation, four achieved significant symptom relief after surgery. Blood ammonia levels decreased from 67.58 μmol/L [IQR: 54.61–105.95] to 42.19 μmol/L [IQR: 22.26–100.16]. Portal pressure increased from 19.63 ± 6.9 cmH_2O to 22.12 ± 3.12 cmH_2O. ICG-R15 decreased from 37.13 ± 11.31% *vs.* 23.17 ± 19.17%. Liver volume increased from 673.6 ± 46.78 cm^3 to 768.07 ± 105.08 cm^3.

Among the five patients who underwent shunt occlusion combined with splenic artery ligation, all achieved significant relief of symptoms after surgery. Blood ammonia levels increased from 49.18 μmol/L [IQR: 22.73–51.00] to 56.34 μmol/L [IQR: 12.38-72.14]. Portal pressure increased from 14.1 ± 5.64 cmH_2O to 21.4 ± 1.52 cmH_2O. ICG-R15 increased from 28.9 ± 21.15% to 33.87 ± 24.58%. Liver volume increased from 1000.33 ± 692.06 cm^3 *vs.* 1156.25 ± 683.62 cm^3.

All eight patients who received shunt occlusion combined with DSRS achieved symptom relief. Among the five hyperammonemia patients, blood ammonia levels decreased from 69.31 ± 15.58 μmol/L to 33.72 ± 11.13 μmol/L. Portal pressure decreased from 24.0 cmH_2O [IQR: 15.75–28.0] to 22.0 cmH_2O [IQR: 17.75–31.0]. ICG-R15 decreased from 44.57 ± 8.31% to 25.83 ± 14.15%. Liver volume remained relatively stable from

Table 2. Detailed Information (n = 31)

Case No.	Sex	Age	Fistula Classification and Anatomy (Blanc's Classification)	CPS Pattern	Type II CEPS Complications	Management
1	F	2	Superior Mesenteric Vein - Inferior Mesenteric Vein - Left Iliac Vein	EHPS	Hematochezia, NSHN	Open surgical ligation of the anomalous shunt + Splenic artery ligation
2	F	3	Common Trunk of SMV & SV - Left Renal Vein, Portal Vein arising from the trunk	ESPR	FNH, RNH	Open surgical ligation of the anomalous shunt
3	M	10	Common Trunk of SMV & SV - IVC, Portal Vein arising from the trunk	SSPC	PaHT, NSHN, Accessory Spleen	Open surgical ligation of the anomalous shunt
4	M	15	Main Portal Vein - Right Atrium	SSPA	PaHT, FNH, Upper Abdominal Pain	Open surgical ligation of the anomalous shunt + Splenic artery ligation
5	M	15	Inferior Mesenteric Vein - Iliac segment of IVC	EHPC	lower extremity edema	Two-stage shunt occlusion, Subsequent IVC shunt bypass surgery
6	M	18	Portal Vein - Right Hepatic Vein shunt	PH	PaHT	DSA-guided embolization of the porto-hepatic shunt
7	M	19	Main Portal Vein - IVC	SSPC	FNH	Laparoscopic shunt flow restriction, Subsequent transhepatic arterial embolization
8	F	21	Main Portal Vein - IVC	ESPC	FNH, NSHN, Congenital Heart Disease	Open Portal vein ligation + Splenic artery ligation
9	F	27	Common Trunk of SMV & SV - Left Renal Vein, Main Portal Vein - Left Renal Vein	ESPR	Multiple FNH	Open surgical shunt flow restriction
10	M	31	Main Portal Vein - IVC	SSPC	Hematemesis due to Cirrhosis	Open shunt ligation + Splenic artery + Gastric coronary vein ligation, DSRS
11	F	32	Splenic Vein - Left Renal Vein	EHPR	Melena due to Cirrhosis, CN, Cavernous Transformation of Portal Vein, and Splenomegaly	Laparoscopic Splenic vessels ligation, Subsequent endovascular embolization
12	F	33	Splenic Vein - Left Renal Vein	EHPR	CTPV, Cirrhosis	Open splenic vessels ligation + Shunt vessel - Left Renal Vein shunt
13	M	35	Common Trunk of SMV & SV - Left Renal Vein	EHPR	Hepatic Adenoma, FNH, CN	Open surgical shunt narrowing + Liver Nodule Resection
14	M	35	Inferior Mesenteric Vein - Iliac Vein	EHPC	lower extremity edema	Open partial shunt occlusion, IVC shunt bypass surgery
15	F	37	Common Trunk of SV & SMV - Esophagogastric Variceal Shunt	EHPS	Fatigue, Autoimmune Cirrhosis, CN	Shunt vessel occlusion + Splenic artery ligation + DSRS

Abbreviations: CPS, congenital portosystemic shunts; SMV, superior mesenteric vein; SV, splenic vein; IMV, inferior mesenteric vein; FNH, focal nodular hyperplasia; CN, cirrhotic nodules; NSHN, non-specific hepatic nodules; RNH, regenerative nodular hyperplasia; PaHT, pulmonary arterial hypertension; HPS, hepatopulmonary syndrome; HE hepatic encephalopathy; CTPV, cavernous transformation of portal vein; DSRS, distal splenorenal shunt; DSA, digital subtraction angiography; IVC, inferior vena cava.

Table 2. Detailed Information (n = 31) (continued)

Case No.	Sex	Age	Fistula Classification and Anatomy (Blanc's Classification)	CPS Pattern	Type II CEPS Complications	Management
16	F	38	Superior Mesenteric Vein - IVC near Right Iliac Vein	EHPS	CTPV, NSHN, Hematemesis due to Cirrhosis, HPS	Open surgical ligation of the anomalous shunt
17	F	43	Splenic Vein - Left Renal Vein	EHPR	PaHT, Cirrhosis	Splenic vessels ligation
18	F	46	Main Portal Vein - Left Renal Vein	SSPR	Hematemesis due to Cirrhosis, NSHN, CN	Open portal vein ligation + Splenic artery ligation + DSRS
19	F	47	Gastric Coronary Vein - Left Renal Vein	EHPR	Melena due to Cirrhosis, NSHN	Open shunt ligation + Splenic artery ligation + DSRS, Subsequent DSA-guided splenic embolization
20	F	52	Superior Mesenteric Vein - IVC (near Right Iliac Vein)	EHPC	Hematochezia, CN	Open shunt ligation + Splenic artery ligation
21	F	54	Common Trunk of SV & SMV - Esophagogastric Variceal Shunt	EHPS	CTPV, FNH, Cirrhosis, Splenomegaly	Splenic vessels ligation + DSRS
22	F	55	Common Trunk of SV & SMV - Left Renal Vein	ESPR	HE	Balloon occlusion of splenorenal shunt
23	M	55	Splenic Vein - Left Renal Vein	EHPR	HE, Cirrhosis	Balloon occlusion of splenorenal shunt, Subsequent splenic vessels ligation
24	M	56	Splenic Vein - Left Renal Vein	EHPR	HE, Cirrhosis, NSHN	Splenic vessels ligation
25	F	56	Gastric Coronary Vein - Left Renal Vein	EHPR	Asymptomatic initially, jaundice developed one year later.	DSA-guided shunt occlusion
26	M	57	Splenic Vein - Left Renal Vein	EHPR	HE, Cirrhosis, CN	Splenic vessels ligation
27	F	61	Inferior Mesenteric Vein - IVC	EHPC	HE, CN	Laparoscopic occlusion of varices, DSRS
28	M	63	Portal Vein - IVC , Gastric Coronary Vein - Left Renal Vein	ESPC, EHPC	HE, NSHN	Open shunt ligation, Splenic artery ligation, Subsequent gastric coronary vein embolization & shunt occlusion
29	M	64	Splenic Vein - Left Renal Vein	EHPR	IVC Stenosis, HE, Cirrhosis, CN	DSA-guided porto-hepatic shunt embolization
30	F	65	Portal Vein - IVC	SSPC	Abdominal Pain, Cirrhosis	Open shunt ligation + Splenic artery ligation + DSRS
31	F	71	Portal Vein - Left Renal Vein	ESPR	HE	Laparoscopic coronary vein ligation + Splenic artery ligation

Abbreviations: CPS, congenital portosystemic shunts; SMV, superior mesenteric vein; SV, splenic vein; IMV, inferior mesenteric vein; FNH, focal nodular hyperplasia; CN, cirrhotic nodules; NSHN, non-specific hepatic nodules; RNH, regenerative nodular hyperplasia; PaHT, pulmonary arterial hypertension; HPS, hepatopulmonary syndrome; HE hepatic encephalopathy; CTPV, cavernous transformation of portal vein; DSRS, distal splenorenal shunt; DSA, digital subtraction angiography; IVC, inferior vena cava.

Table 3. Efficacy of five surgical procedure types

Characteristics	Shunt Occlusion (*n* = 11)	Splenic vessels ligation (*n* = 5)	Shunt Occlusion + Splenic Artery Ligation (*n* = 5)	Shunt Occlusion + DSRS (*n* = 8)	IVC Shunt Bypass surgery (*n* = 2)
Procedure Type					
Surgical	6	5	5	8	2
Endovascular	5	0	0	0	0
Clinical Indication & Outcome					
HE	3 (All improved)	3 (All improved)	1 (All improved)	1 (All improved)	-
PaHT	2 (All improved)	1 (1 Death)	1 (All improved)	-	-
GIB	1 (All improved)	1 (All improved)	2 (All improved)	3 (2 improved)	-
Abdominal Pain	2 (All improved)	-	1 (All improved)	1 (All improved)	-
Jaundice	1 (1 Death)	-	-	-	-
Claudication	-	-	-	-	2 (All improved)
Prophylactic Treatment	2	-	-	3	-
Complications	5 (1 Death)	2 (1 Death)	4	3	0

Abbreviations: HE, hepatic encephalopathy; PaHT, pulmonary arterial hypertension; GIB, gastrointestinal bleeding; DSRS, distal splenorenal shunt; IVC, inferior vena cava.

Table 4. Hemodynamic and volumetric changes before and after surgery

Procedure	Before Surgery	After Surgery	*p* value
Overall (*n* = 31, 100%)			
Blood ammonia (μmol/L) [hyperammonemic patients, *n* = 20]	68.38 [53.25–78.93]	32.87 [21.40–53.78]	0.001*
Portal pressure (cmH_2O) [*n* = 22]	15.75 [10.5–19.25]	21.00 [15.0–22.5]	0.008*
ICG-R15 (%)[*n* = 17]	35.73 ± 14.68	27.81 ± 18.38	0.04*
Liver volume (cm^3)[*n* = 25]	811.17 ± 315.94	915.07 ± 338.76	< 0.001*
Spleen volume (cm^3)[*n* = 13]	367.31 ± 264.14	369.65 ± 231.61	0.923
Shunt occlusion (*n* = 11, 35.5%)			
Blood ammonia (μmol/L) [hyperammonemic patients, *n* = 7]	73.40 ± 22.72	36.20 ± 20.67	< 0.001*
Portal pressure (cmH_2O) [*n* = 8]	11.45 ± 6.18	16.40 ± 4.39	0.015*
ICG-R15 (%)[*n* = 6]	33.67 ± 18.39	26.48 ± 20.9	0.207
Liver volume (cm^3) [*n* = 9]	734.61 ± 227.08	864.22 ± 247.04	0.024*
Spleen volume (cm^3) [*n* = 8]	333.48 ± 242.84	363.89 ± 243.16	0.19
Splenic vessels ligation (*n* = 5, 16.1%)			
Blood ammonia (μmol/L) [hyperammonemic patients, *n* = 4]	67.58 [54.61–105.95]	42.19 [22.26–100.16]	0.47
Portal pressure (cmH_2O) [*n* = 4]	19.63 ± 6.90	22.12 ± 3.12	0.47
ICG-R15 (%)[*n* = 3]	37.13 ± 11.31	23.17 ± 19.17	0.404
Liver volume (cm^3)[*n* = 3]	673.60 ± 46.78	768.07 ± 105.08	0.376
Shunt occlusion + splenic artery ligation (*n* = 5, 16.1%)			
Blood ammonia (μmol/L) [hyperammonemic patients, *n* = 2]	49.18 [22.73–51.00]	56.34 [12.38-72.14]	0.655
Portal pressure (cmH_2O) [*n* = 5]	14.10 ± 5.64	21.40 ± 1.52	0.044*
ICG-R15 (%)[*n* = 3]	28.90 ± 21.15	33.87 ± 24.58	0.18
Liver volume (cm^3)[*n* = 4]	1000.33 ± 692.06	1156.25 ± 683.62	0.005*
Shunt occlusion + DSRS (*n* = 8, 25.8%)			
Blood ammonia (μmol/L) [hyperammonemic patients, *n* = 5]	69.31 ± 15.58	33.72 ± 11.13	< 0.001*
Portal pressure (cmH_2O) [*n* = 5]	24.0 [15.75–28.0]	22.0 [17.75–31.0]	0.492
ICG-R15 (%)[*n* = 3]	44.57 ± 8.31	25.83 ± 14.15	0.11
Liver volume (cm^3)[*n* = 7]	806.09 ± 161.89	807.16 ± 129.53	0.89

Notes: Data are presented as mean ± SD or median [IQR]. *indicates $p < 0.05$. *Abbreviations*: DSRS, distal splenorenal shunt; ICG-R15, indocyanine green retention rate at 15 min; IQR, interquartile range; IVC, inferior vena cava; SD, standard deviation.

806.09 ± 161.89 cm^3 to 807.16 ± 129.53 cm^3.

Two patients underwent IVC shunt bypass surgery due to lower extremity edema, and their symptoms were effectively relieved after postoperative management and treatment strategy adjustment.

3.3. Perioperative complication management and outcomes

Among the 31 treated patients, 9 experienced postoperative complications of Clavien-Dindo grade III or higher; detailed postoperative grading is shown in Table 5.

Of the patients who underwent shunt occlusion, case 25 (jaundice) had been found to have a splenorenal shunt 1 year earlier and presented at admission with obvious decompensated cirrhosis. Interventional treatment was selected because it was considered less invasive. Although portal venous flow recovered after the procedure, the patient developed sudden cardiopulmonary

Table 5. Clavien-Dindo Complication Classification (*n* = 14)

Grade	Complication	*n*	Management
Grade II			
	Portal System Thrombosis	4	Anticoagulation
	Pulmonary Embolism	1	Anticoagulation
Grade III			
	Portal Hypertension	2	No effective intervention
	New Shunt Formation	4	Interventional occlusion
	Recurrent hepatic encephalopathy	1	Medical therapy
Grade IV			
	Multi-organ Failure	1	No effective intervention
Grade V			
	Acute Myocardial Infarction	1	No effective intervention

arrest on postoperative day 2, and embolic occlusion of a vital organ was considered a possible cause. Four other patients developed postoperative complications: 2 with portal hypertension, 1 with HE, and 1 with portal vein thrombosis. Case 22 (HE) had an elevated ICG-R15 value after interventional treatment and developed portal hypertension symptoms (manifested as ascites) 1 month postoperatively. Case 23 (HE) had a reduced liver volume postoperatively (1002.9→911.4 cm^3) and recurrent HE two months later. After splenic vessels ligation, the ICG-R15 value decreased to 40.1% (48%→40.1%), and the blood ammonia level dropped to 84.9 μmol/L (113.4→84.9 μmol/L). Case 7 (prophylactic treatment) developed portal hypertension-related HE six months postoperatively; after segmental hepatic artery embolization, the blood ammonia level decreased significantly (40.9→10.4 μmol/L) with favorable recovery. Case 13 (Liver Nodule) was found to have shunt thrombosis by postoperative ultrasound; and no significant changes were observed after three months of warfarin treatment.

Among the five patients who underwent splenic vessels ligation, Case 17 (PaHT) had severe pulmonary arterial hypertension (pulmonary artery pressure 122 mmHg) and right heart insufficiency for 3 years before surgery. Preoperative evaluation suggested insufficient operative reserve. Because marked thrombocytopenia secondary to hypersplenism contraindicated interventional treatment and no other alternative was available, the patient underwent surgery and subsequently developed postoperative multi-organ failure. Case 11 (melena) had an elevated ICG-R15 value (5→34%) 2 months postoperatively. Interventional examination revealed a new shunt (splenic vein-left ovarian vein shunt), which was occluded interventially; and the patient recovered well with a decreased ICG-R15 value (34→25.9%).

Among the five patients who underwent shunt occlusion combined with splenic artery ligation, 4 developed postoperative complications: 3 had elevated ICG-R15 values. Case 4 (PaHT) had an increased ICG-R15 value (17.6→23.7%), developed pulmonary embolism at 1-year follow-up, and multiple abdominal collateral circulations at 5-year follow-up. Case 8 (Congenital Heart Disease) developed superior mesenteric vein and main portal vein thrombosis 10 days postoperatively with an elevated ICG-R15 value (15.8→16.0%). After thrombolytic therapy and regular warfarin administration after discharge, the thrombosis disappeared at 1-month follow-up. Case 28 (HE) had an elevated ICG-R15 value (53.3→61.9%); and a new shunt (gastroepiploic vein- IVC shunt) was detected 3 months postoperatively. After interventional occlusion, the portal pressure increased (12.5→20 cmH_2O), and the blood ammonia level decreased (62.13→28.95 μmol/L). Case 1 (a child with a portoiliac shunt and hematochezia) had symptom recurrence 2 years later due to a new abnormally dilated drainage tract. Interventional examination revealed that the previously ligated shunt vessel (inferior mesenteric vein) drained into abnormally dilated pelvic veins.

Among the eight patients who underwent shunt occlusion combined with DSRS, three developed complications: Case 18 (hematochezia) had elevated portal pressure (24→30 cmH_2O) postoperatively, recurrent hematochezia due to gastrorenal shunt 2 years later, and multiple hepatic nodules 4 years later. Case 10 (GIB) had decreased portal pressure (28→14 cmH_2O) postoperatively but developed extensive portal vein and splenic vein thrombosis 10 days later. Anticoagulant therapy was ineffective, and hematemesis, melena, and portal hypertensive gastropathy occurred within 1 year. Case 19 (hematochezia) had decreased portal pressure (21.5→18.5 cmH_2O) postoperatively, developed portal vein thrombosis complicated by hilar and gastric fundus varices, and splenic artery thrombosis within 10 days. After heparin anticoagulation, the thrombosis resolved, and the extent of splenic infarction decreased.

Two patients underwent IVC shunt bypass surgery due to claudication. Case 5 (lower extremity edema) initially underwent a two-stage shunt occlusion. Postoperative indicators improved (decreased blood ammonia, elevated portal pressure), but symptoms did not. Long-term follow-up showed lower extremity flushing, thrombosis, and portal hypertension complications due to the formation of superior mesenteric vein-iliac vein collateral circulation. After

careful consideration, IVC shunt bypass surgery was performed, and symptoms were relieved. Case 14 (lower extremity edema) showed no symptom relief after splenic artery occlusion in the interventional department. Thus, restrictive portacaval shunt combined with IVC shunt bypass surgery was performed, and symptoms were relieved postoperatively. However, the patient had persistently elevated blood ammonia during long-term follow-up.

4. Discussion

In this study, drawing on a relatively large cohort for this rare condition, we described five surgical strategies tailored to different shunt anatomies and clinical scenarios, and evaluated their perioperative and long-term outcomes. These findings may provide practical guidance for the future management of CEPS.

Bernard summarized occlusion portal pressures in 59 children with congenital portosystemic shunts and showed that pressures varied widely after shunt occlusion. They also emphasized that no precise cut-off value could be defined for deciding between one-stage and two-stage closure, and that small bowel tolerance during occlusion was a key intraoperative consideration (*13*). Compared with this approach, in our center we used 25 cmH_2O as a practical reference threshold for procedure selection. In our cohort, shunt occlusion significantly increased portal pressure and liver volume, suggesting improved hepatic inflow. Additionally, no significant differences were found in the changes of blood ammonia level, ICG-R15, liver volume, or spleen volume between surgical ligation and interventional occlusion for shunt occlusion. These results suggest that interventional treatment, a less invasive approach, can be prioritized for type II CEPS patients undergoing shunt occlusion who meet the criteria above.

Relevant literature has indicated that Abernethy malformation is associated with portal hypertension-related complications, with gastroesophageal varices as the main manifestation in reported cases (*15*). According to related studies, treatment of type II CEPS patients requires a balance between "restoring portal perfusion, avoiding excessive postoperative portal hypertension","controlling complications", and individualized combined surgical or interventional decompression regimens can be adopted (*16*). Therefore, we explored surgical approaches for this patient group.

This study identified that some patients with splenorenal shunts exhibited retrograde portal venous flow into the splenic vein. In such patients, the abnormal shunt diverts blood from both the portal venous system and the splenic arterial system. Splenic vessels ligation was therefore performed to interrupt this abnormal flow. Among the patients in this study, five underwent splenic vessels ligation. Postoperatively, symptoms were significantly alleviated in four of these patients. Although no statistically significant differences were observed in blood ammonia levels, portal pressure, ICG-R15, or changes in liver volume, a trend toward improvement was noted.

For type II CEPS patients with high portal pressure, splenic artery ligation may be considered. Its main purpose is to reduce abnormal splenic inflow, thereby alleviating portal hypertension and hypersplenism while preserving as much splenic immune function as possible. Splenic vessels ligation can directly reduce blood flow from the spleen to the portal venous system, thereby helping to lower abnormally elevated portal pressure and relieve portal hypertension (*13*). Among patients undergoing shunt occlusion, some still have high intraoperative portal pressure after shunt ligation. Combining splenic artery ligation with shunt occlusion can stabilize portal pressure and avoid the risk of secondary surgery. In our cohort, postoperative portal pressure and liver volume increased in this subgroup, consistent with improved portal perfusion. This suggests that shunt occlusion combined with splenic artery ligation can effectively regulate portal pressure and hepatic blood perfusion in patients.

DSRS is widely used for surgical decompression of esophagogastric variceal bleeding in cirrhotic patients and pediatric patients with portal hypertension. It maintains significant hepatopetal perfusion of the main portal vein and mesenteric vein after surgery, while effectively shunting splenic blood flow, thereby reducing portal venous system pressure and the risk of variceal bleeding (*17*). In our study, shunt occlusion combined with DSRS or side-to-side splenic vein-IVC anastomosis was used in patients with severe portal hypertension or high-risk gastric varices. This approach appeared more suitable than shunt occlusion with splenic artery ligation alone in patients with established portal hypertension and marked varices.

All eight patients who underwent shunt occlusion combined with DSRS experienced symptom relief, and blood ammonia levels decreased in patients with hyperammonemia, suggesting improved metabolic status after surgery.

In portoiliac variants of type II CEPS, high-flow drainage into the iliac venous system may generate pelvic and lower-limb venous hypertension, leading to refractory edema, venous claudication, flushing, and thrombotic events. In our cohort, two patients underwent IVC shunt bypass surgery because of disabling claudication and persistent lower-extremity symptoms despite prior interventions. Postoperative symptom relief was achieved, although persistent hyperammonemia was observed in long-term follow-up in one patient.

However, postoperative complications and mortality should be interpreted in the context of heterogeneous baseline risk. In our cohort, the most serious adverse outcomes appeared more likely to occur in patients with advanced disease, major comorbidities, and limited

physiologic reserve, as illustrated by Case 17 with severe pulmonary arterial hypertension and longstanding right heart insufficiency, and Case 25 with decompensated cirrhosis at admission. These outcomes should therefore not be attributed to procedural failure alone. This point is important when comparing treatment strategies, because the five procedures were applied to patients with substantially different anatomy, hemodynamics, symptoms, and operative tolerance. Direct comparison of postoperative safety across procedures is therefore not appropriate in this cohort. In addition, grade III complications, including portal hypertension and new shunt formation, could not be clearly linked to specific baseline characteristics or to a particular surgical strategy. These associations remain speculative and require further study.

Previously, surgical treatment for type II CEPS patients mostly involved one-stage/multi-stage shunt ligation (*3,18,19*). In this study, for some patients with excessively elevated portal pressure after shunt ligation, splenic vessels ligation or DSRS was performed (*20,21*). On the basis of successful restoration of portal pressure and hepatic blood flow, the incidence of surgery-related complications was not significantly increased. Nevertheless, postoperative complications were observed across subgroups, including portal hypertension, hepatic encephalopathy, portal vein thrombosis, and new collateral shunt formation. Most complications improved after anticoagulation, re-intervention, or other active management.

This study also has limitations. It is a retrospective study, with follow-up bias in some patients. Additionally, the study mainly focuses on adult and elderly type II CEPS patients, with a small sample size of infants and children. Furthermore, the sample size of several subgroups was small, and the heterogeneity of shunt anatomy, clinical presentation, and surgical strategies limited direct inter-group comparison. Therefore, the findings should be interpreted with caution and regarded as descriptive rather than confirmatory. Despite the small sample size, it is a large-sample study for such a rare disease as type II CEPS. We believe that the new combination of surgical treatment approaches is beneficial for improving patient outcomes, achieving more thorough symptom relief, and reducing recurrence. However, it still needs further research and clinical practice to be improved. In conclusion, surgery centering on shunt occlusion demonstrates promising therapeutic value and remains the mainstay in treatment of type II CEPS.

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Brief Report

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Prevalence and maternal-child clinical and socioeconomic factors associated with congenital anomalies in a Mexican hospital-based setting

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SUMMARY: There is controversial evidence that some selected congenital anomalies (CA) are associated with sex, maternal age, urban-rural residence, or socioeconomic status among the Hispanic population. This study aimed to assess the prevalence and maternal-child clinical and socioeconomic factors across a wide range of CA in a hospital-based setting from northwest Mexico. From January to December 2023, a cross-sectional study for CA and live births at Durango General Hospital was performed. Hospital-based prevalence was calculated for all CA subtypes and grouped anatomical system defects. Associations with CA and subgroup analysis were conducted to assess newborn sex, maternal age, residence, and socioeconomic factors on CA prevalence, using Pearson's chi-squared test and Fisher's exact test. Probability of CA was estimated based on logistic regression analysis along with odds ratio (OR) and its 95% confidence interval. All tests were two-sided with p values < 0.05 considered statistically significant. A total of 6,784 newborns and 306 CA were assessed (hospital-based prevalence 4.5%). Males, maternal age < 20 and ≥ 35 years, urban residence, and lowest socioeconomic status were associated with CA (all OR > 1.0 and p < 0.05). Subgroup analysis indicated associations between males and cardiovascular and genitourinary defects; maternal age < 20 years and craniofacial and abdominal defects; maternal age ≥ 35 years and digestive and chromosomal abnormalities; mother's urban residence and craniofacial, cardiovascular, genitourinary, and abdominal defects; socioeconomic levels D-E and craniofacial and cardiovascular defects (all OR > 1.0 and p < 0.05). These findings reflect noticeable components associated with several CA and might be relevant for prevention and maternal-child health.

Keywords: congenital abnormalities, maternal age, Mexico, socioeconomic status, prevalence

1. Introduction

Congenital anomalies (CA) are structural abnormalities that encompass a broad array of phenotypes with an accepted prevalence of 3%, causing 240,000 neonate deaths each year (*1*), and imposing a considerable cost of care on societies and healthcare systems (*2*). Around one in three cases of CA can be attributed to a known cause and thought to result from complex gene-environment interactions (*3*), whereas evidence on the association of CA with common epidemiological features seems limited (*4*). Overall, CA may be more common in males (*5*), young and advanced maternal ages (*6*), urban residence (*7*), and adverse socioeconomic conditions (*8*). In contrast, other studies have shown a decreased effect of advanced maternal age or sex differences according to specific CA (*9,10*). Thus, the above discussion shows that risk factors for CA vary considerably across studies.

Moreover, race and ethnicity as social constructs may depend on socioeconomic features and are known to be substantial contributors to healthcare disparities (*11*). In this sense, Mexican patients may have particular epidemiological and socioeconomic characteristics derived from limited-resource settings, bypassing preventive healthcare which could be related to CA (*12,13*). Therefore, understanding differences in these factors can also provide clues about plausible social and biological mechanisms that may influence the occurrence of CA in vulnerable populations.

To date, population-based studies addressing clinical and socioeconomic factors in CA among the Hispanic race remain controversial and have been

limited to analyzing its influence on selected CA (*14-19*). Furthermore, no study has estimated the aforementioned influences across a wide range of CA in Mexico, hence preventing the recognition of clinical and socioeconomic-related factors and their differences from other populations. To contribute to the aforementioned, this study aimed to assess the prevalence and maternal-child clinical and socioeconomic factors associated with CA in a Mexican hospital-based setting.

2. Materials and Methods

2.1. Study design and ethics statement

A cross-sectional study was conducted on data of mother-child pairs from January to December 2023 at Durango General Hospital. The latter is a regional center for maternal and child care for low-income population attending to 25% annual births of Durango state in northwest Mexico. Newborns with birth weight > 500 g or gestational age > 20 weeks whose parents were Mexican mestizo origin were included. Informed consent was obtained from all participants for epidemiological and research purposes (*3*). Major exclusion criteria included stillbirths, records of participants residing outside Durango state, and missing data for covariates of interest. Approval for human participants research was obtained from the Ethics Committee of Durango Secretary of Health (number 007/2023). The study was conducted under the Declaration of Helsinki and was strictly voluntary, confidential, and safe. Strengthening the reporting of observational studies in epidemiology guidelines were followed.

2.2. Data collection and study variables

Using a standardized form, data were collected through the hospital-based birth defect surveillance program by experienced doctors and the principal investigator supervised the process daily to conduct comprehensive quality control (*3*). Cases were identified as those with at least one major CA and were evaluated by a clinical geneticist, who performed a thoughtful clinical dysmorphology examination of all potential cases and also interviewed at least one parent to collect and verify background data.

According to the World Health Organization International Classification of Diseases (tenth revision) (*20*), CA were classified into 20 subtypes and grouped by anatomical system defects: craniofacial (anencephaly, encephalocele, hydrocephalus, spina bifida, cleft lip with/without cleft palate, anotia/microtia), cardiovascular (congenital heart defects), digestive (esophageal atresia, anal atresia), genitourinary (hypospadias, undetermined sex, bladder exstrophy), musculoskeletal (talipes equinovarus, polydactyly, syndactyly, limb reduction), abdominal (diaphragmatic hernia, omphalocele, gastroschisis), chromosomal (Down syndrome), and "other" (excluding the CA mentioned above).

The study consisted of maternal-child clinical and socioeconomic covariates of interest: newborn sex, maternal age (grouped in < 20, 20–24, 25–29, 30–34, and ≥ 35 years), residence (considering an administrative criterion, urban was defined as those participants living within Durango city, linked to postal codes 34000–34299 for more than one year before pregnancy, otherwise defined as rural), and socioeconomic status (ability to provide well-being for household members through the Mexican Association of Market Intelligence and Opinion Agencies, AMAI) (*21*).

2.3. Socioeconomic status measurement

A six-item questionnaire was used to produce an estimate of socioeconomic level based on participant's clinical records, as well as supplemented by direct interviews (particularly among CA) to avoid bias and verify background data. The items include: *a*) highest educational level of the head of household (none–master's/doctorate, 0–101 points); *b*) number of bathrooms including shower, sink, and toilet (none–two, 0–47 points); *c*) number of cars / trucks / vans (none–two, 0–37 points); *d*) internet connection (no–yes, 0–31 points); *e*) number of individuals who are employed ≥ 14 years old (none–four, 0–61 points); and *f*) number of bedrooms (none–four, 0–23 points) (*21*).

Then, a series of points were assigned, which were added and compared with the cut-off points to establish the respective household to its corresponding socioeconomic level: A/B (202–300 points), C+ (168–201 points), C (141–167 points), C- (116–140 points), D+ (95–115 points), D (48–94 points), and E (0–47 points); with higher scores indicating more favorable socioeconomic status. Regarding the cut-off points defined by AMAI, to prevent biasing from extreme data incorporated into the algorithmic and statistical model, maximum scores were distributed proportionally to 95th percentile of the distribution of each variable as stated by 2020 Mexican National Survey of Household Income and Expenses database (*21,22*).

2.4. Statistical analysis

Data were expressed as number (*n*) and percentage (%) with an estimation of the 95% confidence interval (CI). Hospital-based prevalence was calculated as the total number of CA (numerator) divided by the total number of live births (denominator), including an adjusted calculation for all CA subtypes and grouped anatomical system defects. Associations between CA and newborn sex, maternal age, residence, and socioeconomic status were analyzed using Pearson's chi-squared test and Fisher's exact test as appropriate. Subgroup analysis was performed using regression models adjusted to covariates

of interest and grouped anatomical system defects (due to the small number of events). Probability of CA and specific categories were estimated based on logistic regression analysis to identify independently associated variables, and were expressed through odds ratios (OR) along with 95% CI. All tests were two-sided with statistically significant p values of < 0.05. Data analysis was performed employing SPSS version 21 software (IBM, Armonk, New York).

3. Results and Discussion

3.1. Hospital-based prevalence of congenital anomalies and anatomical system defects

A total of 6,784 newborns without major CA and 306 newborns with at least one major CA were considered. Overall hospital-based prevalence of CA was 4.5% (95% CI: 4.0%–5.0%) and spina bifida was the most frequent (13.0%, n = 40, 95% CI: 9.3%–16.8%). Furthermore, craniofacial defects were the most prevalent with 36.9% (n = 113, 95% CI: 31.5%–42.3%), followed by musculoskeletal and "other" 15.0% (n = 46, 95% CI: 11.0%–19.0% respectively), cardiovascular 12.7% (n = 39, 95% CI: 9.0%–16.5%), digestive 7.1% (n = 22, 95% CI: 4.3%–10.1%), abdominal 5.5% (n = 17, 95% CI: 3.0%–8.1%), genitourinary 3.9% (n = 12, 95% CI: 1.7%–6.1%), and chromosomal 3.5% (n = 11, 95% CI: 1.5%–5.7%). Distribution of CA subtypes is presented in Supplementary Table S1 (*https://www.irdrjournal.com/action/getSupplementalData.php?ID=296*).

The hospital-based prevalence of CA was found to be higher (4.5%) in relation to the reported global prevalence (3%). However, estimations on CA may vary (1–5%) despite the differences in sample sizes, methodologies, or geographical settings (*1*). In this study, the single-center design may account for this outcome, whereas other plausible influences may include polygenic defects, gene-environment interactions, racial composition, or sources of CA ascertainment across studies (*2-4*).

3.2. Associations of congenital anomalies with maternal-child clinical and socioeconomic factors

Analysis of CA and maternal-child clinical and socioeconomic variables is depicted in Table 1. Variables associated with CA included male sex (OR = 1.26, 95% CI: 1.01–1.58, p = 0.048), maternal age < 20 and ≥ 35 years (OR = 1.83, 95% CI: 1.22–2.76, p = 0.017 and OR = 1.43, 95% CI: 1.02–2.01, p = 0.038, respectively), urban residence (OR = 1.82, 95% CI: 1.45–2.29, p < 0.001), and socioeconomic levels D and E (OR = 1.81, 95% CI: 1.04–3.15, p = 0.031 and OR = 3.69, 95% CI: 1.93–7.02, p < 0.001, respectively).

Notwithstanding the identified associations, it must be noted that these cross-sectional findings limit causal inference. To address this, an individual approach to these associations is discussed.

3.3. Subgroup analysis according to newborn sex

Supplementary Table S2 (*https://www.irdrjournal.com/action/getSupplementalData.php?ID=296*) shows the subgroup analysis between anatomical system defects and newborn sex. Males were more frequently associated with cardiovascular and genitourinary defects compared to females (OR = 2.23, 95% CI: 1.13–4.42, p = 0.023 and OR = 8.94, 95% CI: 1.13–70.6, p = 0.021, respectively). There were no statistically significant differences among the rest of categories.

Findings in this study diverge from a study of male and female twins with similar risks for cardiovascular defects (*10*), but are in agreement with a population-based study suggesting a greater risk for CA among males (*5*). In addition to disparities in the methodological design, clearly, sample sizes in the former are not as extensive as in the latter. Also, these differences may be influenced by hormonal and other physiologic differences in male/female embryos after gonadal differentiation, in which the effects of testosterone may be critical for strength of fetal connective tissue (*5,10*). Additionally, the overwhelming prevalence of genitourinary defects is probably etiologically related to development of the male reproductive system (*5,10*). These patterns of CA may be female biased and suggest that sex influence may also take place during early blastogenesis (*23*). Combined, these disparities may provide a hint about the relationship between sex and CA.

Table 1. Analysis of congenital anomalies and maternal-child clinical and socioeconomic variables

Variable	Congenital Anomalies, *n* (%)		OR (95% CI)
	Yes	No	
Newborn sex			
Male	170 (55.5)	3402 (50.1)	1.26 (1.01–1.58)*
Female	134 (43.7)	3382 (49.8)	Reference
Residence			
Urban	152 (49.6)	2381 (35.0)	1.82 (1.45–2.29)**
Rural	154 (50.3)	4403 (64.9)	Reference
Maternal age (years)			
< 20	39 (12.7)	568 (8.3)	1.83 (1.22–2.76)*
20–24	64 (20.9)	1714 (25.2)	0.87 (0.62–1.22)
25–29	80 (26.1)	1875 (27.6)	Reference
30–34	61 (19.9)	1615 (23.8)	0.88 (0.63–1.24)
≥ 35	62 (20.2)	1012 (14.9)	1.43 (1.02–2.01)*
Socioeconomic status			
A / B	15 (4.9)	542 (7.9)	Reference
C+	24 (7.8)	746 (11.0)	1.16 (0.60–2.23)
C	42 (13.7)	1017 (14.9)	1.49 (0.82–2.71)
C-	46 (15.0)	1085 (16.0)	1.53 (0.84–2.76)
D+	52 (16.9)	1153 (17.0)	1.62 (0.90–2.92)
D	99 (32.3)	1967 (28.9)	1.81 (1.04–3.15)*
E	28 (9.1)	74 (4.0)	3.69 (1.93–7.02)**

Notes: * p value < 0.05; ** p value < 0.01. *Abbreviations*: OR, odds ratio; CI, confidence interval.

3.4. Subgroup analysis stratified by residence

Subgroup analysis among the anatomical system defects and residence is shown in Supplementary Table S3 (*https://www.irdrjournal.com/action/getSupplementalData.php?ID=296*). In contrast to the rural area, urban residence was significantly associated with craniofacial defects (OR = 2.89, 95% CI: 1.98–4.24, $p < 0.001$), cardiovascular defects (OR = 3.32, 95% CI: 1.72–6.41, $p = 0.001$), genitourinary defects (OR = 3.69, 95% CI: 1.11–12.20, $p = 0.031$), and abdominal defects (OR = 3.39, 95% CI: 1.25–9.17, $p = 0.018$). There were no statistically significant associations in other anatomical system defects.

Benavides *et al*. identified several CA that were less prevalent in rural areas (*7*). These urban-rural differences may be related to several factors or surveillance of CA. For instance, multiple pesticides exposure in the urban environment is employed for industrial and indoor pest control. While parental exposure to pesticides and agricultural compounds (nitrate, atrazine, and desethylatrazine detected in drinking water) may be associated with CA, notably hypospadias (*24,25*). Furthermore, due to the increased concentrations of several pollutants, such as particulate matter (≤ 10 and ≤ 5 μm), carbon monoxide, nitrogen dioxide, and ozone, urban air pollution has been associated with CA, namely cardiovascular defects (*26*). It is unknown whether women in this study were systematically different due to the inherently cross-sectional design. Further research will be required to assess these factors.

3.5. Subgroup analysis regarding maternal age

Compared to mothers between 25–29 years, craniofacial and abdominal defects were significantly associated among mothers < 20 years (OR = 2.09, 95% CI: 1.16–3.74, $p = 0.016$ and OR = 3.96, 95% CI: 1.20–13.02, $p = 0.024$, respectively). Meanwhile, advanced maternal age (≥ 35 years) seems highly associated with digestive and chromosomal abnormalities (OR = 3.33, 95% CI: 1.11–9.97, $p = 0.044$ and OR = 11.10, 95% CI: 1.33–92.4, $p < 0.001$, respectively) (Supplementary Table S4, *https://www.irdrjournal.com/action/getSupplementalData.php?ID=296*). No statistically significant associations were found in other anatomical system defects.

As previously reviewed (*6*), results in this study support the striking evidence between maternal age and CA, namely, chromosomal abnormalities. Of note, Down syndrome within the current analysis as part of those clinically recognizable disorders was included, even though it is not a birth defect but rather a genetic syndrome. In contrast, a decreased effect of advanced maternal age among CA has been reported (*9*). Gametogenesis in females begins before birth and may take a long time to be completed (*e.g*. up to 45 years). Such biological scenarios, represent a sizable window of susceptibility to telomere shortening, increased oxygen free radical levels, or errors in sister chromatid segregation from early exposure to tobacco, alcohol, and illicit drugs, or nutrient deficiencies affecting normal chromosomal differentiation of oocytes (*6,9*). The methodological design in this study prevents relating such influences to the occurrence of CA.

3.6. Subgroup analysis across socioeconomic status

Compared to level A/B (highest), levels D and E were more frequently associated with craniofacial defects (OR = 2.59, 95% CI: 1.02–6.54, $p = 0.039$ and OR = 3.95, 95% CI: 1.33–11.65, $p = 0.011$, respectively). Moreover, cardiovascular defects were highly associated with socioeconomic level E (OR = 6.92, 95% CI: 1.42–33.5, $p = 0.009$) (Supplementary Table S5, *https://www.irdrjournal.com/action/getSupplementalData.php?ID=296*). Other categories did not show a systematic variation in the association with anatomical system defects through socioeconomic levels.

Adverse socioeconomic status among a wide range of CA has been shown to be associated with cardiac and digestive anomalies (*8*), as well as craniofacial and cardiovascular defects among the Hispanic population (*14-19*). Such associations may be related to social and prenatal care inequalities as well as maternal psychosocial factors (*2-4,11*). Despite socioeconomic status having multiple dimensions; no single indicator can encompass all perspectives and represents a diverse set of factors in different populations (*27*). Socioeconomic findings reflect components as measured by education, basic infrastructure, and human capital among the current Mexican households that might influence the current results. It should be noted that near to 60% of CA were distributed between levels D+, D, and E, which are deemed as the lowest socioeconomic status according to AMAI (*21*). Although these cross-sectional findings preclude causality, women in this study may experience heterogeneous socioeconomic and health circumstances, leading to low educational attainment, unemployment, household crowding, poverty, or a limited-resource setting (*28,29*). Such sources might provide clues about social influences in CA.

3.7. Limitations and strengths

First, there is a possibility of underdiagnosing of CA among cardiovascular and renal anomalies and stillbirths were not examined for this study. Such instances may be diagnosed after the neonatal period or could represent cases of stillbirth due to the type of anomaly and hence, providing a potential source of bias. Likewise, some subgroups anomalies (*e.g.*, genitourinary and chromosomal anomalies) may also be subject to early fetal demise and the number of events was small; therefore, the CI were wide potentially limiting

interpretation of the magnitude of the effect size. Caution is recommended concerning overinterpretation of these findings.

Second, analysis for specific birth defects was not carried out. Yet, subgroup analysis by anatomical system defects were performed, obtaining noteworthy results which might aid for clinical CA disparities prevention. Third, there may be unmeasured individual-level environmental components, as residence and the socioeconomic status environment fluctuate over time; therefore, it cannot be assured to its exact boundaries. Caution should be considered when interpreting these results. Finally, the cross-sectional design restricts causal inference, whereas current findings from a single hospital-based setting may not be generalizable to other ethnicities. Thus, the relationship mechanisms between these associations are speculative. However, given that a wide range of CA was explored and most of these phenotypes are rare with an unknown etiology, the sample size was sufficient for examining maternal-child clinical and socioeconomic disparities.

Strengths include the well-characterized hospital-based ascertainment of cases and its standardized diagnostic of a comprehensive range of CA. Further strength is the employment of socioeconomic levels by AMAI, which is based on a Mexican conceptual framework considering the Mexican National Survey of Household Income and Expenses database (*21,22*). This validated socioeconomic index was available for all studied mother-child pairs, consequently, it was possible to maximize sample size and improve precision of results.

4. Conclusions

Prevalence of CA in this hospital-based setting indicate that sex, maternal age, residence, and socioeconomic differences are common. Increased associations to male sex, young and advanced maternal age, urban residence, and adverse socioeconomic status may be used as proxies for epidemiological characteristics associated with several CA. The latter suggests complex gene-environment interactions in CA; though the cross-sectional design limits generalizability and causality on this topic. By examining the hospital-based prevalence of these CA, this study research may support the development of preventive strategies including maternal age-, residence-, and socioeconomic-specific features. These findings provide region-detailed epidemiological evidence that might be relevant to maternal-child health and reduce the occurrence of CA in the future.

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Corrigendum

Corrigendum to "**A scoping review of dietary interventions to treat obesity among Prader-Willi syndrome individuals**", *Intractable Rare Dis Res*. 2025; 14(4):240-248. doi:10.5582/irdr.2025.01029.

The authors regret that two errors appeared in the published version of the above article. The correct values and statements are provided below.

Page 243, Table 1, regarding Hirsch HJ, *et al.* (2021) (*19*):

- *Incorrect*: *n* = 34 / (4–19 years)
- *Correct*: *n* = 34 / (19.8 ± 4.8 years)

- *Incorrect*: High adherence due to structured and supervised hostile environment
- *Correct*: The hostel environment plays a central role in the success of the intervention

Page 245, left column, regarding the age reported in reference 19:

- *Incorrect*: Similarly, a study from Israel by Hirsch *et al*. (*19*) examined the impact of multidisciplinary interventions on weight management among obesity in 34 children and adolescents aged 4–19 years old living in residential care homes with an average follow-up of 6.9 years.
- *Correct*: Similarly, a study from Israel by Hirsch *et al*. (*19*) examined the impact of multidisciplinary interventions on obesity-related weight management among 34 adults with PWS living in residential hostels. The mean age of the participants was 19.8 years (SD, 4.8 years; range, 10.4–32.4 years).

The authors confirm that these corrections do not affect the conclusions of the article. They apologize for any inconvenience this may have caused.

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