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CLINICAL MEDICINE & PHARMACOLOGY

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CMP serves as a global platform for disseminating high-quality clinical findings, practical innovations, and translational research that bridges disciplines and supports real-world medical advancement. CMP particularly values clinician-led studies, practice-based evidence from primary care institutions, and collaborative contributions that translate emerging medical knowledge into improved patient outcomes.

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CMP

Review article

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Transition Experiences of Adolescents with Type 1 Diabetes from Pediatric to Adult Care: A Meta-Synthesis of Qualitative Studies

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Abstract:

Background: Effective long-term management of type 1 diabetes requires adolescents to transition from pediatric to adult healthcare services. This process is often accompanied by complex emotions, changing attitudes, and multiple challenges. Understanding adolescents' experiences during this period may help identify transition-related barriers and support a smoother transfer of care.

Objective: To explore the perceptions, experiences, and attitudes of adolescents with type 1 diabetes during the transition from pediatric to adult healthcare services.

Design: A systematic review and qualitative evidence synthesis.

Methods: PubMed, Web of Science, Cochrane Library, Embase, and CINAHL were searched from inception to October 2025 using pre-specified search terms. Studies were screened according to predefined inclusion and exclusion criteria. Qualitative findings were extracted and synthesized using the JBI meta-aggregation approach.

Results: Twelve studies were included. Three synthesized themes were identified: diverse attitudes and emotions toward transition; challenges during the transition process; and recommendations and expectations for improving transition care. Five subthemes were graded as having high confidence and three as having moderate confidence. The findings indicate that transition experiences are shaped by emotional uncertainty, increasing self-management demands, discontinuity in care, and unmet expectations regarding adult services.

Conclusions: Adolescents with type 1 diabetes experience multiple barriers during the transition to adult healthcare services. These barriers are closely related to the transfer of disease-management responsibility, difficulties adapting to self-care, and insufficient support from healthcare providers, families, and peers. Strengthened transitional support may improve continuity of care and reduce transition-related difficulties.

Keywords: Adolescents; Young adults; Experiences; Transition; Type 1 diabetes

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Introduction

Type 1 diabetes has traditionally been regarded as a primarily childhood-onset disorder of insulin deficiency, requiring life-long treatment with exogenous insulin [1]. According to the International Diabetes Federation released the 10th edition of the Global Diabetes Map: more than 1.2 million children and adolescents worldwide have type 1 diabetes [2]. Furthermore, the prevalence of Type 1 diabetes and the number of adolescents with diabetes is increasing annually [3]. Given the increase in life expectancy and morbidity, providing appropriate care for adolescents and young adults with Type 1 diabetes has become an important issue [4]. However, an increasing number of children with type 1 diabetes are being transferred from pediatrics to adult care

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because pediatrics care is overloaded and pediatrics care is less able to provide care that meets the special needs of patients as they age, including exercise, diet, weight control, and pregnancy management. Although healthcare transition has commonly been conceptualized as the process of transferring between child and adult services, it has recently been more broadly defined as: 'the purposeful, planned process that addresses the medical, psychosocial, educational and vocational needs of adolescents and young adults as they grow up learning to live with their lifelong health condition [5]. At the outset of the transition, taking into account the disparities between pediatrics and adult healthcare settings in terms of culture, atmosphere, focus of care, medical equipment, and healthcare practices, among others, some adolescent patients may face difficulties in adjusting to the unknown adult healthcare milieu in a timely manner [6, 7].

In pediatrics, parents play a key role in managing diabetes and are responsible for providing medical advice, monitoring blood glucose levels, overseeing medication, and observing physical changes [8]. However, moving to an adult healthcare setting can be a stressful and challenging transition for patients who have relied heavily on their parents, as adolescents are required to take on more autonomy and responsibility, while parents shift from a primary management role to a supportive one [9]. The transitional period is delicate, and adolescents who fail to adjust their disease management roles promptly are at risk of experiencing impaired glycemic control, detachment from healthcare services, and complications during the transition phase [10]. Successful transitions often require the collaboration of various parties, such as pediatrics healthcare providers, adult healthcare providers who are ready to take on the emerging adolescent, the adolescent's parents who shift away from their main role to offer supportive companionship, and the patient who proactively adjusts to the new environment and seeks their own healthcare information for managing diabetes [11]. Transition is a crucial aspect of personal development, and it is imperative to establish effective strategies to assist adolescents with type 1 diabetes in acclimating to their surroundings and adapting to new roles in order to manage the challenges associated with transition.

Prior qualitative assessments have revealed the advantages and shortcomings of existing transition initiatives, and the goal should be to concentrate on the transition experiences and expectations of patients to gain a comprehensive understanding of the obstacles and difficulties involved in transitioning adolescents with diabetes to adult healthcare. Identifying the emotions of adolescents in transition, challenges during the process, and suggestions for improvement can enable healthcare organizations to modify their transition plans to fulfill the requirements of their patients. As a result, adolescents can efficiently transition to more self-governing roles, promote health-related outcomes, and make the transition timely. Accordingly, this study analyses the experiences of patients with type 1 diabetes as they move from pediatric to adult healthcare.

Methods

This systematic review was guided by the Joanna Briggs Institute Manual for Evidence Synthesis and reported by the guidelines of the Enhancing Transparency in Reporting the Synthesis of Qualitative Research (ENTREQ) Statement [12, 13].

Search strategy

PubMed, Web of Science, Cochrane, Embase and CINAHL were systematically searched for qualitative and mixed methods studies related to the experience of transitioning adolescents with type 1 diabetes from pediatrics to adult care, with a timeframe up to October 2024. The search was conducted by combining subject terms and free words using Boolean logic operations and simultaneously tracing relevant references.

Study selection

The studies thus retrieved were exported to the Endnote 21 software, and duplicate citations were removed. Two reviewers (YWH, JZH) independently screened the titles and abstracts, and the full texts were subsequently retrieved for further assessment. Any disagreements were resolved through discussion. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram was used to report the selection process [14].

Inclusion and exclusion criteria

The inclusion and exclusion criteria were formulated based on four elements: type of participants, phenomena of interest, context and type of studies, as shown in **Table 1**. Only studies published in English were considered.

Quality appraisal

Quality assessment was undertaken using the Critical Appraisal Skills Programme (CASP) tool [15] (**Table 2**). Two researchers (CC, LH) with training in evidence-based medicine or evidence-based nursing initially selected one piece of literature each for assessment. Following standardization and harmonization of the evaluation methodology, a back-to-back literature quality assessment was conducted on the screened and included literature. The CASP tool for assessing the authenticity of qualitative studies comprises 10 evaluation items, for which the evaluator is required to provide a 'yes', 'no', or 'unclear' response. In the event of any inconsistencies, the evaluator is expected to make a 'yes', 'no', or 'unclear' judgment on each item and request the input of a third individual (SHY) to facilitate a negotiated resolution.

Data extraction

Information was extracted from the included literature for this study using an Excel spreadsheet, including authors, year of publication, country, purpose, study design, data collection and analysis, participants, and scenarios. Data were extracted independently by two reviewers (LH, LB) and then

Table 1 | Eligibility criteria

Criteria	Inclusion	Exclusion
Types of participants	Adolescents diagnosed with type 1 diabetes	Adolescents diagnosed with type 1 diabetes mellitus not receiving treatment or follow-up
Phenomena of interest	Experiences and feelings of transition from a pediatric to an adult healthcare setting	Experiences or feelings not related to the medical transition or from others
Context	Transition in health-care facilities	
Types of studies	Qualitative research and the qualitative component of mixed-method research based on qualitative data collected from interviews, participant observations, field notes, open-ended questions from surveys	Studies in which qualitative data could not be identified

Table 2 | Results of the critical appraisal of the included studies

Author, year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
Iversen et al., 2019	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Vidal et al., 2022	yes	yes	yes	yes	yes	no	yes	yes	yes	yes
Ritholz et al., 2014	yes	yes	yes	yes	yes	no	yes	yes	yes	yes
Price et al., 2011	yes	yes	yes	yes	yes	no	no	yes	yes	yes
Leung et al., 2021	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Ladd et al., 2022	yes	yes	yes	yes	yes	no	yes	yes	yes	yes
Visentin et al., 2006	yes	yes	yes	yes	yes	no	yes	yes	yes	yes
Hilliard et al., 2014	yes	yes	yes	yes	yes	no	yes	yes	yes	yes
Garvey et al.,2014	yes	yes	yes	yes	yes	no	yes	yes	yes	yes
Butalia et al., 2020	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Olsson et al., 2023	yes	yes	yes	yes	yes	no	yes	yes	yes	yes
McDowell et al., 2020	yes	yes	yes	yes	yes	no	yes	yes	yes	yes

Y: Yes; N: No; ?: Can't tell.
Adapted from Critical Appraisal Skills Programme (2018), https://casp-uk.net/wp-content/uploads/2018/01/CASP-Qualitative-Checklist.pdf

cross-checked [16]. Codes with similarities were integrated by both reviewers to form descriptive themes. Finally, the themes were analyzed and synthesized to generate analytical themes and develop new interpretations.

Assessing confidence in the findings

The Credibility of Evidence from Qualitative Reviews (CERQual) research methodology was used to evaluate the credibility of review conclusions on a scale of high, moderate, low, or very low [17]. Credibility refers to the extent to which the synthesis results adequately describe the phenomenon of interest. The assessment of the credibility of the findings of each review consists of four components: methodological limitations, relevance, consistency, and adequacy of data.

RQ1. Was there a clear statement of the aims of the research?

RQ2. Is a qualitative methodology appropriate?

RQ3. Was the research design appropriate to address the aims of the research?

RQ4. Was the recruitment strategy appropriate to the aims of the research?

RQ5. Was the data collected in a way that addressed the research issue?

RQ6. Has the relationship between researcher and participants been adequately considered?

RQ7. Have ethical issues been taken into consideration?

RQ8. Was the data analysis sufficiently rigorous?

RQ9. Is there a clear statement of findings?

RQ10. How valuable is the research?

Findings

A total of 1318 records were retrieved, 12 studies met the inclusion criteria and were included in this review [7–27] (**Figure 1**). These studies were conducted in the United States, United Kingdom, Canada, Australia, Norway, Sweden and Japan and included a total of 213 adolescents with type 1 diabetes.A number of these studies were qualitative and used interviews to collect data, and only one was a mixed study [24]. Study characteristics are reported in **Table 3**.

The qualitative evaluation findings indicate that only three studies acknowledged the relationship between researcher and participants been adequately considered [18,

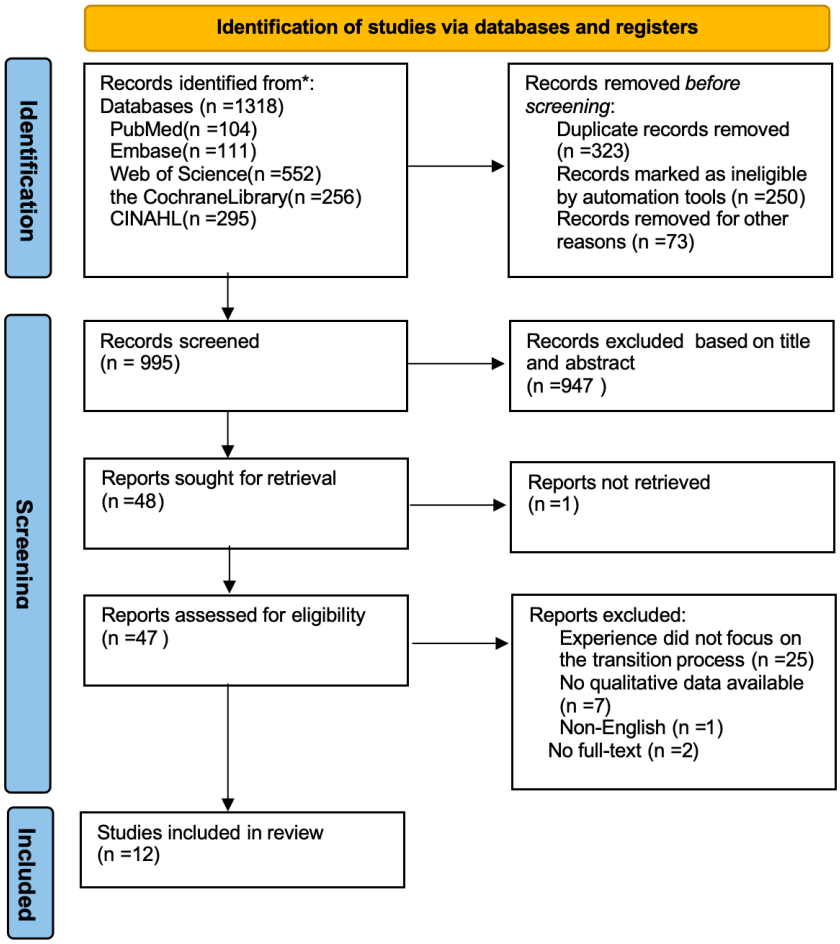

Figure 1 | Search flow diagram

22, 26]. Furthermore, only one study did not take ethics into consideration [21] (**Table 2**). The CERQual assessment of confidence in individual review findings showed that 5 themes were graded as exhibiting high confidence, whilst 3 themes were graded as exhibiting moderate confidence (**Table 4**).

The integration of the results showed that different adolescents with type 1 diabetes had more complex transition feelings and attitudes and encountered many challenges in the transition, as well as suggestions and expectations for the transition process.

Adolescents exhibit varying attitudes and emotions towards transitions

Attitudes towards transitioning among adolescents with type 1 diabetes were diverse, mainly categorized into two fields: over-reliance on pediatric healthcare and unease about moving to adult healthcare, or a perception of transitioning as a vital aspect of personal development, with an anticipation of further self-direction in adult healthcare.

Excessive attachment to pediatric care and concerns about transition to adult care

This subtheme is associated with a high degree of confidence

Most adolescents with type 1 diabetes form a robust relationship with their health-care providers as a result of prolonged engagement in pediatric care. The pediatric team had a thorough understanding of the illness and provided customized treatment and care. This familiarity led to adolescents forming an excessive attachment to the pediatric setting. Adolescents are concerned about losing this strong bond when transitioning to an adult health care setting [7], and as a result, some adolescents express a desire to continue to be seen in a pediatric setting when they reach to adults [18]. Many adolescents struggle to form a fresh relationship with the adult healthcare team [20], and the vagueness connected with transitioning to adult healthcare exacerbates the psychological burden on patients [22]. The stronger the relationship with pediatrics, the weaker the willingness to transition, and the greater the fear of adult healthcare providers, with a particular fear of losing close personal contact [7].

Table 3 | General characteristics of the included studies

Author, year	Country	Aim	Study design	Data collection and analysis	Participants	Setting
Iversen et al., 2019	Norway	To explore how young adults with Type 1 diabetes experienced the transition from pediatric to adult health care services.	Exploratory qualitative design.	Individual semi-structured interviews, data were analysed using interpretive description.	11 young adults aged between 19 and 23 years, had been living with diabetes for 9–19 years, and transitioned to adult care between 1 and 4 years before the study took place.	All but one interview were held in a meeting room at the hospital.
Vidal et al., 2022	Spain	Determine the expectations of young Type 1 diabetes patients prior to transfer; Evaluate the transfer process between the 2 centres; Evaluate the therapeutic education and care programme (TECP) in the adult centre from their point of view.	Qualitative study.	Focus group and semi-structured interviews.	11 youths accepted to participate: 7 in Phase 1, 4 repeated in Phase 2 and 4 more transferred 2 years previously were added.	Hospital Sant Joan de Déu and Hospital Clínic de Barcelona.
Ritholz et al., 2014	USA	To explore perceptions that emerging adults with Type 1 diabetes have of their patient-provider relationships across the transition from pediatrics to adult care.	Qualitative study.	Focus groups.	26 emerging adults with Type 1 diabetes.	Not mentioned.
Price et al., 2011	UK	To evaluate one such model indiabetes, the 'Transition Pathway' via interviews with young people who have experienced it first-hand.	Qualitative study.	Semi-structured interviews, framework approach.	11 young people opted to be interviewed, two of whom agreed toreturn again for a second interview.	Not mentioned.
Leung et al., 2021	Canada	To explore adolescent perspectives on program design in the transition to adult care.	Qualitative study.	Focus groups.	22 adolescents aged 16-18 with Type 1 diabetes.	Conference room in a pediatrics diabetes clinic.
Ladd et al., 2022	Canada	To detailed understand the perspectives of adolescents in their final year of pediatric care.	Qualitative study.	Semi-structured interviews, thematic analysis.	61 adolescents with Type 1 diabetes.	Academic institution.
Visentin et al., 2006	Australia	To develop a sustainable and coordinated approach to facilitating the transition between diabetes services for adolescents.	Qualitative study.	Focus groups.	21 diabetes health professionals and 10 adolescents , aged between 15 and 18 years who had been diagnosed with Type 1 diabetes for a minimum of 12 months.	Health professionals were interviewed at their workplaces; eight adolescents were interviewed at the diabetes clinic, and two at home.
Hilliard et al., 2014	USA	To understand the concerns, expectations,preferences, and experiences of pretransition adolescents and parents andposttransition young adults.	Mixed research.	Semistructured interviews.	14 youths with Type 1 diabetes and 8 parents.	Not mentioned.
Garvey et al., 2014	USA	To explore the experience of transition from pediatrics to adult diabetes care reported by posttransition emerging adults with Type 1 diabetes.	Qualitative study.	Focus groups, Thematic analysis.	26 Type 1 diabetes emerging adults.	Not mentioned.
Butalia et al., 2020	Canada	To gain insight on how to improve the transition of youth with Type 1 diabetes from pediatrics to adult diabetes care from the patients' and parents' perspective.	Qualitative descriptive study.	Focus groups.	7 youth with Type 1 diabetes who were pre-transfer participated in group 1, 4 young adults with Type 1 diabetes who were posttransfer participated in group 2, and 3 parents of youth with Type 1 diabetes who had transferred from pediatrics to adult care participated in group 3.	Not mentioned.
Olsson et al., 2023	Sweden	To explore young adults' experiences of living with Type 1 diabetes in the transition to adulthood, including experiences of the transfer from pediatric to adult care.	Qualitative study.	Semi-structured interviews, qualitative content analysis.	10 young adults aged 19–29 years.	Not mentioned.
McDowell et al., 2020	USA	To identify the barriers and facilitators adolescents face during their emerging adult years with Type 1 diabetes.	Qualitative descriptive study.	Individual interviews.	25 young adults aged 24–35, have a diagnosis of Type 1 diabetes prior to 18 years of age.	Not mentioned.

Table 4 | Summary of findings and CERQual assessments

Review finding		Studies contributing to the review finding	CERQual assessment
Adolescents exhibit varying attitudes and emotions towards transitions.	Excessive attachment to pediatric care and concerns about transition to adult care.	Iversen et al., 2019 Vidal et al., 2022 Ritholz et al., 2014 Leung et al., 2021 Ladd et al., 2022	High confidence
	Treating transition as a natural process and as an essential part of personal growth.	Vidal et al., 2022 Ritholz et al., 2014 Price et al., 2011 Ladd et al., 2022 Olsson et al., 2023	Moderate confidence
Challenges encountered in the transition process	Changes in major disease management roles.	Ritholz et al., 2014 Ladd et al., 2022 Visentin et al., 2006 Hilliard et al., 2014	High confidence
	Differences between pediatric and adult medical facilities.	Iversen et al., 2019 Ritholz et al., 2014 Visentin et al., 2006 Olsson et al., 2023	Moderate confidence
	Barriers to self-care in type 1 diabetes.	Leung et al., 2021 Ladd et al., 2022 Garvey et al.,2014 Olsson et al., 2023 McDowell et al., 2020	High confidence
Recommendations and expectations for the transition process	Expectations of support from healthcare organisations.	Iversen et al., 2019 Ritholz et al., 2014 Leung et al., 2021 Visentin et al., 2006 Garvey et al.,2014 Olsson et al., 2023	High confidence
	Desire for help from peers.	Leung et al., 2021 Garvey et al.,2014 Butalia et al., 2020 Olsson et al., 2023 McDowell et al., 2020	High confidence
	Expectation of adequate medical information.	Price et al., 2011 Leung et al., 2021 Ladd et al., 2022 Butalia et al., 2020	Moderate confidence

"My concern mostly would be that [in adult care] we would lose a little bit of the personal connection with the doctors. [In pediatrics] I feel like it's a lot more, it's warm, and it's very friendly, so ... I'm scared of it being very cold." [7]

"I know that I will be seen in the Hospital Clinic, I mean, I imagine it as a hospital that is very ... very cold." [19]

Treating transition as a natural process and as an essential part of personal growth

This subtheme is associated with a moderate degree of confidence.

Some adolescents with type 1 diabetes see the transition from pediatric to adult care as an inevitable process that is a standard part of the overall healthcare experience, requiring a move from a pediatric setting where everything is in place to continue to be seen and cared for in a more independent adult healthcare setting [19, 21]. Transition is a natural part of an individual's growth process and is expected [20]. Some adolescents with type 1 diabetes have a positive attitude towards transition and look forward to the new medical environment and care [20]. For adolescents, the transition to an adult healthcare setting is symbolic of both the transition to adulthood and the potential for full autonomy; adult healthcare settings often require independence in medical consultations, and such health consultations without parental intervention are attractive to some adolescents [19]. And the transition to an adult healthcare setting can help patients become more skilled at managing their diabetes autonomously and practising self-care [7]. Additionally, some adolescents expect to make self-management decisions independently without the involvement of family members, whether or not they are mature enough to do so [8].

"I think it was a natural progression. It was just kind of what I thought. You move to the Boston area, go to col lege . . . so it's not forced. It's just the next logical step. (male, 24 years old, transitioned at age 18)" [20]

"I got it [i.e., the disease] at an early age. I suppose that's better than later. I was already managing my diabetes when I got to that age [i.e., the transition to adulthood] for that reason. It was not a big deal—it was already part of my daily life." [8]

Challenges of the transition process

Despite the proliferation of transition programmes now available, adolescents with type 1 diabetes continue to face a number of barriers to transition, including a shift in the pri-

mary role of managing the disease, differences in healthcare providers before and after transition, and barriers to self-management of their diabetes.

Changes in major disease management roles

This subtheme is associated with a high degree of confidence.

One significant change during the transition of adolescents with type 1 diabetes from pediatric to adult healthcare settings is the transfer of primary responsibility for managing the condition from the parent to the patient [23]. During pediatric appointments, parents typically serve as the main communicators and recipients of medical information, whereas the shift to adult healthcare necessitates personal medical consultations [20] Many adolescents Many teenagers report that it is harder to adjust to this sudden change in roles and to take on the responsibility of self-care for their illness independently [7], During their first appointment at an adult healthcare facility, they particularly appreciate having a parent present to offer the patient a sense of security. However, adolescents discussed the change in parental roles before and after the transition with their parents. They expected their parents to shift towards a monitoring and supportive role from merely fulfilling diabetes management tasks [24].

"I think that part of the issue with the adult endocrinologist versus the pediatrics is that when you're a pediatrics patient, you have a parent there as well. And the parent is the advocate for the child whereas when you're an adult, you're your own advocate." [20]

Differences between pediatric and adult medical facilities

This subtheme is associated with a moderate degree of confidence.

It is well-established that there are distinct differences between pediatric and adult healthcare settings in terms of environment, atmosphere, staffing, medical equipment, methods of diabetes management, definition of responsibilities and parental roles [23]; therefore, many adolescents do not receive relevant information about adult healthcare settings prior to the transition, making it more difficult to adapt to the new environment. Many adolescent patients reported feeling well looked after whilst in pediatrics, whereas adult facilities were perceived as more distant and aloof, like a business arrangement [18, 20]. Adolescent patients also felt more at ease in pediatrics due to the regularity, frequency, and comprehensiveness of their follow-up appointments, where pediatric healthcare practitioners conducted thorough evaluations and provided superior advice and guidance. In contrast, follow-up appointments in adult outpatient clinics were less consistent and less organized [18].

"It's [adult care] less of the dictating and more of the collaboration, which has been good. . . . So, it's more of a conversation rather than a, "this is what you have to do" type of thing. So that's been helpful." [20]

"There was a great focus on everything that was regarded as positive at the pediatric clinic. But at the adult clinic, it was more like "Your HbA1c outcomes are bad and you are doing this and that wrong". It led to me frequently leaving the clinic angry." [8]

Barriers to self-care in type 1 diabetes

This subtheme is associated with a high degree of confidence.

After the transition, the majority of adolescents must manage diabetes on their own. Self-care for diabetes demands additional effort and time from adolescents, leading to increased patient burden [22]. Some patients have reported that self-care is awkward and they might even forget to take insulin because they are preoccupied with other activities, rendering reminders ineffective [27]. The age of type 1 diabetes diagnosis in adolescence is a crucial element in determining the patient's capacity for autonomous diabetes management. Patients diagnosed at a young age have sufficient time and experience to adjust to their condition and its management, while those diagnosed later face greater difficulty adapting to self-management responsibilities [7].

Furthermore, alcohol consumption poses a new challenge for both adolescents and adults. Patients must regulate blood glucose, avert nocturnal hypoglycemia, and estimate glucose levels in drinks. Adult healthcare providers have cautioned patients against drinking alcohol, a harder management issue for some adolescent individuals. Socializing at parties which include alcohol is deemed significant, even more so than controlling blood glucose [8].

Moreover, certain diabetes self-care practices are met with scrutiny, stigma, and discrimination, leading to an aversion to prioritizing self-care needs [22]. Additionally, numerous young adult patients express difficulties in juggling diabetes management with school, work, and other obligations, consequently impeding their transition. Many patients may experience feelings of being overwhelmed by the emergence of complications in patients with diabetes during their transition to an adult healthcare setting [25].

"That is a huge shock, when you come in and you see these elderly people with walkers and canes and everything, and you're like [...] OK [...] is that going to be me in 6 years? Like, am I going to still be here? And it was kind of overwhelming to go from one end of the spectrum to the opposite." [25]

"It was difficult finding time to manage my health and school. I knew how to plan meals, cook them, etc.;however, just eating out all of the time or using a meal plan, like my peers, was not a good option. (26 years old, female)" [27]

Recommendations and expectations for the transition process

Expectations of support from healthcare organisations

This subtheme is associated with a high degree of confidence.

Most adolescents with type 1 diabetes desire assistance and support from both pediatric and adult providers before transitioning. A few of these patients have advised that adult

facility healthcare providers participate in the final pediatric clinic visit to establish face-to-face contact with their counterparts and ensure seamless transmission of their medical information [18, 20]. Prior to transitioning to the adult facility, patients express a desire to visit the clinic to obtain information about their new provider and surroundings. During the transition, healthcare professionals specializing in pediatrics were involved in overseeing the transfer to the adult facility and subsequent care. They worked with the patient to monitor the transition's success and, if necessary, took appropriate steps to ensure a seamless process [20]. Numerous patients expressed a desire to consult with the same doctor during their appointments, which would boost their sense of security [18]. To ensure maximal support during their initial visit to an adult pediatric facility [25], patients proposed referral to diabetes nurses, educators and dietitians during the transition process to an adult provider [23]. Adolescents should also commence transitioning as early as feasible, enabling them to become accustomed to engaging with an adult clinic [8]. Furthermore, due to certain equipment being outdated or inaccessible, several patients are seeking novel support technologies for managing diabetes, including insulin infusion systems that assist in diabetes self-management [8].

Desire for help from peers

This subtheme is associated with a high degree of confidence.

Peer navigation and support are essential for adolescents undergoing the transition with type 1 diabetes. In pediatric healthcare settings, parents of adolescents frequently provide the required support for the patient. As transitioning adolescents mature and move away from parental influence, they seek alternative sources of support, recognizing the value of receiving treatment from people who have experienced diabetes firsthand [26]. Communicating with peers with type 1 diabetes provides a sense of empathy that can facilitate this support [22]. Simultaneously, a number of adolescents believe that peer mentoring from emerging adults who have already undergone the healthcare transition would be an advantageous resource for support [25]. Additionally, exchanging insights about disease self-care and the transition process could also prove to be beneficial [26]. Although many found it difficult to meet others with diabetes, those who were able to connect with peers through diabetes camps or social media found it helpful to have someone that related to their experience living with a chronic disease [27]. Several forms of peer support are now being modernized, with a few adolescents turning to digital communities like Facebook groups that contain Type 1 diabetes content or following Type 1 diabetes profiles on Instagram to offer support. However, the disadvantage is the scarcity of useful information provided. Healthcare professionals can utilize hospital resources to establish an internet-based platform for peer support and furnish expert knowledge to augment its effectiveness.

"I would have liked to have had some kind of support system when I entered into adult care. I remember asking my doctor, 'are there any other college students that are doing this as well?' " [25]

"I know some people with Type 1 diabetes and when I meet them, it's having somebody with the same disease as yourself. Somehow, you become different [when living with the disease], but when you meet these people, you're some kind of "normal". I see people who I can speak to." [8]

Expectation of adequate medical information

This subtheme is associated with a moderate degree of confidence.

Sufficient healthcare information and smooth transition processes are crucial for type 1 diabetes patients moving into adult healthcare settings. Notably, a considerable proportion of adolescents have communicated a need for pre-transition information prepare for the shift, and several others have expressed an insufficient understanding of diabetes self-management [7, 26]. This lack of knowledge can impede prompt adaptation to the post-transition environment, resulting in suboptimal self-care maintenance. There was variation in how different adolescents required access to health education knowledge. Therefore, it is recommended that health education be personalized, with some adolescents showing high support for online resources, while others prefer written materials. Additionally, some viewed educational workshops with enthusiasm, while others found them reminiscent of school lessons [22]. Therefore, offering a range of health education materials based on individual requirements can enhance the acceptance by young people.

"Well I think it's important not to generalize, you have to get to know the patient on a personal level before you can kind of tailor the advice for them and help them out in that way" [21]

Discussion

Organized and systematic healthcare transition from pediatric to adult healthcare may be linked to better health outcomes and decreased acute care usage. Transition is a constantly evolving procedure and not just a transfer from pediatric to adult healthcare. An effective transition requires a personalized plan that takes into account the needs of the adolescent before the transition and involves the adolescent, parents, and healthcare providers in both pediatric and adult healthcare environments. This review presents the experiences of patients with type 1 diabetes during the transition from adolescent to adult healthcare. During the pre-transition period, adolescents exhibit complex attitudes towards the transition with a coexistence of attachment, resistance, and anticipation. Throughout the transition period, adolescent patients encounter a range of challenges. Finally, in the post-transition period, many patients provide suggestions and have expectations after going through the transition.

During the pre-transition period, adolescents exhibit intricate attitudes towards transition. Some patients have concerns about the timing of transition, which could be a contributing factor. It is worth noting that recognized organizations, including the American Diabetes Association, are progressively recognizing the significance of transition but do not provide universally standardized recommendations for transition timing or processes [28]. The National Health Care Transition Resource Centre recommends commencing transition education earlier, at approximately 14 years of age [29]. Nevertheless, the diagnosis and management timing of diabetes differ among patients, and their acceptance of the transition also varies. Additionally, adolescents and young individuals receiving care at the clinic vary between nations and regions, making a completely standard transition timing impractical. Transition ranges can be established to personalize the timing of transfer for patients within a sensible transition interval.

Comprehensive management of adolescents with type 1 diabetes by pediatric healthcare professionals may result in over-reliance and an inclination to develop a habit of complete dependence on care, leading to worries regarding an independent healthcare environment in adulthood. Negative attitudes towards transitioning can frequently pose a hurdle in the process of a seamless transition. Healthcare professionals in both healthcare organizations have a crucial role in preparing for patient transitions. Nursing staff, in particular, play an important role in providing health education for patients during the transition process. This study identifies abrupt transition processes as a primary hindrance, with the survey results demonstrating a lack of transition readiness in adolescents with chronic illnesses [30]. The Transition Assessment Tool was utilized pre-transition to appraise patients' capacity to manage medications, uphold appointment schedules, keep track of health concerns, communicate with healthcare providers, and fulfill daily activities before the transition [31]. The tool then adjusted the transition timeframe based on the patient's readiness for transition, guaranteeing optimum preparedness for the transfer. Adequate Transition Preparation developed the "On TRAck" assessment instrument specifically for adolescents with type 1 diabetes. As a health care provider, you can choose the appropriate scale for your situation [32].

Upon transition to adult healthcare providers, adolescents must assume autonomous responsibility for managing their illnesses. Results from a US study indicate that over a period of 6 months, parents and adolescents reported a decrease in glucose monitoring frequency and an increase in hemoglobin A1C as the primary responsibility for type 1 diabetes management transferred to the adolescent [33]. Following the transition, some parents found it difficult to relinquish their primary role in managing their child's diabetes due to concerns about their adolescent's ability to self-manage. A qualitative study in Ireland revealed that parents perceived a continued need to be involved in the management of type 1 diabetes despite this not being included in the transition plan [34]. However, for a smooth and successful transition for the adolescent patient, it is essential for parents to transfer the responsibility for diabetes management to their adolescents at the earliest opportunity and adapt to the changing dynamic of the parent/adolescent relationship. However, according to a phenomenological study [35], many adolescent patients have poor diabetes self-management skills. They encounter various challenges in managing their diabetes, such as misunderstandings about glycaemic control, conflicts when relying on or dissociating from parental glycaemic control, interruptions in glycaemic control due to changes in plans, and a lack of motivation for glycaemic control. These challenges are comparable to some of the integrative findings of this study. Some teenagers reported experiencing unease during the transition. They experienced a loss of security once their parents no longer took charge, and found it tough to remember all the numerous duties that came with treatment once they did not receive any prompt from their parents [36].

Therefore, the transition between healthcare providers ought to be more than a mere transfer; it should involve a handover of crucial management responsibilities. As the primary executor of the transition plan, the caregiver plays a pivotal role in instructing the adolescent on how to achieve self-management; hence it is vital to select an appropriate and effective care model. A systematic assessment of models of care transition for type 1 diabetes identified three primary models of care: structured transition education programmes, multidisciplinary team transition support, and telemedicine/virtual care [11]. The results revealed that some of the transition models offer health and psychosocial advantages, leading to improved health outcomes such as better glycaemic control, increased regular appointment attendance, and fewer emergency department visits and reviews. Nevertheless, a portion of these studies yielded no advantages. This indicates that as the creator of a transition of care plan, it is crucial to methodically implement and assess the transition procedure to boost patient health outcomes and guarantee a seamless transition.

Adolescents diagnosed with type 1 diabetes possess several expectations concerning the transition process. According to the findings of this study, adolescents anticipate an accurate transfer of patient information regarding the illness from pediatric to adult healthcare professionals. Adequate information on diabetes is also expected from healthcare providers. Adolescents acknowledge that taking responsibility for their diabetes involves greater understanding and proficiency. Before the transition, parents are usually informed about diabetes management and education. However, following the transition, it is essential to be familiar with dealing with new situations, such as regulating blood glucose levels when consuming different foods, adjusting insulin doses during physical activity or alcohol consumption, and other scenarios. Not only does this facilitate teenagers in acquiring adequate knowledge about diabetes management, but it also boosts parents' confidence in their autonomous management. The study scrutinizes the opinions of healthcare professionals who specialize in diabetes care and

education on the transition to adult healthcare services for adolescents with type 1 diabetes, highlights the significance of smooth healthcare transition from pediatrics to the adult healthcare sector for adolescents suffering from type 1 diabetes [37].

Although the present study provides a comprehensive overview of the transition from pediatric to adult healthcare for individuals with type 1 diabetes, the participants included in our study comprised adolescents or emerging adults with type 1 diabetes at varying stages of pre-transition, transition, and post-transition, but the evidence was not categorized during the evidence summary, which may have implications for the feasibility of some of the evidence. In addition, the study incorporated a broad spectrum of literature from various years, with certain sources being dated. This may not align with the contemporary state of type 1 diabetes transition, potentially impacting the study's outcomes.

Implications for Practice and Research

The study findings highlight that young individuals suffering from type 1 diabetes encounter several challenges when transitioning into adulthood. Insufficient support from healthcare providers, families, and peers during the transition phase, combined with the patient's reluctance to change, can adversely impact an adolescent's transition experience. This, in turn, may impede their ability to efficiently assume new disease management responsibilities and potentially result in ineffective diabetes management during and post-transition, as well as the development of diabetes-related complications. Before the transition of adolescents, it is advisable for pediatric healthcare providers to communicate with their patients beforehand to notify them about the transition requirements. Simultaneously, healthcare providers for both pediatric and adult patients should formulate a communication channel that enables adolescent patients to comprehend adult healthcare providers' situation promptly, eliminate concerns and apprehensions regarding the patients' transition and guarantee the precise conveyance of the patient's condition between the two healthcare providers. Furthermore, it is advised that pediatric healthcare professionals gradually initiate patients into diabetes self-care, instruct them on diabetes self-management strategies, and aid patients in promptly identifying symptoms relating to diabetic complications to enable timely decisions and effective control of the condition. As parents of patients are the primary caregivers and responsible for medical consultations until adulthood, patients must transition to independence as soon as possible. However, some parents are accustomed to overprotecting their children and find it difficult to adjust their roles, particularly when it comes to the patients' independent management of diabetes. Therefore, it is recommended that healthcare professionals explain the self-care requirements to patients' parents while also educating the patients. Healthcare professionals are advised to communicate information regarding diabetes self-care to patients, as well as to enlighten the parents of patients that their role must transition from the primary management of the disease to that of supporting and nurturing adolescents at the earliest opportunity. The findings of this research emphasize the vital significance of peer support during the transition and advise healthcare organizations to establish both online and offline peer support groups to offer an effective communication forum for young people with diabetes. It is also advised that healthcare professionals lead peer communication sessions to provide adept responses to concerns regarding the disorder, in order to ensure an unobstructed transition for adolescents.

Conclusion

This review synthesizes the experiences and feelings of adolescents with diabetes as they transition from pediatric to adult healthcare settings, with patients having different attitudes to the transition. During the transition, individuals may encounter obstacles such as adapting to new disease management roles, uneasiness due to dissimilarities among adult healthcare professionals, and managing their diabetes independently. In the aftermath of the transition, several adolescents convey their hopes and aspirations for motivation and aid from pediatric and adult healthcare providers, parents, peers, and other support systems.

Declaration of Competing Interest. The authors declare no conflict of interests.

Ethics Approval. Ethical approval was not required for this review as this was a secondary study and citations were retrieved from previous studies.

Contribution statement. Wanhui Yu: Conceptualization, Writing-Original draft, Project administration; Ziheng Jin: Methodology, Writing-Reviewing and Editing; Hui Li: Visualization, Methodology, Data Curation. Cheng Chi: Methodology, Software; Bing Liu: Validation; Shuang Wang: Supervision; Haiya Sun: Writing-Reviewing and Editing, Funding acquisition.

Data Availability Statement. Additional information could be accessed through the corresponding author upon reasonable request.

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CLINICAL MEDICINE & PHARMACOLOGY

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Review article

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Study on Traditional Chinese Medicine Syndrome Types in NPC

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Abstract: As one of head and neck tumors, nasopharyngeal carcinoma (NPC) occurs most frequently in the south of China, especially in Hunan, Guangzhou and other places, causing serious harm to people's life and health. NPC patient is mainly treated with radiotherapy in clinic, but most of them have serious side effects. At present, traditional Chinese medicine (TCM) combined with chemoradiotherapy in the treatment of NPC patient has been focused on by Chinese and Western clinicians. Although TCM syndrome differentiation has significant advantages in the treatment of nasopharyngeal cancer, the relevant syndrome type standards for TCM syndrome differentiation guidance are still not unified. Therefore, this paper summarized the clinical experience, clinical data analysis and experimental research of TCM scholars in recent years, discussed the role and influence of TCM syndrome differentiation on the treatment of NPC. It provides some guidance for the standardization of TCM syndrome differentiation of NPC patients.

Keywords: Nasopharyngeal carcinoma; TCM syndrome type; Syndrome differentiation and treatment; Radiation therapy; Constitution theory

Nasopharyngeal carcinoma (NPC) refers to a malignant tumor originating from the epithelium of the nasopharyngeal mucosa, predominantly occurring in southern China regions such as Hunan, Guangzhou, and Fujian, with its incidence ranking first among head and neck malignancies [1]. Most initially diagnosed NPC patients present at intermediate or advanced stages. Concurrent radiotherapy and chemotherapy serve as effective treatment modalities for these patients; however, the therapeutic regimens are associated with significant side effects, reduced patient tolerance, and high recurrence rates, posing major challenges in clinical management [2]. Currently, traditional Chinese medicine (TCM) demonstrates notable advantages in treating head and neck tumors through mitigating the toxic side effects of radiotherapy and chemotherapy, enhancing patients' immune function, and consequently markedly improving their quality of life [3]. Syndrome differentiation and treatment constitute a distinctive TCM diagnostic and therapeutic approach, serving as the cornerstone for effective tumor management. TCM's syndrome differentiation methodology integrates various theories, including the Eight Principles syndrome differentiation and visceral-meridian syndrome differentiation, to identify the disease site, etiology, and pathogenic relationships, thereby establishing comprehensive syndrome patterns and corresponding therapeutic principles [4]. The essence of TCM syndrome differentiation lies in achieving a holistic understanding of disease pathogenesis, symptoms, and signs to formulate targeted prescriptions addressing primary pathogenic factors. However, standardized TCM syndrome classification criteria for NPC remain inconsistent, with variations in treatment protocols and pharmacological approaches. Moreover, syndrome manifestations at pre- and post-surgical or chemoradiotherapy may vary depending on individual physiological differences, underscoring the critical importance of syndrome differentiation in guiding TCM-based treatment strategies. In recent years, numerous scholars have conducted in-depth investigations into the correlation between TCM syndrome patterns and modern medicine in NPC.

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Pathogenesis of NPC in TCM

There is no specific description of "NPC" in traditional Chinese medical literature. Based on the clinical symptoms described in modern medicine and their correspondence with ancient medical texts, it can be termed as "epistaxis," "nasal abscess," "upper stone carbuncle," "depletion of vital energy," "scrofula," "loss of vitality," "malignant nodule," or "true headache." Shigong Chen of the Ming Dynasty described it in The Authentic Treatise on Surgery [5]: "Over time, the lesion gradually enlarges, becoming hard like stone; it does not move when pushed or pressed. Alternatively, it may swell like a lotus flower, emitting foul odor continuously day and night." Bingjun Gao of the Qing Dynasty noted in Collected Insights on Ulcerology [6], "Similar to a tree losing its vitality..., It arises around the ears and neck, gradually enlarging followed by dull pain, chest tightness, and irritability..." Qian Wu of the Qing Dynasty stated in The Golden Mirror of Medicine [7], "Yellow, turbid nasal discharge flows continuously... If it persists without healing...". Regarding the pathogenesis of NPC, Shigong Chen explained in The Authentic Treatise on Surgery [5] that it results from "the stagnation of stagnant fire, leading to phlegm obstruction and subsequent accumulation"; Collected Insights on Ulcerology [6] attributed it to "depletion of vital energy and drying up of collateral vessels"; Zhang's Medical Compendium [8] described it as "vital energy depletion due to prolonged consumption of expensive foods followed by frugality—even without exposure to pathogens, essential fluids are gradually lost, resulting in internal depletion of vital energy"; while Ma Pei's Surgical Cases [9] linked it to "deficiency of liver and spleen vitality." After reviewing ancient medical literature on NPC, Xiaojun Zhou concluded that the fundamental cause lies in deficiency of vital qi; when this deficiency is compounded by invasion of external pathogens or emotional distress, it further weakens vital qi, ultimately leading to "deficiency of vitality and drying up of collateral vessels" and death [10].

Currently, different scholars of TCM hold varying interpretations regarding the pathogenesis of NPC, but their discussions generally revolve around phlegm, blood stasis, deficiency, and toxicity. Wei Hou [11] posited that the primary pathogenesis of NPC is "yin deficiency with toxin accumulation," where the body lacks nourishment, allowing pathogenic factors to invade. The essence lies in the disruption of the dynamic balance of "yin equilibrium and yang secretion" in the human body; thus, the therapeutic principle should prioritize replenishing qi and nourishing yin, supplemented by clearing heat and resolving phlegm. Xiaojun Zhou et al. [12] concluded that the pathogenesis of NPC involves "failure of Yangming to descend based on the theory of the Five Phases and Six Qi", it means that the failure of Yangming to descend causes fire to rise upward, leading to dryness-heat in the upper jiao. The treatment approach should focus on descending Yangming and tonifying the spleen and stomach. Yueheng Li [13] argued that the fundamental pathogenesis of NPC is "deficiency of the root and excess of the branch", where deficiency of healthy qi serves as the root cause, while phlegm, blood stasis, and toxins interact as the branch manifestations. And this should be addressed differently across stages, patients during chemotherapy, radiotherapy, or/and surgery, exhibit intense heat-toxin accumulation and qi-yin deficiency, requiring that the treatment focuses on tonifying the spleen and replenishing qi. During recovery, patients suffer from dual deficiency of yin and yang, necessitating efforts to restore healthy qi. At post-treatment, the patients occur with coexisting phlegm-blood stasis when disease recurrence or metastasis, the treatment should emphasize softening hard masses and dispersing nodules. Comprehensive analysis of these TCM perspectives revealed that deficiency of healthy qi and generation of internal toxins are pivotal factors in NPC pathogenesis. Dysfunction of visceral organs and qi stagnation with phlegm condensation lead to the accumulation of various pathological products, such as tumor-forming factors, which aligns with classical TCM theories. Professor Daofa Tian [14], drawing on years of clinical experience, posited that most diseases in the human body, including tumors, are closely associated with a qi-deficient constitution from innate constitutional differences. This condition involves an inherent deficiency of the body's vital qi and the endogenous generation of pathogenic toxins. The interaction between these factors leads to progressive depletion of vital qi and the accumulation of internal toxins, producing pathological products such as phlegm and blood stasis, thereby triggering disease onset. This constitutes the fundamental basis of Professor Tian's independently developed "qi-deficiency and toxin accumulation" theory. In this framework, the qi-deficient constitution serves as the root cause of disease; dysfunction of the visceral organs and disruption of yin-yang balance act as internal factors inducing toxin endogenesis, while external exposure to pathogenic toxins constitutes the external factor. The combined impact of these internal and external factors drives the continuous progression of the disease.

Guidelines for TCM Syndrome Types in NPC Patients

Due to regional differences and various understandings among medical practitioners regarding the pathogenesis of NPC, the established TCM syndrome differentiation guidelines have not been standardized, leading to discrepancies in treatment methods and herbal formulations. Moreover, the clinical manifestations of the patients may change after treatments such as radiotherapy, chemotherapy, or surgery. Therefore, the TCM principle of syndrome differentiation and treatment is crucial for guiding the patient management. The 2008" Guidelines for TCM Diagnosis and Treatment of Oncology" [15], issued by the China Association of Chinese Medicine, classified NPC patients into four syndrome patterns: Heat Pathogen Invading the Lungs Syndrome, Liver Stagnation with Phlegm Condensation Syndrome, Blood Stasis Obstructing Collaterals Syndrome, and Qi-Yin Deficiency Syndrome. The guidelines categorize NPC

patients under traditional TCM classifications such as "Nasal Discharge," "Tinnitus Syndrome," "Superior Stone Gangrene," and "Deficiency of Vital Energy." Its primary clinical symptoms include epistaxis, rhinorrhea, tinnitus, and headache, it is accompanied by dry mouth and fever. The core TCM therapeutic principles are: aggressive treatment in the early stage, a combination of aggressive and tonifying therapy in the middle stage, and tonifying therapy in the advanced stage, all guided by the principle of detoxification and collateral dredging. The 2011 edition of "Traditional Chinese Medicine Oncology," edited by Daihan Zhou [16], further classified nasopharyngeal carcnoma into four subtypes: Lung Heat with Phlegm Condensation, Qi Stagnation with Phlegm Stasis, Internal Fire-Toxin Obstruction, and Qi-Yin Deficiency. Zhou emphasized that NPC originates in the nasopharynx, the respiratory tract closely linked to internal organs. The lungs govern qi and open into the nose; internal heat obstruction impairs lung qi circulation, causing nasal congestion and cough; ascending fire transforms fluids into phlegm, resulting in foul-smelling nasal discharge; heat scorches collaterals, forcing blood out of its channels, leading to epistaxis. Concurrent emotional disturbances exacerbate liver qi stagnation and internal fire-toxin obstruction, potentially causing headaches and hearing loss. When phlegm-fire obstructs collaterals and forms masses, cervical phlegm nodules may develop hard as stones and progressively enlarge over time. Therefore, the pathogenesis of NPC is closely related to functional disorders of organs such as the lungs and liver. Clinically, the patients with NPC often present with a mixture of deficiency and excess patterns: nasal obstruction due to impaired lung qi circulation; hemoptysis or epistaxis caused by lung fire scorching the collaterals and forcing blood out of its normal pathways; hearing loss and tinnitus resulting from liver-gallbladder fire stagnation; headache induced by qi rebellion ascending; and neck masses formed by phlegm-stasis and blood stasis. Thus, clinical treatment should differentiate between deficiency and excess patterns, employing therapeutic principles such as clearing heat and toxins to resolving stasis and unblock collaterals, and to replenish qi and nourishing yin [17]. In 2016, the report edited by Tian Daofa [18] classified NPC patients into five syndrome types: qi-blood stasis with blockage at the Hals (pharyngeal region), excessive fire-toxin accumulation causing stagnation at the Hals, dual deficiency of qi and yin with pathogenic stagnation at the Hals, equilibrium between pathogen and healthy qi leading to pathogenic stagnation at the Hals, and qi-yang deficiency with pathogenic toxin dissemination. Through observing tongue manifestations and analyzing constitutional profiles of newly diagnosed NPC patients, Tian et al identified qi deficiency with toxin invasion as the primary TCM pathogenesis. By integrating congenital genetic factor and virulence characteristics of Epstein-Barr virus (EBV) infection, he established a pathogenic axis involving "innate constitution–physical constitution–latent pathogens–new external infections interacting", which holds significant clinical implications for medication guidance in NPC patient management.

TCM Syndrome Differentiation and Classification in NPC Patients

TCM constitution-related syndromes in NPC patients

The incidence of NPC exhibits a gender bias and is influenced by genetic factors, diet, and lifestyle habits [19, 20]. TCM categorizes this comprehensive disease pattern under the framework of TCM constitution theory. In recent years, significant progress has been made in basic research on constitution-related theories and clinical trials involving constitutional regulation interventions for NPC. Variations in patient constitutions exert distinct impacts on TCM diagnosis and treatment; thus, constitution investigations hold substantial scientific significance for the prevention, diagnosis, and management of NPC through TCM approaches.

In 2002, Zhou et al. developed the initial constitution survey questionnaire based on the constitutional clustering analysis results conducted by He et al. They systematically investigated NPC patients and their families according to normal or abnormal constitutions (including weak constitution and dysregulated constitution) [21]. Through multiple regression analysis, they identified weak constitution as a significant risk factor for familial genetic etiology of NPC. Influenced by Tian's theory of "qi deficiency with toxin accumulation", they reclassified weak constitution as qi deficiency constitution, focusing particularly on the progression of cancer driven by qi deficiency [22, 23]. As constitutional advanced studies, a series of classification criteria, including constitutional syndromes, were established with additional composite constitutions such as damp-heat and deficiency-stasis incorporated [24]. Subsequent studies revealed that high-risk NPC populations predominantly exhibited qi deficiency constitution; most NPC patients displayed dysregulated constitution; and post-radiotherapy cases often exhibited composite constitutions involving qi deficiency mixed with phlegm, heat, and dampness, demonstrating that constitutional changes permeate the entire course of NPC development [25]. The clinical study on NPC patient constitutional syndrome scores found that qi deficiency constitution predominates among precancerous lesions, while composite constitutions were more common in post-treatment patients [26]. This classification aligns well with the constitutional characteristics of the Lingnan population, where qi deficiency constitution ranked highest in traditional Chinese medicine constitution scales [27], indicating that NPC constitutional classification reflects disease progression patterns and exhibits regional correlations with affected populations.

Epstein-Barr virus (EBV) exhibits a close association with NPC. Epidemiological analyses of the constitution of EBV-infected individuals revealed that EBV-positive populations predominantly exhibit a qi-deficient constitution. Upon EBV invasion, the immune system promptly activates to eliminate the virus, manifesting as symptoms such as fever and sore throat due to the interaction between pathogenic and healthy qi. In cases of compromised or impaired

immune function, EBV may remain latent within the body, presenting as EBV infection, a condition where TCM characterizes the constitution as qi-deficient. Without proper regulation, this may progress NPC. The entire process of EBV latency leading to carcinogenesis aligns closely with the TCM principle of "deficiency harboring pathogenic factors" [28]. Yang et al., through analysis of the constitution of EBV-positive individuals, identified qi-deficient and yang-deficient constitutions as the predominant patterns among these patients, and they applied constitutional intervention therapy to the early management of NPC patients [29].

The constitutional theory of NPC exhibits a certain correlation with genetic factors. With science and technology development, fundamental investigation on this theory has become increasingly robust. Some studies have revealed significant proteomic differences among individuals with distinct constitutions in NPC [30]. Notably, microRNA profiles differ markedly between patients with qi-deficient constitution and those without qi-deficient constitution, with the former exhibiting a promoting effect on malignant behavior of cancer cells [31]. He et al. employed gene recombination technology to construct a dual-gene eukaryotic expression vector targeting human p53 protein and EBV latent membrane protein 1 for investigating the qi-deficient constitution in NPC. Animal experiments demonstrated that, compared to the control group, 117 genes in the nasopharyngeal epithelium of the rats with qi-deficient constitution exhibited differential expression, including interleukin-1β and glutathione synthase [32]. Cheng et al. induced rat with qi-deficient constitution NPC using dinitrophenylpiperazine (DNP), finding a significantly higher incidence of cancer cases in the qi-deficient group compared to the DNP-only induction group, indicating a close association between NPC development and the qi-deficient constitution [33].

Evolutionary patterns of TCM syndrome types in patients with NPC undergoing radiotherapy and chemotherapy

Currently, due to the significant divergence between modern lifestyles and dietary patterns from those described in ancient Chinese medical texts, the diagnosis and treatment of this disease require not only reliance on the experience of traditional physicians but also integration with modern medical technologies. Modern clinicians advocate that the pathogenesis of NPC under TCM should be analyzed in conjunction with different stages of radiotherapy and chemotherapy. Wu et al. [34, 35] posited that the pathogenic mechanism of NPC involves carcinogenic toxins, deficiency of vital qi, progressive impairment of vital qi following multiple radiotherapy sessions, with dual deficiency of qi and yin as the root cause and the interplay of phlegm, stasis, and toxins as the clinical manifestation; thus, treatment should prioritize nourishing yin and clearing heat while addressing liver and kidney function, along with anticancer and detoxification therapies. Xu et al. [36] emphasize that early-stage NPC management should focus on eliminating pathogens through medications that resolve phlegm, dissipate masses, remove stasis, and clear heat, whereas advanced-stage treatment should prioritize reinforcing vital qi, with the therapeutic key lying in "regulating qi and blood circulation and balancing yin and yang" through using herbs to tonify lung yin and nourish kidney fluids. Sun et al. [37] identified the core pathogenesis as initial deficiency of vital qi followed by accumulation of phlegm-heat, internal obstruction by toxic heat, and subsequent tumor formation. Post-radiotherapy complications primarily warrant treatment principles centered on "clearing heat and promoting fluid production." Currently, radiotherapy remains the primary treatment for NPC patients, often accompanied by vital qi deficiency and spleen-kidney impairment. He et al. [38] asserted that spleen-kidney deficiency constitutes the fundamental etiology of NPC, with clinical and pathological manifestations predominantly including heat-toxin and blood stasis. Li et al. [39] contended that post-radiotherapy complications such as throat dryness are closely associated with spleen-stomach dysfunction, rooted in yin deficiency and accompanied by symptoms of heat-toxin, phlegm-turbidity, and blood stasis. Chen et al. [40] posited that the toxic and adverse reactions in NPC patients after radiotherapy are attributed to pathogenic mechanisms involving excessive heat-toxin, yin deficiency with dryness-heat, spleen-stomach qi deficiency, and latent pathogenic factors. Treatment should focus on reinforcing healthy qi, eliminating pathogens, promoting fluid production, and replenishing qi. Lin et al. [41, 42], from a TCM meridian perspective, analyzed that NPC involves the liver and lung organs, with its primary pathogenesis being pathogenic heat invading the lungs and liver qi stagnation leading to phlegm coagulation. Therapeutic approaches should emphasize lung ventilation to clear heat and nourishing the liver and kidneys. Huang et al employed systematic cluster analysis to investigate the patterns of TCM syndrome changes in NPC patients at pre- and post- chemoradiotherapy, revealing that these syndromes undergo continuous evolution from predominantly excess patterns to deficiency patterns or mixed patterns, while emphasizing that both chemoradiotherapy and radiotherapy introduce "toxic pathogens" that exacerbate systemic "deficiency, toxicity, and blood stasis" [43]. Pan et al. suggested that post-chemoradiotherapy patients typically present with dual qi-yin deficiency and internal blood stasis-toxicity accumulation, advocating treatments aimed at replenishing qi and yin while resolving stasis and dispersing nodules [44]. Chen et al. concluded that post-chemoradiotherapy manifestations primarily involve dual qi-blood deficiency, necessitating "dual supplementation of qi and yin" as the therapeutic principle [45]. These studies collectively indicate that the core pathogenesis of NPC involves fundamental deficiency with superficial excess and impaired healthy qi. Post-treatment, patients often experience qi depletion and fluid loss, compounded by upper-jiao dryness-heat and middle-jiao deficiency-cold, resulting in complex pathological mechanisms characterized by concurrent cold-heat manifestations, such

as phlegm-heat interaction and phlegm-dampness stagnation.

Correlation between pathological staging and TCM syndrome differentiation in NPC patients

Zhang et al. found that in NPC patients, as the TNM pathological stage advanced, the syndrome patterns evolved from "fire-toxin stagnation type" to "qi deficiency congealing type", and further to "deficiency of healthy qi with toxin retention type" [46]. Li et al. observed that, with increasing pathological stages, the syndrome patterns progressed from "pathogenic heat obstructing the lungs type" to "phlegm-turbidity accumulation type," and then to "blood stasis with phlegm coagulation type" [47]. Zhou et al. demonstrated a negative correlation between pathological stages and the lung-heat predominance type or qi stagnation with phlegm coagulation type, while showing a positive correlation with blood stasis obstructing collaterals type or yin deficiency with fire hyperactivity type [48]. These findings indicate that phlegm, blood stasis, and heat are consistently present throughout all pathological stages of NPC; the lung-heat pattern is predominantly observed in early-stage cases, whereas intermediate and advanced-stage patients typically exhibit deficiency of healthy qi accompanied by mutual entanglement of phlegm and blood stasis.

Correlation between prognostic indicators and TCM syndrome differentiation types in NPC patients

The study found that serum C-reactive protein (CRP) levels exhibit a certain correlation with the TCM syndrome differentiation patterns in newly diagnosed NPC patients. Specifically, CRP levels from low to high correspond to the following patterns: heat pathogen invading the lungs type, liver qi stagnation with phlegm obstruction type, dual deficiency of qi and yin type, and blood stasis obstructing collaterals type [49]. Gao et al. observed that, among patients with different TCM syndrome types, those with blood stasis obstructing collaterals type exhibited higher serum TGF-β1 expression levels, suggesting a potential association with poorer prognosis [50]. Li et al. reported that newly diagnosed NPC patients predominantly presented with phlegm-turbidity accumulation syndrome or qi-blood stasis syndrome. The patients with qi-blood stasis syndrome showed higher serum EGFR levels compared to other syndrome types, leading to the conclusion that their prognosis may be worse [51]. Yan et al. found that the patients with phlegm-turbidity accumulation syndrome or deficiency with toxic stagnation syndrome exhibited higher EGFR expression levels in NPC tissues than those with qi-blood stasis syndrome or fire-toxicity accumulation syndrome, indicating potentially poorer prognosis for these groups [52]. Li et al. demonstrated that patients with phlegm-turbidity internal obstruction syndrome had higher VEGF expression in tumor tissues, while post-radiotherapy/chemotherapy patients with phlegm-stasis and qi stagnation syndrome exhibited the highest VEGF levels in tumor tissues [53].

TCM syndrome differentiation and typing therapy for NPC

There is no unified standard for the TCM syndrome differentiation and classification of NPC patients. Based on previous reports, the patterns can be summarized as follows: Lung Heat Excess Pattern (with the primary treatment principle being lung ventilation and heat clearance), Liver Stagnation with Phlegm Condensation Pattern (with the main therapeutic approach being liver regulation and depression relief), Qi Stagnation with Blood Stasis Pattern (with key treatments including liver regulation, qi circulation improvement, stasis resolution, and nodule dispersion), Qi-Yin Deficiency Pattern (with emphasis on qi replenishment and yin nourishment), and Qi-Blood Deficiency Pattern (with focus on qi and blood supplementation). Guo et al. posited that NPC patients exhibited deficiency of vital qi, with prolonged accumulation of pathogenic toxins leading to cancer development. Therefore, the therapeutic principle should emphasize heat-clearing, yin-nourishing, and fluid generation, often employing herbs such as honeysuckle (Lonicera japonica) and forsythia (Forsythia suspensa) for heat-clearing and detoxification [54]. Jia et al. argueed that post-radiotherapy NPC patients resembled those with warm-heat syndromes, thus frequently prescribing Wuwei Xiaodu Decoction combined with Yangyin Qingfei Decoction to tonify lung qi, achieving excellent efficacy [55]. Based on extensive clinical experience, Zhang et al identified that advanced-stage NPC most commonly presents dual qi-yin deficiency, particularly in the patients treated with radiotherapy and chemotherapy. Consequently, late-stage patients often receive herbs such as Rehmanniae Radix (Shengdi), Pseudostellariae Radix (Taizi Shen), Scrophulariae Radix (Yuanshen), and Hedyotis diffusa (Baihua Shecao) for their heat-clearing, detoxifying, yin-nourishing, and fluid-promoting properties [56]. Tian et al. developed a qi-tonifying and detoxifying formula grounded in the "qi deficiency with toxin accumulation" theory, demonstrating remarkable therapeutic efficacy in treating NPC patients [57]. The study found that the Yiqi Jiedu Formula can induce autophagy in NPC cells by inhibiting the PI3K/AKT/mTOR signaling pathway [58]; suppress NPC cell proliferation by downregulating the Wnt/β-catenin signaling pathway [59]; and regulate the proliferation, migration, and apoptosis of NPC stem cells by inhibiting the CD44/Ras signaling pathway [60]. Zou et al. employed network pharmacology and bioinformatics techniques to demonstrate that the Yiqi Jiedu Formula may treat NPC through signaling pathways such as TNF and NF-κB [61]. These findings highlight the significant advantages of TCM syndrome differentiation in treating NPC, where tailored medication based on distinct TCM syndromes helps stabilize tumor growth, enhance patients 'immune function, mitigate the toxic side effects of radiotherapy and chemotherapy, alleviate clinical symptoms, and improve patients' quality of life.

Summary and Prospects

Differential diagnosis and treatment constitute the core of TCM. Accurate "differential diagnosis" guiding appropriate "treatment" is a critical guarantee for achieving optimal clinical efficacy. The disease names used in ancient TCM texts primarily reflect specific symptoms, differing from those in modern medicine, leading to the phenomenon of multiple disease names for a single condition. Although advancements in technology have expanded human understanding of diseases, the traditional TCM diagnostic approach relies predominantly on clinicians' experience in assessing disease patterns, resulting in a lack of objectivity in TCM differential diagnosis. Currently, there is no unified standard for TCM differential diagnosis criteria for NPC patients, and different practitioners derive varying conclusions and recommendations based on their clinical experience and investigation. In recent years, the application of big data statistical analysis to clinical data, including retrospective and prospective studies, has gradually reduced variations in TCM clinical practice caused by geographical or dietary factors, thereby providing a more objective and accurate representation of TCM syndrome types for NPC. This offers essential evidence for standardizing TCM syndrome classification. Particularly, noteworthy are studies on TCM differential typing after radiotherapy and chemotherapy; following "precise differential diagnosis" and "targeted treatment", these approaches can effectively mitigate the toxic side effects induced by chemoradiotherapy. The patients with NPC may exhibit varying clinical manifestations due to differences in constitution, clinical-pathological stages, age, and gender. However, the correlation between these influencing factors and TCM syndrome differentiation remains unclear in existing studies. Currently, TCM syndrome differentiation of NPC at post- radiotherapy and chemotherapy is predominantly based on clinicians' empirical judgment, lacking objective data support, a potential contributing factor to the significant variability in TCM syndrome outcomes. Future study should integrate comprehensive patient data, including clinical stage, tumor size and location, pre-and post-treatment parameters, specific chemoradiotherapy regimens, and imaging findings, to investigate correlations. Such efforts will enhance the practical application of TCM syndrome differentiation in clinical practice, and provide robust evidence for the effective use of TCM in NPC treatment.

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Correlation Analysis of HCV Genotyping with Viral load, Liver Function, and Liver Fibrosis in Anti-HCV Positive Patients in Yueyang Area

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Abstract:

Objective: To analyze the distribution of HCV genotypes among anti-HCV-positive patients in Yueyang using next-generation sequencing (NGS), and to examine their associations with sex, age, viral load, liver function, and liver fibrosis markers.

Methods: A total of 133 anti-HCV-positive patients admitted to Yueyang People's Hospital from October 2024 to January 2026 were included. Demographic data, HCV-RNA viral load, HCV genotyping results, liver function indicators, and liver fibrosis markers were collected. Genotype distribution, NGS detection performance, and differences in clinical indicators among genotypes were analyzed.

Results: Five HCV genotypes were identified among the 133 patients. Genotype 1b was predominant, accounting for 42.9%, followed by 6a at 26.3%, 3a at 10.5%, mixed genotype infection at 4.5%, and 2a at 2.3%. Sex distribution did not differ significantly among genotypes ($P>0.05$). Age distribution showed an overall significant difference ($P<0.05$), but no between-group difference remained significant after correction for multiple comparisons. No significant differences were found among genotypes in HCV viral load, ALT, AST, ALP, GGT, TBIL, TBA, HA, CIV, PIIIP, or LN ($P>0.05$), while DBIL differed significantly ($P<0.05$). The positive agreement rate, negative agreement rate, and overall agreement rate of NGS for HCV genotyping were all 100.0%, with a Kappa value of 1.000.

Conclusion: HCV genotype 1b was the predominant genotype in Yueyang, followed by 6a. Most clinical indicators did not differ significantly among genotypes, except for DBIL. The FASTASeq 300 Dx gene sequencer showed high accuracy in HCV genotyping and may provide reliable evidence for individualized treatment of hepatitis C.

Keywords: Chronic hepatitis C; Genotype; Viral load; Liver function; Liver fibrosis

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Introduction

Hepatitis C virus (HCV) is a single-stranded RNA virus belonging to the Flaviviridae family. It has a positive liver effect and can cause acute and chronic hepatitis. Chronic hepatitis C infection with progressive liver damage may lead to cirrhosis and related complications, including compensated liver disease and hepatocellular carcinoma [1]. According to the World Health Organization, in 2015, there were 71 million people with chronic HCV infection worldwide, and 399,000 people died from cirrhosis or hepatocellular carcinoma (HCC) caused by HCV infection. In 2019, there were 58 million people with chronic HCV infection worldwide, and 290,000 people died from cirrhosis or HCC caused by HCV infection [2]. Therefore, early diagnosis and treatment of HCV infection are extremely important. There are about 5.6 million people with HCV infection in the general population in China. If we include HCV infection in high-risk groups and high-incidence areas, the number is estimated to be about 10 million [2]. HCV has high genetic heterogeneity, and at least 7 genotypes and multiple subtypes have been

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discovered to date. The distribution of different genotypes varies significantly across the globe and is closely related to antiviral treatment response, disease progression and prognosis [3]. For example, genotype 1b has a relatively low response rate to direct-acting antiviral drugs (DAAs), while genotype 3, especially genotype 3a, is associated with accelerated progression of liver fibrosis [4]. Therefore, accurate HCV genotyping results are a key prerequisite for developing individualized treatment plans and improving treatment success rates. At the same time, the HCV RNA viral load level can directly reflect the degree of viral replication activity and is closely related to hepatocellular damage, liver inflammation and fibrosis process. It is a core indicator for laboratory assessment of disease activity. Traditional HCV genotyping methods include PCR-restriction fragment length polymorphism analysis, sequencing, etc., but they have shortcomings such as low throughput and limited resolution [5]. Next-Generation Sequencing (NGS) technology has been gradually applied to viral genotyping and mutation analysis due to its advantages of high throughput, high accuracy and single-base resolution [6]. The FASTASeq 300 Dx gene sequencer uses Sequencing By Synthesis (SBS) technology to achieve efficient and accurate nucleic acid sequence determination. Based on this sequencing platform, this study analyzed the genotypes of 133 HCV antibody-positive patients in Yueyang area, aiming to clarify the distribution characteristics of HCV genotypes in the region and explore their relationship with viral load, liver function and liver fibrosis detection results. At the same time, it verified the application value of NGS technology in clinical HCV genotyping detection and provided a scientific basis for regional hepatitis C prevention and control and precision treatment.

Material and Methods

General Information

This study included 133 patients with positive anti-HCV antibodies admitted to Yueyang People's Hospital between October 2024 and January 2026. The study population consisted of 76 males (57.1%) and 55 females (41.4%), with an age range of 29–83 years and a mean age of (56.2±11.1) years, predominantly middle-aged individuals. Based on HCV-RNA viral load detection results, patients were divided into high viral load group (>10^6 IU /ml), medium viral load group (10^4–10^6 IU /ml), low viral load group (<10^4 IU /ml), and undetectable group. The high viral load group comprised 88 cases (66.2%), the medium viral load group 24 cases (18.0%), the low viral load group 6 cases (4.5%), and the undetectable group 15 cases (11.3%), indicating that viral replication was active in most patients. A retrospective analysis was conducted on the patients' general clinical data, genotyping results, liver function test results, and liver fibrosis test results.

Inclusion criteria

1) Positive HCV antibody test; **2)** Willing to participate in this study and sign informed consent form; **3)** Complete clinical data.

Exclusion criteria

1) Insufficient sample size or failure to collect and preserve samples as required; **2)** Missing information that cannot be traced; **3)** Duplicate samples from the same patient; **4)** Other circumstances deemed unsuitable for inclusion by the investigator.

This study was approved by the Ethics Review Committee for Clinical Trials of Drugs/Medical Devices of Yueyang People's Hospital (Ethics Approval No.: 2024040) and was conducted in strict accordance with the requirements of the Good Clinical Practice for Medical Devices (No. 28 of 2022).

Methods

HCV genotyping

1) Next-Generation Sequencing (NGS) Technology: FASTASeq 300 Dx gene sequencer (Shenzhen Zhenmai Biotechnology Co., Ltd.), along with a matching Hepatitis C Virus Genotyping Kit (reversible terminator sequencing method) and a universal sequencing reaction kit; **2)** Comparison Reagent: Hepatitis C Virus (HCV) Genotyping Kit (PCR-fluorescent probe method, Taipu Bioscience (China) Co., Ltd., National Medical Device Registration Certificate No. 20143401926); **3)** Verification Method: Sanger sequencing kit (Applied Biosystems , USA); **4)** Nucleic Acid Extraction Reagent: Nucleic acid extraction reagent (Minxia Medical Device Registration No. 20150045) and QIAamp Viral RNA Mini Kit (Qiagen , Germany , Catalog No.: 52904); **5)** Detection Steps: Sample Collection and Processing: Collect 5 mL of venous blood from the subject, centrifuge to separate the serum, and store as required (store at 2~8℃ for no more than 72 hours, at -25~-15℃ for no more than 3 months , and below -70℃ for no more than 1 year). Avoid repeated freeze-thaw cycles and bring to room temperature before testing. Nucleic Acid Extraction: Use the nucleic acid extraction reagents for the experimental group and control group respectively , and extract nucleic acid from the serum samples according to the instructions. The sample input for the experimental group is 200 μL of serum, and the initial sample input for the control group is 200 μL of serum. Detection Procedure: 1. Experimental Group: Take 15 μL of the extracted product for PCR amplification and library construction (PCR amplification product concentration ≥10 ng/μL). Add the 4 nM library to the sequencer, set the sequencing read length PE150, the cycle number of strand 1 and strand 2 to 150, and the tag sequence length to 8+8, and perform sequencing detection. The required sequencing data volume is ≥0.5 Gb, the Q30 base ratio is ≥80%, and the sequence alignment to the reference genome ratio is ≥90%. 2. Control Group: 10 μL of the extracted product was used for PCR-fluorescent probe detection. Reaction parameters were strictly set according to the kit instructions. Negative control solutions showed no typical S-type amplification curve or a ct

Table 1 | liver function biomarkers

Biomarker	Method Principle
Alanine aminotransferase (ALT)	IFCC enzymatic rate method (kinetic UV assay, pyridoxal-5′-phosphate activated)
Aspartate aminotransferase (AST)	IFCC enzymatic rate method (kinetic UV assay)
Alkaline phosphatase (ALP)	Kinetic colorimetric method (p-nitrophenyl phosphate substrate)
γ-Glutamyl transferase (GGT)	Enzymatic rate method (γ-glutamyl-3-carboxy-4-nitroanilide substrate)
Total bilirubin (TBIL)	Colorimetric method (dichlorophenyldiazonium, DPD, or vanadate oxidation method)
Direct bilirubin (DBIL)	Colorimetric method (DPD diazo method or bilirubin oxidase method)
Albumin (ALB)	Colorimetric method (bromocresol green, BCG)
Total protein (TP)	Colorimetric method (biuret reaction)

value > 26.5. Positive control HCV 1b PCR reaction tubes showed a typical S-type FAM-labeled curve with a ct value ≤ 25.1. Other reaction solutions showed no typical S-type amplification curve or a ct value > 26.5. Otherwise, the experiment was invalid and needed to be repeated. 3. Result Verification: Samples with inconsistent results from the two groups were verified using Sanger sequencing. Positive Criterion: A genotype is considered positive if the specific read length ratio (RPM) per million sequences is ≥ 119778.

HCV RNA detection

HCV RNA quantification was performed using the Sansure High-Sensitivity HCV RNA Quantitative Detection Kit (PCR-Fluorescence Probing Method; Sansure Biotech, Changsha, China). Nucleic acid extraction was conducted manually using a superparamagnetic nano-bead-based method according to the manufacturer's protocol. Real-time PCR amplification and detection were carried out on compatible thermocyclers, including the SLAN-96P (Hongshi) and ABI 7500 (Thermo Fisher Scientific).

The assay is based on a one-step reverse transcription real-time quantitative PCR (RT-qPCR) using fluorescence-labeled probes targeting conserved regions of the HCV genome. Briefly, 0.2 mL of serum or plasma was subjected to room-temperature chemical lysis without heating, followed by RNA capture using nano-core-shell magnetic beads (nanoscale magnetic core with a molecular polymer shell) to efficiently enrich and purify nucleic acids. The extracted RNA was then added to the PCR reaction mixture containing specific primers, a fluorescence-labeled probe, heat-activated DNA polymerase, deoxynucleotide triphosphates (dNTPs), and an internal control (IC) included throughout the extraction and amplification process to monitor PCR inhibition and prevent false-negative results. The reaction system also contained ROX passive reference dye to normalize well-to-well variations and pipetting errors, thereby improving quantitative accuracy.

HCV antibody detection

HCV antibody screening was performed using the AiD™ anti-HCV ELISA kit (Beijing Wantai Biological Pharmacy Enterprise Co., Ltd., Beijing, China). The assay was read on a KHB ST-360 microplate reader (Shanghai Kehua Experimental System Co., Ltd., Shanghai, China), and plate washing was performed using a KHB ST-36W microplate washer (Shanghai Kehua). All reagents were used within their stated shelf life.

The assay is based on a third-generation enzyme-linked immunosorbent assay (ELISA). HCV recombinant antigens (Core, NS3, NS4, and NS5 regions) are pre-coated onto polystyrene microwells. Serum or plasma samples (typically 100 µL) are added to the antigen-coated wells and incubated. Anti-HCV antibodies, if present, bind to the immobilized antigens. After washing to remove unbound material, horseradish peroxidase (HRP)-conjugated anti-human IgG is added, which binds to any antigen–antibody complexes formed. Following a second wash, the 3,3′,5,5′-tetramethylbenzidine (TMB) chromogenic substrate is added and hydrolyzed by the bound HRP to produce a blue-colored product. The reaction is terminated by adding stop solution, and the optical density (OD) is measured at 450 nm (with a reference wavelength of 630 nm) on the KHB ST-360 reader. The intensity of the color is proportional to the concentration of anti-HCV antibodies in the sample.

Liver function biochemical index testing

Liver function tests were performed on the DxA 5000 Fit total laboratory automation system (Beckman Coulter, Brea, CA, USA), which integrates pre-analytical sample processing with connected clinical chemistry and immunoassay analyzers. The connected chemistry analyzers (e.g., UniCel DxC or AU5800 series, Beckman Coulter) were operated with Beckman Coulter original reagents according to the manufacturer's instructions. All assays were conducted under standardized laboratory conditions with routine calibration and quality control procedures.

The liver function biomarkers were quantified in serum or plasma are listed in **Table 1**.

Liver fibrosis marker detection

Serum liver fibrosis markers were quantified on the MAGLUMI X8 fully automated chemiluminescence immunoassay (CLIA) analyzer (Shenzhen New Industry Biomedical Engineering Co., Ltd. [Snibe], Shenzhen, China). The system was operated with Snibe original reagents, including the following assay kits: Hyaluronic Acid (HA) assay kit, Laminin (LN) assay kit, Type IV Collagen (CIV) assay kit, and Type III Procollagen N-terminal Peptide (PIIINP) assay kit. All reagents and calibrators were used within their stated

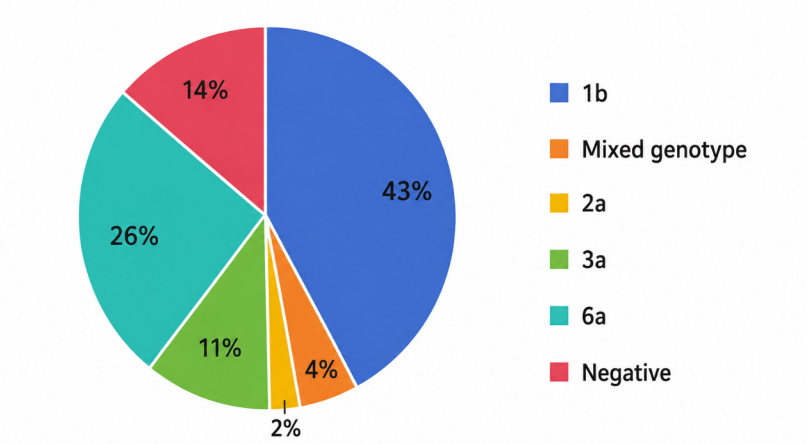

Figure 1 | Distribution of HCV genotypes

shelf life and stored at 2–8℃ according to the manufacturer's instructions.

The assay is based on a direct chemiluminescence immunoassay (CLIA) with magnetic microparticle separation. Briefly, serum samples (typically 20–50 µL, depending on the specific marker) are incubated with nano-magnetic bead–coated capture antibodies (or antigens, depending on the assay format) and acridinium ester–labeled detection antibodies. The antigen–antibody complexes are captured on the magnetic microparticles, and unbound substances are removed by a magnetic separation and wash step. Subsequently, a trigger solution is added to initiate the chemiluminescent reaction of the acridinium ester label, and the emitted light is measured in relative light units (RLU) by the photomultiplier tube of the MAGLUMI X8. The RLU value is proportional to the concentration of the target analyte in the sample. Quantification is achieved by interpolation from a master calibration curve stored on board the analyzer, which is recalibrated using two-point calibration with Snibe calibrators according to the manufacturer's protocol.

Statistical analysis

SPSS 27.0 software was used for statistical analysis. First, the normality of the measurement data was tested. The measurement data in this study did not conform to the normal distribution after the normality test, and were expressed as medians (interquartile range) [M (P25 ~ P75)]. The Kruskal -Wallis test was used for comparisons between groups , and the χ^2 test was used for count data. A $p < 0.05$ was considered statistically significant.

Results

HCV genotype distribution

Anti -HCV patients included: genotype 1b in 57 cases (42.9%), genotype 2a in 3 cases (2.3%), genotype 6a in 35 cases (26.3%), genotype 3a in 14 cases (10.5%), and mixed genotype in 6 cases (4.5%). See Figure 1.

Correlation analysis of HCV genotype with sex and age

In this study, there were 34 males (60.0%) and 23 females (40%) with genotype 1b; 1 male (33%) and 2 females (66%) with genotype 2a; 8 males (57%) and 6 females (43%) with genotype 3a; 5 males (83%) and 1 female (17%) with mixed genotype; and 20 males (57%) and 15 females (43%) with genotype 6a. Sex comparisons were performed among the patients with the five genotypes. The results showed that, according to the chi-square test, there was no statistically significant difference in the gender distribution of patients with different HCV genotypes (χ^2=4.461, P=0.669 $>$0.05); according to the Kruskal -Wallis H test, there was a statistically significant difference in the age distribution of patients with different HCV genotypes (χ^2=9.877, df =4, P=0.043<0.05), with the highest median age for genotype 2a (65 years) and the lowest for genotype 6a (53 years). However, after post-hoc multiple comparison correction, there was no statistically significant difference in age among the genotype groups (P>0.05). See Table 2 and Figure 2.

Correlation analysis between HCV genotype and viral load

HCV RNA is a direct marker of viral replication and an important laboratory basis for confirming HCV infection in clinical practice. It is also a standard for evaluating the efficacy of antiviral treatment. Therefore, exploring the relationship between HCV genotype and viral load is of great significance for clinical diagnosis and treatment. In this study, the median HCV RNA viral load for genotype 1b was 3.28×10^6 IU/mL, for genotype 2a it was 2.20×10^4 IU / mL , for genotype 3a it was 5.14×10^6 IU/ mL , for genotype 6a it was 5.02×10^6 IU/ mL , and for mixed genotype HCV RNA it was 3.24×10^6 IU / mL . Comparison of viral load among different genotypes showed no statistically significant difference (P > 0.05). See Table 3 and Figure 3.

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Table 2 | Sex distribution of different genotypes

Genotype	Male (n%)	Female (n%)
1b	34 (60%)	23 (40%)
2a	1 (33%)	2 (66%)
3a	8 (57%)	6 (43%)
Hybrid	5 (83%)	1 (17%)
6a	20 (57%)	15 (43%)

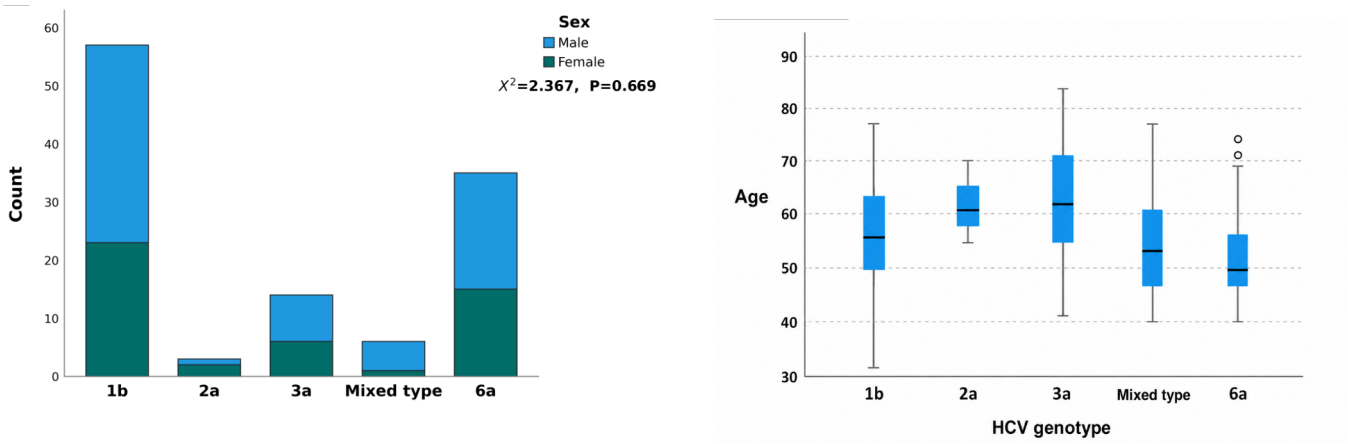

Figure 2 | Comparison of different HCV genotypes by age and sex

Table 3 | Comparison of viral load of different HCV genotypes [M(P25~P75)]

HCV genotype	Number of examples	Viral load (IU/ mL)
1b	57	3.28×10^6 (1.21×10^6 ~ 1.38×10^7)
2a	3	2.20×10^4 (1.71×10^4 ~ 7.94×10^4)
3a	14	5.14×10^6 (3.86×10^5 ~ 9.23×10^6)
Hybrid	6	3.24×10^6 (5.33×10^5 ~ 6.60×10^6)
6a	35	5.02×10^6 (1.23×10^6 ~ 2.35×10^7)
H value		9.306
p -value		0.054

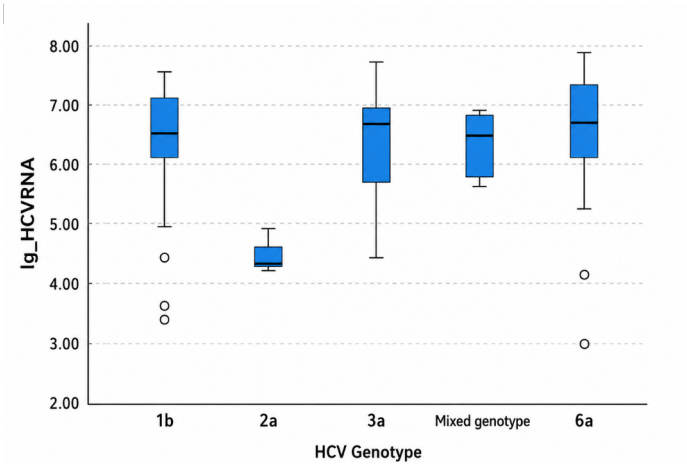

Figure 3 | Comparison of viral load of different HCV genotypes

Table 4 | Comparison of liver function test results for different HCV genotypes [M(P25~P75)]

index	1b	2a	3a	6a	Hybrid	H value	p -value
ALT(U/L) (n=115)	47.80 (25.20~96.20)	27.80 (16.00~27.80)	79.60 (47.83~138.23)	84.70 (13.85~139.05)	37.60 (18.30~72.40)	7.159	0.128
AST(U/L) (n=115)	59.00 (29.25~93.55)	59.30 (31.60~59.30)	62.35 (43.93~136.93)	61.00 (42.60~106.08)	43.00 (24.50~72.20)	6.29	0.178
ALP(U/L) (n=102)	32.60 (21.05~76.15)	46.80 (19.30~46.80)	80.50 (29.90~132.95)	70.60 (41.55~187.70)	56.40 (17.20~143.05)	5.824	0.213
GGT(U/L) (n=100)	76.10 (51.40~95.45)	88.20 (62.00~88.20)	109.50 (66.55~155.65)	128.40 (55.00~168.30)	77.80 (58.15~104.50)	6.149	0.188
TBIL (μmol/L) (n=115)	18.10 (12.15~23.50)	24.70 (23.40~24.70)	17.95 (13.48~31.43)	13.80 (7.53~19.60)	13.10 (10.10~20.30)	8.324	0.8
DBIL (μmol/L) (n=114)	4.50 (3.00~6.95)	6.60 (6.50~6.60)	4.50 (3.45~8.90)	4.15 (2.10~7.33)	2.85 (2.28~4.33)	12.636	0.013
TBA (μmol/L) (n=113)	8.00 (3.45~14.40)	25.00 (25.00~25.00)	9.10 (4.35~51.70)	6.75 (4.85~11.30)	5.70 (2.68~10.83)	3.955	0.412

Table 5 | Comparison of liver fibrosis detection results for different HCV genotypes [M(P25~P75)]

Index	1b (n=31)	2a (n=3)	3a (n=7)	6a (n=15)	Mixed type (n=2)	H value	p -value
HA (ng/mL)	128.00 (72.90~190.00)	158.00 (76.70~158.00)	100.00 (57.10~140.00)	93.30 (76.00~139.00)	194.05 (58.10~194.05)	2.39	0.664
CIV (ng/mL)	26.60 (18.10~51.60)	50.90 (36.80~50.90)	24.10 (17.60~56.40)	26.80 (13.90~85.90)	37.00 (21.50~37.00)	2.789	0.594
PIIIP (ng/mL)	33.00 (20.20~50.50)	52.60 (36.10~52.60)	24.90 (10.80~47.70)	39.90 (16.40~83.30)	295.30 (84.60~295.30)	5.243	0.263
LN (ng/mL)	68.10 (40.60~113.00)	561.00 (122.00~561.00)	51.60 (30.30~114.00)	96.30 (53.80~220.00)	65.60 (31.20~65.60)	8.367	0.079

Correlation analysis between HCV genotype and liver function indicators

Liver function biochemical indicators are important indicators for assessing the degree of liver damage in patients with chronic hepatitis C. Different HCV genotypes may differ in viral replication, pathogenicity, and the degree of liver damage induced due to differences in their biological characteristics. Exploring the relationship between HCV genotype and liver function indicators is of great significance for clinical assessment and prognosis. This study compared and analyzed the levels of ALT, AST, ALP, GGT, TBIL, DBIL, and TBA in patients with different HCV genotypes. The results showed no statistically significant differences in ALT, AST, ALP, GGT, TBIL, and TBA levels among different genotypes ($P > 0.05$). Only the DBIL level showed a statistically significant difference among different genotypes ($H = 12.636$, $P = 0.013 < 0.05$). Post-hoc multiple comparison analysis did not find pairwise differences between specific genotypes, suggesting that this difference may be due to uneven distribution within groups. See Table 4.

Correlation analysis between HCV genotype and liver fibrosis markers

Liver fibrosis is a key pathological stage in the progression of chronic hepatitis C to cirrhosis. Serological liver fibrosis markers (HA, CIV, PIIIP, LN) directly reflect the dynamics of extracellular matrix synthesis and degradation, and are important biomarkers for assessing the degree of liver fibrosis, predicting disease progression, and prognosis. Different HCV genotypes exhibit significant differences in viral replication efficiency, host immune response induction, and liver tissue inflammation patterns, affecting the occurrence and progression rate of fibrosis. Exploring the relationship between HCV genotype and liver fibrosis markers is of great significance for clinical assessment and prognosis. This study compared and analyzed the levels of HA, CIV, PIIIP, and LN in patients with different HCV genotypes. The results showed no statistically significant differences in liver fibrosis markers (HA, CIV, PIIIP, LN) among different genotypes ($P>0.05$). Post-hoc multiple comparisons did not reveal pairwise differences between specific genotypes, which may be related to the small sample size of some genotypes and uneven distribution among groups. See Table 5.

Detection performance analysis

The main evaluation indicators were: the positive concordance rate of the experimental group was 100.00% (95% CI: 94.50%~100.00%), and the negative concordance rate was 100.00% (95% CI: 96.79%~100.00%), which was completely consistent with the test results of the control group.

Secondary evaluation indicators: Overall concordance rate 100.00% (95% CI: 97.93%–100.00%); Kappa coefficient 1.0000 (95% CI: 1.0000–1.0000), indicating that the two detection methods are almost identical. The concordance rates for each subtype were 100.00%, with positive concordance rates of 95% CI for type 1b (90.11%–100.00%), 72.25%–100.00% for type 3a (95% CI: 72.25%–100.00%), 43.85%–100.00% for type 3b (95% CI : 43.85%–100.00%), and 85.13%–100.00% for type 6a.

Data quality analysis

Overall data indicators: The effective sequencing throughput of the experimental instruments ranged from 187.95 to 372.9 M reads, all of which were no less than 100 M reads; the base recognition quality index (Q30) ranged from 82.65% to 92.63%, all of which were no less than 80%. The average raw data volume (number of bases) of the total sample was 141,307,9978.02, the average ratio of high-quality data to overall coarse data was 71.11%, the overall target region coverage was 99.98%, and the overall target region uniformity was 1.00. All indicators met the expected requirements.

Sample quality control indicators: Sequencing data volume (Raw reads) 1,922,416~11,130,218; total number of sequencing bases (Raw bases) 576,724,800~333,906,5400;

Q30 base percentage 86.46%~97.63%; sequence alignment to reference genome percentage 97.02%~99.98%; target region coverage 97.03%~100.00%; average sequencing depth 492,507.90~5,777,965.46, all meeting the quality control targets.

Stratified analysis: After stratifying the total number of sequencing bases, there were no significant differences in the effective sample base recognition quality value Q30, the proportion of sequence aligned to the reference genome, and the target region coverage among the different regions (P=0.2868, 0.2422, 0.7553, respectively); there were no significant differences in the positive judgment value (RPM) of effective positive and negative samples among the different regions (P>0.05 for all), and the detection performance of each subgroup was consistent.

Safety evaluation

Five batches of the test equipment were run without any malfunctions. The equipment stability, safety, and ease of use were all rated at 100%. No system-wide leakage, loose or detached components, or abnormal software interruptions occurred. The researchers were satisfied with all six evaluation criteria , including ease of operation and software usability. No adverse events, serious adverse events, or equipment defects occurred throughout the entire testing process.

Discussion

Hepatitis C is a disease caused by HCV infection, characterized by liver damage. It is one of the main causes of serious liver diseases such as cirrhosis and liver cancer [1]. HCV is a single positive-sense RNA virus. Due to the lack of proofreading activity of HCV NS5B RdRP , the fidelity is low, resulting in a high error rate during replication, which promotes the genetic heterogeneity and population complexity of HCV. It has now been divided into at least 7 genotypes and multiple subtypes . The distribution of HCV genotypes has obvious geographical differences. Understanding the genotype prevalence characteristics in specific regions is the basis for improving the prevention and control strategy of hepatitis C [8]. In northern China, types 1b and 2a are the main types, while types 3 and 6 are more prevalent in southern China [9]. As time goes by, population mobility intensifies and transmission routes diversify, the epidemiological patterns of HCV genotypes in various regions also change. HCV genotyping is not only a key basis for guiding the selection of direct antiviral drugs (DAA), but also an important basis for assessing disease progression, judging prognosis and carrying out regional prevention and control [2]. Therefore, understanding the distribution characteristics of HCV genotypes in this region and clarifying the HCV genotyping of hepatitis C patients is of great clinical significance for diagnosis and treatment. This study is the first to use next-generation sequencing (NGS) technology to perform genotyping on 133 anti - HCV positive patients in Yueyang area and explore its correlation with gender, age, viral load, liver function and liver fibrosis indicators.

This study shows that the most common HCV genotype in Yueyang is type 1b (42.9%), followed by type 6a (26.3%), type 3a (10.5%), mixed type (4.5%), and type 2a (2.3%). The results are consistent with the survey on hepatitis C virus infection in Yueyang by Liu Feng et al. [10], showing obvious regional characteristics in central China. Multicenter epidemiological data across the country show that type 1b is the absolute dominant subtype in mainland China, accounting for 52.18%~62.78%, followed by type 2a; type 6a was previously more common in South China and Southwest China, but has shown a significant upward trend in Central China in recent years [11]. In this study, the proportion of type 6a reached 26.3%, which is significantly higher than the national average. From the perspective of regional epidemiology, Yueyang is located in the northeast of Hunan Province, and the Beijing-Guangzhou Railway runs through the area. It is an important regional transportation hub and a key node connecting Central China and South China. Its HCV genotype distribution retains the characteristics of type 1b as the traditional dominant strain in the central region of China. At the same time, the proportion of type 6a has increased significantly, approaching the prevalence level in South China. This suggests that Yueyang is a transitional zone between the prevalence of HCV in Central China and South China. This unique distribution pattern is closely related to geographical location, population flow and transmission chain, and has important regional representativeness. The proportion of type 2a is relatively low, which is consistent with the gradual decline in the spread of type 2a throughout the country [9]. Mixed infection accounted for 4.5%, suggesting the possibility of repeated exposure or multiple infection. Previous domestic studies have mostly used fluorescent PCR or reverse dot hybridization technology to detect HCV genotypes. This study used the NGS high-throughput system for detection, which has higher accuracy and more reliable type identification, and is superior to traditional typing methods. The above-mentioned HCV genotype distribution characteristics are of practical significance for hepatitis C prevention and control in Yueyang. The high proportion of genotype 1b indicates that existing infections related to previous blood transmission remain an important component; the high prevalence of genotype 6a suggests the existence of active transmission chains in the region, requiring strengthened management of the source of infection and control of transmission routes. Furthermore, clarifying the local HCV genotype distribution helps clinicians directly select targeted antiviral treatment regimens, improving treatment success rates.

HCV RNA viral load directly reflects the degree of viral replication activity and is a core laboratory indicator for judging disease progression and monitoring the efficacy of DAA treatment [12]. The results of this study showed that the median viral load of HCV 1b, 6a, 3a and mixed HCV infections were all at a high level, and there was no statistically significant difference between the groups (P=0.054 > 0.05).

Multiple domestic and foreign studies have confirmed that there is no clear correlation between HCV genotype and viral load [13, 14]. The level of viral replication is mainly affected by the host's immune status, duration of infection, and complications, rather than the genotype itself. In this study, 66.2% of patients had high viral load, suggesting that the overall viral replication of HCV infected individuals in this region is relatively active, but this characteristic is not significantly related to genotype.

Serum ALT, AST, ALP, GGT, TBIL, DBIL, TBA, and other liver function indicators can directly reflect the degree of hepatocellular damage and the excretory and metabolic function of the hepatobiliary system. This study showed no statistically significant differences in ALT, AST, ALP, GGT, TBIL, and TBA among different HCV genotypes, except for DBIL (H=12.636, P=0.013). However, subsequent multiple comparisons did not reveal clear differences between genotypes, suggesting that this result may be due to fluctuations in group distribution and lacks clear clinical interpretability. Multiple clinical observations in Wuhan, Jiangsu, Qinghai, and other regions in China have confirmed that there is no stable association between HCV genotype and liver function indicators [14, 15]. Elevated transaminases mainly reflect host immune- mediated liver inflammation rather than the direct pathogenicity of the viral genotype itself. Although some reports suggest that type 3 liver injury is more significant, these are often due to selection bias or confounding factors such as alcohol consumption and fatty liver, and large-scale unbiased cohort studies have mostly shown negative results [16, 17]. Our results further support that the degree of liver function abnormalities in hepatitis C patients mainly depends on host-related factors rather than HCV genotype differences.

Liver fibrosis is the core pathological link in the progression of chronic hepatitis C to cirrhosis. Serum HA, CIV, PIIIP, and LN liver fibrosis indicators can reflect the dynamics of extracellular matrix synthesis and degradation, and are classic and commonly used indicators for non-invasive clinical assessment of liver fibrosis [18]. This study showed that there were no statistically significant differences in the four liver fibrosis indicators among different HCV genotypes (P>0.05), which is consistent with the consensus of experts on non-invasive laboratory diagnosis of liver fibrosis and the conclusions of many clinical studies at home and abroad [14, 19]. The progression of liver fibrosis is the result of the combined effects of long-term chronic injury, inflammation repair and host metabolism. It is affected by multiple factors such as age, unhealthy drinking, obesity, and diabetes, and has no independent strong correlation with HCV genotype [20]. Viral load and genotype are not independent predictors of liver fibrosis progression, and fluctuations in serological markers are difficult to reflect the differences between genotypes [21, 22]. These results suggest that when assessing liver fibrosis in patients with chronic hepatitis C, a comprehensive consideration of liver fibrosis risk factors should be taken into account, and judgment should not be based solely on HCV genotype.

The accuracy of detection technology directly affects genotyping and treatment selection. This study used the FASTASeq 300 Dx gene sequencer, based on sequencing-by-synthesis technology, which boasts high throughput and high sensitivity. Results showed that the sequencer achieved a 100.00% positive concordance rate, negative concordance rate, and overall concordance rate, with a Kappa coefficient of 1.0000, completely consistent with traditional PCR-fluorescent probe methods. Furthermore, the concordance rate for each subtype was 100.00%, indicating extremely high accuracy in HCV genotyping. In addition, the sequencing throughput, Q30 base ratio, and other data quality indicators met quality control requirements, and the target region coverage reached 99.98%, ensuring the reliability of the genotyping results. Regarding safety, no adverse events or instrument defects occurred during the experiment. The equipment stability, safety, and ease of use were all rated at 100.0%, demonstrating the sequencer's good safety and practicality in clinical applications and its suitability for routine HCV genotyping. Compared with traditional Sanger sequencing, next-generation sequencing technology can detect multiple genotypes at the same time without the need to design specific primers for different subtypes, which greatly improves the detection efficiency and is especially suitable for large-scale screening in areas with multiple subtypes [23].

This study also has certain limitations. As it is a single-center study, it only included patients treated at our hospital, which introduces selection bias and limits representativeness. Due to geographical factors, the sample size for HCV 2a and mixed subtypes is limited, resulting in limited statistical power. Confounding factors such as prior antiviral treatment, hepatitis B co-infection, alcohol consumption, and metabolic diseases were not adjusted for; only univariate analysis was performed, without multivariate regression, and no follow-up analysis was conducted on patients' clinical outcomes and treatment responses. Future research should expand the sample size to include patients from different levels of medical institutions in Yueyang, and incorporate more laboratory serological indicators and confounding factors for multivariate analysis. Long-term follow-up of treatment responses and disease progression in patients with different genotypes is necessary to provide more reliable scientific evidence for further in-depth research into the immunopathological mechanisms of HCV infection and for precise prevention and control of hepatitis C and individualized diagnosis and treatment of HCV infection in Yueyang.

Conclusion

In Yueyang District, the predominant HCV genotype was 1b, followed by 6a, 3a, mixed, and 2a. There were no statistically significant differences in viral load, sex, age, ALT, AST, ALP, GGT, TBIL, TBA, HA, CIV, PIIIP, and LN among different genotypes, but a statistically significant difference was observed in DBIL. The FASTA Seq 300 Dx gene sequencer demonstrated extremely high accuracy and safety in HCV

genotyping, providing reliable genotypic evidence for individualized clinical treatment of hepatitis C.

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