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Profiling the real-world management status of high-risk human papillomavirus infection: A protocol to establish a prospective cohort of high-risk human papillomavirus-infected women in Lueyang County, China

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Abstract

Introduction: Persistent infection with high-risk human papillomavirus (HPV) is the main cause of cervical cancer. Thus, the effective treatment against HPV represents an opportunity to reduce the incidence of cervical cancer. Although various treatments are effective in treating HPV infection, they still provide limited benefit in reducing the rate of cervical cancer due to the lack of implementation of a standardised protocol in many low- and middle-income areas. This proposed cohort study aims to describe the status quo of treatment, attributions of the treatment decision-making process, and potential factors influencing treatment decisions.

Methods and analysis: This is a prospective longitudinal study in Lueyang County, China, one of the areas with the highest cervical cancer incidence rates and lowest mean incomes in China. We will enroll HPV-infected women diagnosed via a county-wide HPV infection and cervical cancer screening programme. The study procedures describe the treatment patterns and explore the potential influencing factors in treatment decision-making through questionnaires and laboratory examinations. All participants will be evaluated at baseline and at six, 12, and 24 months. The primary outcome is the treatment pattern, the type and duration of which will be described later. The secondary outcomes include guideline compliance and changes in the HPV infection status. The HPV impact profile, intimate relationship satisfaction, and costs within different management groups are also described and compared.

Ethics and dissemination: This study was reviewed, and all of the relevant approvals were obtained from the Ethics Committee of the Maternity Service Centre of Lveyang

Maternal and Child Health Care Hospital (2021-001). The findings from this study will be disseminated through peer-reviewed publications, conference presentations, and academic workshops.

Trial registration number: ChiCTR2100053757.

Strengths and limitations of this study

- To our knowledge, this is the first study to consider real-world data regarding the management patterns after diagnosing high-risk HPV infection among women in China.
- We include different potential factors, revealing their internal influence mechanism on treatment decision-making options.
- Implementing this protocol will identify the gap between research and practice and determine why some patients did not receive the recommended therapies.
- It remains a challenge to sustain a high participation rate in a prospective cohort study; working outside the hometown and insufficient knowledge and awareness about the disease in Lueyang County would lead to the loss of participant follow-up.
- This is a community-based observational study of prospectively collected data from Lueyang County, China, so the study design increases the risk for the potential limitations of the presence of selection bias and a decreased generalisability of the findings to other populations.

INTRODUCTION

Cervical cancer ranks fourth among malignant tumours in females worldwide,[1] presenting a serious threat to women. Cervical cancer is a major public health concern.[2] Globally, there was an estimated incidence rate of 15.3 per 100,000 and a mortality rate of 7 per 100,000 for cervical cancer in 2018.[3] In China, the incidence rate is 10.88 per 100,000, and the mortality rate is 3.17 per 100,000.[4] Cervical cancer arises from four processes: human papillomavirus (HPV) infection, persistent HPV infection, multistage squamous intraepithelial lesions, and invasion through the basement membrane.[5] The World Health Organisation (WHO) is developing a global strategy, known as the 90–70–90 triple-intervention strategy, for eliminating cervical cancer as a public health problem by 2030.[6]

Currently, great progress has been made in the prevention of cervical cancer (e.g. HPV vaccination and cervical screening initiatives) and the development of several therapies for cervical cancer. For women who are already HPV-infected, the WHO guidelines recommend safe and effective treatment options, but these do not reach the women who need these services the most.[7-8] Several factors contribute to this failure in health service delivery, access, and utilisation, including a lack of a link between screening and treatment (compliance with treatment and follow-up), variability in service quality, and insufficient continuing education for service providers.[9-10] Thus, the implementation of the standardised management of high-risk HPV infection or HPV-caused precancerous lesions to reduce the prevalence of cervical cancer urgently needs

to be implemented.

Treatments for HPV infection and HPV-induced precancer lesions include conservative observation, ablative treatment (cryotherapy and thermal ablation), and excisional treatment (excision with a cold knife cone (CKC) and electrosurgical excision (LLETZ or LEEP)).[7, 11] Several studies have shown that patients with HPV infection or benign lesions can undergo tissue destruction by thermal (hot or cold), electrical, or chemical means, the success rates for which vary widely, and the variability of the inclusion criteria for each study hampers establishing a standardised management protocol.[8,12] The quality of evidence for all outcomes is low to very low, and the level of heterogeneity is high in all pooled analyses. For instance, although all currently used ablative techniques are effective in reducing cancer risk, there is a lack of data on the long term effectiveness of therapies, reasons for treatment failure, and cost-effectiveness of therapies.

For these reasons, there remains a lack of sufficient real-world evidence to support clinicians and patients in providing optimal treatment decision-making recommendations. Various factors can shape treatment decisions, including decision-maker characteristics, decision-specific criteria, and contextual factors.[13-14] The first are the decision-maker characteristics, including those for both the providers and patients, such as capabilities (i.e. knowledge of HPV), emotions (i.e. worry, anxiety, or stigma from HPV infection), and degree of expertise (i.e. benefits and limitations of

each treatment).[15-16] Second, decision-specific criteria involve classical clinical criteria, such as age, HPV type, duration of infection, sex, or expected treatment complications (i.e. adhesions or bleeding).[17] Contextual factors include the patient's socioeconomic status, healthcare system, treatment costs, and perceived support (i.e. intimate relationships).[18] Currently, it is not yet clear which patient factors affect treatment decision-making after testing positive for HPV.

The All-China Women's Federation and the Ministry of Health launched the 'Two Cancers' (cervical cancer and breast cancer) screening programme in July 2009, which implemented a free cervical cancer screening programme for rural women aged 35–64 years. This programme involved publicity, health education, and examinations.[19] In recent years, with the popularisation of cervical cancer screening, the incidence of cervical cancer in some areas of China has been effectively controlled. Lueyang County is a low-income area in China with high morbidity and mortality rates for cervical cancer. The incidence of cervical cancer has shown a decreasing trend in recent years; however, the morbidity and mortality of the disease remain high. The high prevalence rate of HPV infection (18.5%) in this region was higher than the national overall prevalence rate of HPV infection (15.54%).[20]

Thus, we propose to establish a prospective cohort for women infected with high-risk HPV in Lueyang, Shaanxi, aiming to (1) profile the treatment patterns for high-risk HPV infection in the real-world setting, (2) identify the characteristics that impact

treatment decision-making for high-risk HPV infection, (3) demonstrate compliance with WHO guidelines for high-risk HPV management, and (4) evaluate the long term effects of different treatment approaches. The results will provide real-world evidence to support optimal decision-making in the treatment of high-risk HPV infection and, ultimately, strive to achieve the goal of '90% of women with precancer treated', which was proposed by the WHO in its Cervical Cancer Elimination Initiative.

METHODS AND ANALYSIS

Study design and setting

This prospective cohort study will take place in Lueyang County, one of the economically underdeveloped regions in Shaanxi Province, China. Lueyang County has a high prevalence of HPV infection. All women between 18-65 years old in the county are invited to participant a local government-supported cervical screening programme. The cervical screening services are managed by gynecologists at the Maternity Service Centre of Lueyang Maternal and Child Health Care Hospital. The study was approved by the Maternity Service Centre of Lueyang Maternal and Child Health Care Hospital, and it was started on 4 November 2021 and is planned to be completed by 31 November 2023.

During the screening phase, women aged 18–65 years are recruited through a cervical screening service by gynaecologists and nurses. Basic information, HPV testing, and

inclusion evaluations will be performed. The women diagnosed with high-risk HPV infection during the screening phase will be invited to participate in the study. Written informed consent will be obtained from the women regarding their participation in this prospective cohort study (including the procedures, risks, and options for dropping out of the study). Medical staff with adequate training will clearly explain the study protocol and objectives to the participants. After providing consent, each patient must sign an informed consent form. Subsequently, a participant identification (PID) number will be assigned to facilitate the study, and the other examinations will be performed. In the allocation phase, according to the outcomes of examinations and treatment decision-making, all patients will be divided into conservative observation, ablative treatment, and excisional treatment groups. Figure 1 shows the recruitment process that will be used.

Eligibility criteria

The inclusion criteria are as follows: (1) women aged 18–65 years, who had lived for 5 years in Lueyang County, (2) a diagnosis of high-risk HPV infection in the screening phase, (3) non-pregnancy, (4) history of sexual activity, (5) no history of severe immunodeficiency disease, and (6) able to understand the questions asked by the investigator.

The exclusion criteria are as follows: (1) refusal to participate in this study, (2) a diagnosis of cervical cancer, (3) other malignant tumours or serious illness, and (4) a

diagnosis of mental illness or impaired consciousness.

Definition of outcomes

This study will assess the treatment patterns, compliance with guidelines, and HPV status, including (1) the number of patients who underwent conservative observation, that who underwent ablative treatment, and that who underwent excisional treatment; (2) the duration of each therapy regimen and the time to treatment initiation; (3) the number of patients who received other specific treatments, including the duration of those other specific treatments; and (4) the number of patients who received guideline-recommended treatment. (5) The HPV clearance, persistence, and recurrence will be assessed via cytological and histological evaluations.

Patients in the conservative observation group will undergo routine follow-up.[21] The patients will be observed without any additional treatment. Ablative treatments include cryotherapy and thermal ablation.[6] Abnormal tissue is destroyed by heating with thermal coagulation or freezing with cryotherapy. Excisional treatment involves the surgical removal of abnormal tissue with LLETZ or CKC.[6] The duration of treatment, the duration of each therapy regimen, and time to the initiation of treatment (the start of the initial regimen was the date of the first treatment and all treatments initiated within 90 days of that date).[6, 22] Compliance with guidelines refers to the proportion of patients who achieve the recommended treatment, as judged by experienced gynaecological specialists.[23] HPV clearance was defined as a participant testing

negative for HPV at two consecutive visits after testing positive.[24] Persistent disease was defined as the persistent same-type HR-HPV infection and persistent different-type HR-HPV infection positive at baseline and follow-up.[25] Recurrent disease was defined as the presence of HR-HPV infection at a subsequent follow-up visit in a patient who had at least one negative HPV test after treatment.[26]

Sampling strategy

All women meeting the inclusion criteria will be recruited for the study and followed up for two years. Management patterns describe using proportion and 95% two-sided exact confidence intervals (95% CI). With an estimation that, among the total 40,000 women aged 18–65 years in Lueyang County, 18.5% will be diagnosed with high-risk HPV infection, a total of 7500 women will be eligible for the study. Considering a 20% attrition rate, we will end up with 6000 women in the cohort. Since the proportion of patients' treatment choice is unknown, varying proportions produce different actual widths as follows (Table 1), the CI width was determined by PASS (version 15) with the following parameter settings: CI formula, exact (Clopper-Pearson); confidence level (1-alpha), 0.95; proportion, 0.1 to 0.9 by 0.1.

Table 1. Numeric Results for Two-Sided CIs for One Proportion

n \ *p*	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
6000	0.015	0.020	0.023	0.025	0.025	0.025	0.023	0.020	0.015

Notes: *p*, proportion of patients' treatment choices. n, sample size.

Data collection

The data collection protocol will be performed according to the list outlined in Table 2. All data will be obtained by physicians at the hospital. The participants underwent a comprehensive physical examination and completed a questionnaire through face-to-face interviews. All biochemical test results were obtained from the hospital records. Follow-up visits will be conducted at six, 12, and 24 months.

Table 2. Data collection schedule

Procedure	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
	Screening	Baseline	Month six	Month 12	Month 24
Eligibility criteria	×				
Research participants consent	×				
Individual Information					
Demographic variables	×				
Menstrual history	×				
Marital history	×				
Personal hygiene behaviour	×				
Gynaecological examinations		×			
HPV knowledge	×				
HPV infection	×				

Regular examination	×				
HPV vaccination	×				
Physicians' knowledge regarding treatment		×			
Partner information	×				
Outcomes					
Primary outcome					
Treatment patterns		×	×	×	×
Secondary outcomes					
HPV testing	×		×	×	×
TCT		○	○	○	○
Colposcopy		○	○	○	○
Pathological examination		○	○	○	○
Other assessments					
Intimate relationship satisfaction	×		×	×	×
HIP		×	×	×	×
Costs			×	×	×

Notes: HPV, human papillomavirus. TCT, Thin-prep liquid-based cytology test. HIP, the HPV impact profile. ○, if applicable.

Measures

Baseline

The baseline data includes the individual information, characteristics, and laboratory data. Individual data were collected through a health interview survey and medical records. Demographic variables, such as age, education level, occupation, annual income, ethnicity, and religion, were used in the analysis, as were the data concerning the smoking status, alcohol consumption, total number of sexual partners, frequency of sexual life, forms of contraception, and hygiene habits (i.e. frequency and manner of bathing). Other basic information, such as menstrual history (i.e. time to menarche/menopause), marital history, HPV knowledge (HPV infection, regular examination, and HPV vaccination), physicians' knowledge regarding treatment (benefits and limitations of all treatments), partner information, and gynaecological examinations (i.e. lesions of the vulva, vagina, vaginal secretions, cervix, cervical polyps, uterus, uterine accessories, vaginal cleanliness, and sexually transmitted disease type), were also assessed. All eligible patients underwent gynaecological examinations.

Outcomes

Laboratory data, clinical characteristics, and use of therapies were assessed in the hospital, and all laboratory examinations were performed during the non-menstrual period. All outcomes were collected by gynaecological outpatient doctors, and the diagnoses were made by a specialised gynaecologic pathologist. Treatment patterns, as the primary outcome, will be collected by receiving the available data on the history of therapies from all eligible patients. Secondary outcomes include the clinical

characteristics (HPV status, cytology, colposcopy, and biopsy results) and other assessments (HPV impact profile, intimate relationship satisfaction, and costs). The specific examination procedures were as follows (Figure 2):

(1) HR-HPV testing. The HR-HPV subtypes were tested using the 21 HPV GenoArray Diagnostic Kit (Yaneng Biosciences, Shenzhen, China) from the Tianbo Biomedical Laboratory (Xian, China). This included testing on 13 high-risk subtypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68).

(2) Thin-prep liquid-based cytology test (TCT). Exfoliated cervical cells from women attending the gynaecological outpatient clinic were collected using a specialised cervical brush by a clinician. The cervical cells were detected using TCT, and the results of cytological pathology were diagnosed by senior physicians according to the Bethesda System of cervical cytology.

(3) Standard colposcopic assessment will be performed when a cytological test is abnormal at the threshold of atypical squamous cells of an undetermined significance (or borderline dyskaryosis) or when the HPV 16/18 test result is positive. The colposcopic findings will be reported according to ASCCP terminology for colposcopic practice.

(4) For the pathological examination of the women who undergoing colposcopy, a biopsy will be performed only in cases with abnormal cervical findings, and if the colposcopy is unsatisfactory, a cervical curettage sample will be obtained.

Other assessments

The HPV impact profile (HIP), a self-reported scale, is designed to represent the full spectrum of potential HPV-related impacts. It consists of 29 items measuring worries and concerns, emotional impact, sexual impact, self-image, partner issues and transmission, interactions with doctors, and control/life impact.[28] The HIP item scales were linearly transformed to a scale of 0–100, and each item was a 0–10 point discretised analogue scale. The Mandarin Chinese version of the HIP questionnaire was generated through a standardised process and has been previously used in Taiwan.[29]

An intimate relationship satisfaction questionnaire, a self-made satisfaction questionnaire, is used employed to estimate the satisfaction of patients with HPV infection. It contains two self-reported questions related to partner and sexual satisfaction. The scoring for each item ranges from very dissatisfied (0) to very satisfied (10).

Cost estimates will be calculated using medical information for direct and indirect costs.[30] related to the cervical screening, diagnosis, and treatment of HPV and cervical lesions. The direct costs included patients' medication, health care, and other resources (such as time in seeking/receiving care and post-treatment recovery time). The costs of medication and health service utilisation will be calculated from the medical records using market prices. The indirect cost estimates of economic losses due to spending time on screening, examinations, and treatment are based on hourly wages per capita.

Quality control

The investigators received training on the standard operating procedure before patient recruitment was performed. A standardised operation process manual and operation video were created and distributed to all of the research assistants. Group training was organised once, while individual training was carried out one-on-one. After training was performed, all research assistants were required to pass a test of practical operation to begin their official work. There will be a question-and-answer session to solve operation problems after approximately ten patients are enrolled. In addition, the research assistants will provide feedback on a daily basis for patients who had submitted problems within the working group.

Data management and analysis

All participants will be allocated a PID code at enrolment, which will be used in the samples and documents over the 24-month study period. All data will be collected and managed using an electronic data management platform protected by the firewall of Chongqing Medical University. The data on the platform will be accessible only by authorised researchers using private accounts and passwords. Any change will be automatically recorded in the platform log and saved as a separate file for data monitoring purposes. For the data export process, the de-identification of patient health information will be conducted following the HIPAA rule. The data will be verified by double-checking for erroneous or missing values, and the data analysis will be

performed using SAS version 9.1.3 (SAS Institute, Cary, NC, USA).

The demographic and clinical characteristics of the participants will be summarised using the mean and standard deviation for continuous variables. For categorical variables, the proportion (%) will be reported. Significant associations in the contingency tables (cross-tabulations) will be assessed using standard Pearson's χ^2 test. Analysis of variance will be used to compare differences in the continuous variables among the three groups. The patient demographics, clinical characteristics, treatment therapies (to identify the most common treatments and durations), and guideline adherence will be descriptively reported. In addition, we may apply growth mixture modelling to observe whether subsets of individuals follow distinct trajectories over time.

Management patterns will be described as the proportion and 95% exact CI (95% CI). For this method, p will be the population proportion, and r represents the number of successes from a sample of size n. Let $p\hat{}$ = r /n. Exact test (Clopper-Pearson) using a mathematical relationship.[31] between the F distribution and the cumulative binomial distribution, and the lower and upper confidence limits of a 100(1-α) % exact confidence interval for the true proportion p are given by

$$\left[\frac{r}{r+(n-r+1)F_{1-\alpha/2;2(n-r+1),2r}}, \frac{(r+1)F_{1-\alpha/2;2(r+1),2(n-r)}}{(n-r)+(r+1)F_{1-\alpha/2;2(r+1),2(n-r)}}\right]$$

Multivariate logistic regression models will be used to estimate the potential factors

influencing the treatment choices, including the decision-maker characteristics (patient and physician), specific criteria, and contextual factors. Pearson's χ^2 statistics will be used to compare the treatment differences in clearance, recurrence, and persistence rates among the groups. The Kaplan–Meier method will be used to construct the cumulative clearance rate of HPV from the date of the first HPV diagnosis to the date of HPV clearance in each treatment group. A proportional hazards model will be fitted to evaluate the effects of treatment options and other predictors on the overall persistence and recurrence of HPV, and possible interaction terms of the main effects will be tested by comparing a reduced model with the full model. Missing data will be identified and reported as percentages. We will also include several other key parameters (discount rate, annual number of screened women, screening positivity rate, biopsy rate, and programmatic costs) in the one-way sensitivity analysis.

Patient and public involvement

The patients and the public were not involved in the development of the research questions or the design and analysis of the study. The extent of patient involvement in the study included answering the survey questionnaires at baseline and each follow-up. The results will be disseminated to the applicants in the form of a published article, which will be made available upon request.

Ethics and dissemination

Ethical approval for the study was obtained from the Biomedical Research Ethics

Committee of the Maternity Service Centre of Lueyang Maternal and Child Health Care Hospital. All participants fulfilling the inclusion criteria will commence as full ethics approval is received from the Biomedical Research Ethics Committee. No other independent ethics reviews were conducted. The results of this study will be disseminated in peer-reviewed journals and conferences. We will provide clinicians with feedback following the peer-review process to further strategies optimal treatment decision-making.

DISCUSSION

Women are currently concerned about cervical cancer, owing to its increasing incidence and high mortality in low- and middle-income areas. Despite the availability of safe and effective methods for treating premalignant conditions, real-world evidence of treatment effects in low- and middle-income areas remains limited. To our knowledge, there are no real-world data regarding patients' treatment patterns after being diagnosed with high-risk HPV infection among women in these regions, and the characteristics that affect their decision-making process are rarely reported. In this study, we focus on the characteristics of clinical outcomes in different treatment groups and the relationship between decision-making and the individual's characteristics in terms of individual behaviours, psychological trajectories, and economic burden. Hence, this study is able to evaluate how these factors influence the patient's decision-making process. It will also allow us to study the research-to-practice of discordance in greater detail with the ultimate goal of uncovering the underlying causes of discrepancies

between these formal recommendations and current practices.

Decision-making has acquired crucial importance in disease management over the last 20 years since the introduction of the patient-centred principle. A variety of factors can shape treatment decisions, which include decision-maker characteristics, decision-specific criteria, and contextual factors.[13] Previous studies have stated that there are a variety of factors that influence treatment decisions in oncological diseases and other diseases, such as capabilities, emotions, age, expected treatment risk, the healthcare system, and treatment costs.[18] Little is known about the predictive factors for decision-making in women undergoing high-risk HPV testing. This study intends to include different influencing factors to reveal their internal influence mechanism on decision-making options. We expect that the results can inform clinical practice with the provision of predictive algorithms that provide physicians with a clear profile of the patient at present and their probable trajectory in the long term.

This study has several strengths. First, it provides a comprehensive understanding of the therapeutic status quo in high-risk HPV infection and the possible underlying mechanisms involved, including the treatment patterns and disease outcomes under different treatment decisions. Second, this prospective cohort study has a long follow-up period. Therefore, this study may assist in determining causal associations between the predicted determinants of treatment decision-making and can be used to obtain trajectories of how patients' conditions influence decision-making over time.[32]

Describing and analysing time-invariant and time-variant factors that predict improvement or deterioration in these trajectories will help identify potentially modifiable risk factors for future interventions, as well as patients at risk for poor outcomes. Third, this study identifies the gap between research and practice and why some patients did not receive recommended therapies. It provides an effective mechanism to ensure high compliance to treatment and also provides an opportunity to reduce cervical cancer incidence and mortality in low- and middle-income areas.

High participation rates at follow-up are critical for the validation of cohort studies. A challenge we anticipate is the loss of follow-up, which is generally a common failure in longitudinal studies. The six-month, 12-month, and 24-month follow-up appointments may remain difficult to sustain for the following reasons: (1) some adults in rural areas leave their hometowns to work in cities, which means some data could not be collected promptly; (2) insufficient attention paid by patients, which might be related to the insufficient knowledge and awareness about the disease reported in China.[33] Maintaining follow-up visits is a challenge we anticipate. A research assistant will communicate regularly with the recruited participants through WeChat, the most popular messaging and calling app, allowing one-to-one communication. The research assistant will confirm the appointment dates and send out reminders the week prior. During the study, participants diagnosed with cervical cancer will be referred to anticancer treatments but will continue follow-up assessments, noting the change in their disease status.

Overall, we can explore treatment patterns and their association with individual characteristics and unravel the changing trajectory of potential factors that affect decision-making. Most importantly, new real-world insights will be provided regarding the role of tailored disease management in the prevention and treatment of high-risk HPV infections. These results imply that standardised management could help to reduce the prevalence of cervical cancer in the future. These data may help inform future clinical trial designs, highlight the need for better adherence to treatment guidelines, and inform clinical decision-making.

Authors' Contributions:

QS, SY, RZ, and WX contributed to the study design. LB, DH, RZ, SY, YN and RX performed the study. SY and LBdrafted the initial manuscript. QS and SY revised the draft. All authors have read and approved the final manuscript.

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Competing Interests Statement:

None declared.

References

[1] Sung H, Ferlay J, Siegel RL, *et al*. Global Cancer Statistics 2020: GLOBOCAN

Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021;71:209-249.

[2] Cohen PA, Jhingran A, Oaknin A, *et al*. Cervical cancer. *Lancet* 2019; 393:169-182.

[3] Bray F, Ferlay J, Soerjomataram I, *et al*. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68:394–424.

[4] Jie H. China cancer registration annual report 2018[M], vol. 61. Beijing: People's Publishing House; 2019. p. 63.

[5] Schiffman M, Castle PE, Jeronimo J, *et al*. *Lancet* 2007; 370:890-907.

[6] WHO. Draft global strategy towards the elimination of cervical cancer as a public health problem. https://www.who.int/docs/default-source/documents/cervical-cancer-elimination-draft-strategy.pdf?sfvrsn=380979d6_4 (accessed Oct 9, 2019).

[7] WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention, second edition [Internet]. Geneva: World Health Organization; 2021.

[8] Basu P, Taghavi K, Hu SY, *et al*. Management of cervical premalignant lesions. *Current problems in cancer* 2018;42:129-136.

[9] Rossman AH, Reid HW, Pieters MM, *et al*. Digital Health Strategies for Cervical Cancer Control in Low- and Middle-Income Countries: Systematic Review of Current Implementations and Gaps in Research. *J Med Internet Res* 2021;23:e23350.

[10] Johnson LG, Armstrong A, Joyce CM, *et al*. Implementation strategies to improve

cervical cancer prevention in sub-Saharan Africa: a systematic review. *Implementation Science* 2018;13:1-18.

[11] Hu Z, Ding WC, Zhu D, *et al*. TALEN-mediated targeting of HPV oncogenes ameliorates HPV-related cervical malignancy. *J Clin Invest* 2014;125:425–36.

[12] Castle PE, Murokora D, Perez C, *et al*. Treatment of cervical intraepithelial lesions. *International Journal of Gynecology & Obstetrics* 2017;138:20–25.

[13] Papadakis VM, Lioukas S, Chambers D. Strategic decision-making processes: the role of management and context. *Strategic management journal* 1998;19:115–147.

[14] Elbanna S. The influence of decision, environmental and firm characteristics on the rationality of strategic decision-making. *Journal of Management Studies* 2007;44:4.

[15] Mazzocco K, Masiero M, Carriero MC, *et al*. The role of emotions in cancer patients' decision-making. *Ecancermedicalscience* 2019;13:914.

[16] Nash K, Leota J, Tran A. Neural processes in antecedent anxiety modulate risk-taking behavior. *Scientific reports* 2021;11:2637.

[17] Junius-Walker U, Wiese B, Klaaßen-Mielke R, *et al*. Older patients' perceived burdens of their health problems: a cross-sectional analysis in 74 German general practices. *Patient preference and adherence* 2015;9:811–820.

[18] Glatzer M, Panje CM, Sirén C, *et al*. Decision Making Criteria in Oncology. *Oncology* 2018;98:370–378.

[19] Wang B, He M, Chao A, *et al*. Cervical cancer screening among adult women in China, 2010. *Oncologist* 2015;20:627–634.

[20] Zhu B, Liu Y, Zuo T, *et al*. The prevalence, trends, and geographical distribution

of human papillomavirus infection in China: The pooled analysis of 1.7 million women. *Cancer Medicine* 2019;8:5373–5385.

[21] Namikawa K, Yoshio T, Yoshimizu S, *et al*. Clinical outcomes of endoscopic resection of preoperatively diagnosed non-circumferential T1a-muscularis mucosae or T1b-submucosa 1 esophageal squamous cell carcinoma. *Scientific reports* 2021;11: 6554.

[22] Kabadi SM, Goyal RK, Nagar SP, *et al*. Treatment patterns, adverse events, and economic burden in a privately insured population of patients with chronic lymphocytic leukemia in the United States. *Cancer medicine* 2019;8:3803–3810.

[23] Twomey R, Matthews TW, Nakoneshny SC, *et al*. From Pathways to Practice: Impact of Implementing Mobilization Recommendations in Head and Neck Cancer Surgery with Free Flap Reconstruction. *Cancers* 2021;13:2890.

[24] Giuliano AR, Lee JH, Fulp W, *et al*. Incidence and clearance of genital human papillomavirus infection in men (HIM): a cohort study. *Lancet (London, England)* 2011;377:932–940.

[25] Jia H, Ding L, Han Y, *et al*. Genotype-specific Distribution and Change of High-risk Human Papillomavirus Infection and the Association with Cervical Progression Risk in Women with Normal Pathology and Abnormal Cytology in a Population-based Cohort Study in China. *Journal of Cancer* 2021;12:4379–4388.

[26] Follen Mitchell M. A randomized clinical trial of cryotherapy, laser vaporization, and loop electrosurgical excision for treatment of squamous intraepithelial lesions of the cervix. *Obstetrics & Gynecology* 1998;92:737–744.

[27] Specialized Committee of Human Papilloma Virus Infection Diseases of Cross-Strait Association of Precision Medicine of Fujian Province. Expert consensus on HPV infection and HPV-associated diseases 2017. *J Med Postgra* 2017;12:1238-1241.

[28] Mast TC, Zhu X, Demuro-Mercon C, *et al*. Development and psychometric properties of the HPV Impact Profile (HIP) to assess the psychosocial burden of HPV. *Current medical research and opinion* 2009;25:2609-2619.

[29] Wang KL, Jeng CJ, Yang YC, *et al*. The psychological impact of illness among women experiencing human papillomavirus-related illness or screening interventions. *J Psychosom Obstet Gynaecol* 2010;31:16–23.

[30] Ferretti C, Sarti FM, Nitrini R, *et al*. An assessment of direct and indirect costs of dementia in Brazil. *PLoS One* 2018;13:e0193209.

[31] Fleiss JL, Levin B, Paik MC. Statistical Methods for Rates and Proportions. Third Edition. John Wiley & Sons. New York., 2003. p. 25.

[32] Guralnik JM, Kritchevsky SB. Translating research to promote healthy aging: the complementary role of longitudinal studies and clinical trials. *J Am Geriatr Soc* 2010; 58:S337-S342.

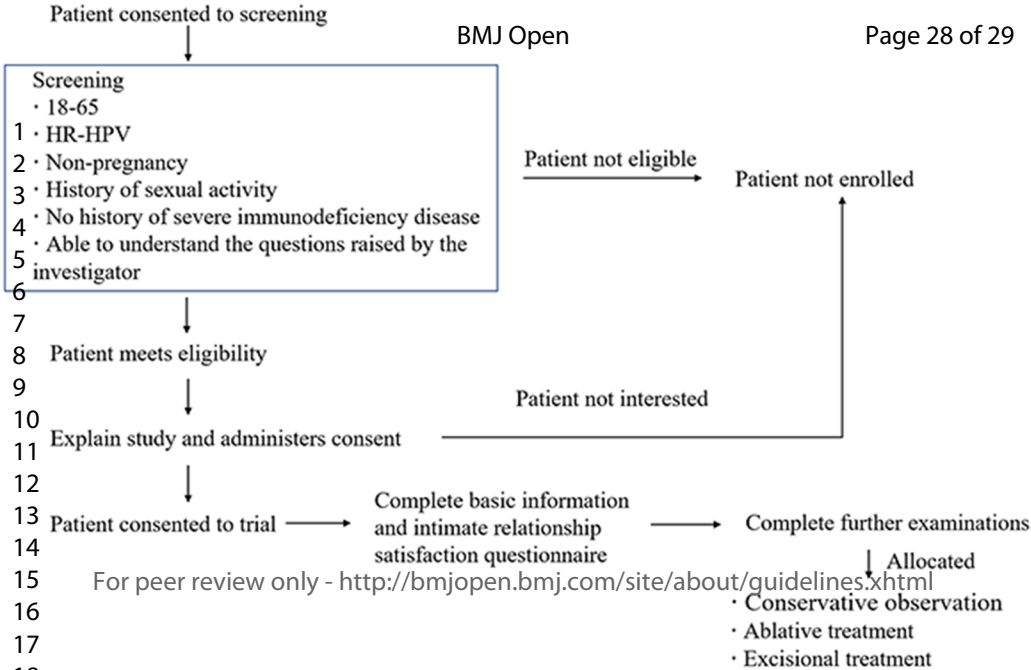
[33] Baloch Z, Yasmeen N, Li Y, *et al*. Knowledge and awareness of cervical cancer, human papillomavirus (HPV), and HPV vaccine among HPV-infected Chinese women. *Medical science monitor: international medical journal of experimental and clinical research* 2017;23:4269.

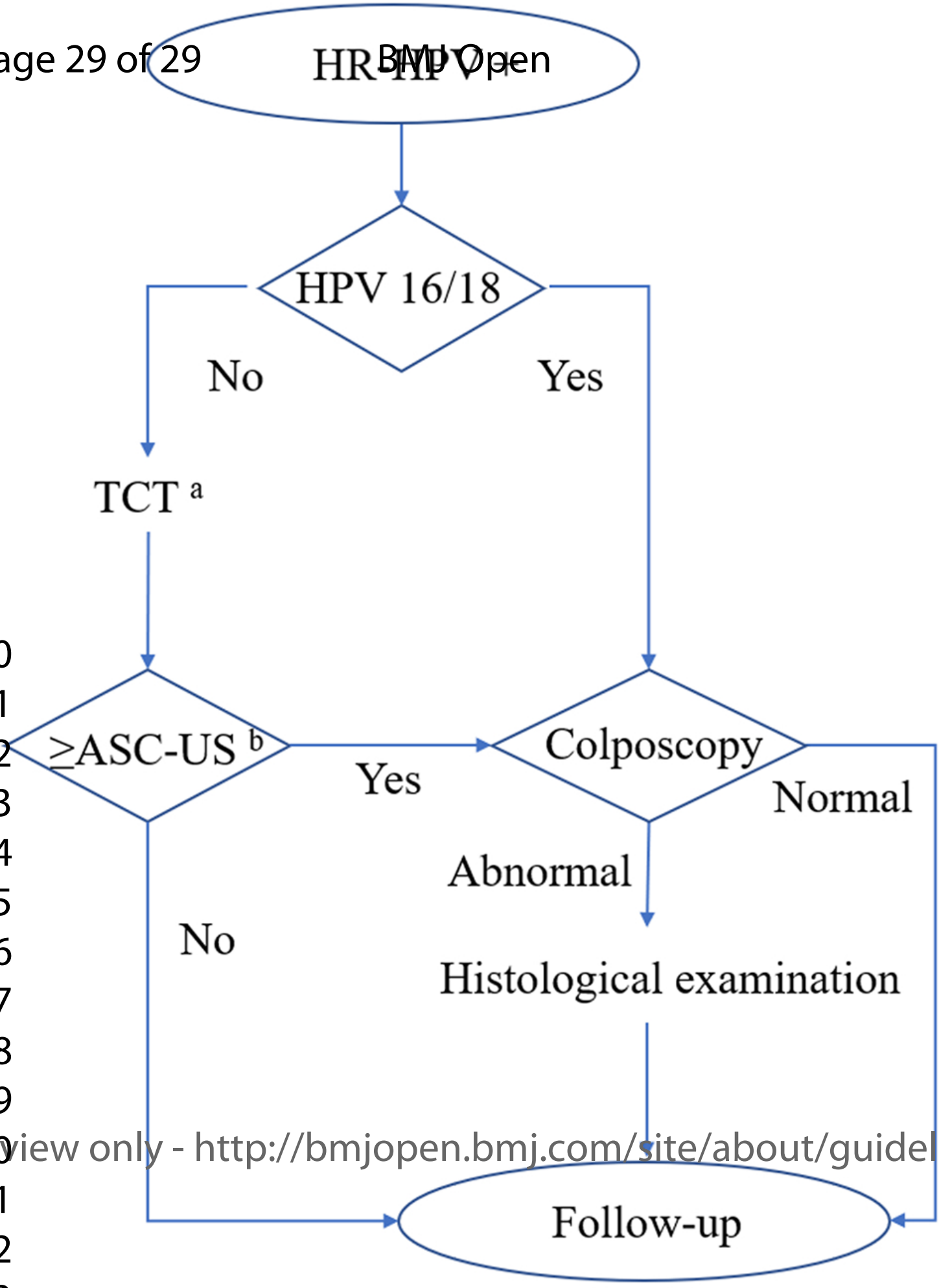
Figure Legends

Figure 1. Workflow for the recruitment procedure.

Figure 2. The specific examination procedures.[27]

Note: [a] TCT, thin-prep liquid-based cytologic test; [b] ≥ASC-US, atypical squamous cells of undetermined significance or above.





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Profiling the real-world management status of high-risk human papillomavirus infection: A protocol to establish a prospective cohort of high-risk human papillomavirus-infected women in Lueyang County, China

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Profiling the real-world management status of high-risk human papillomavirus infection: A protocol to establish a prospective cohort of high-risk human papillomavirus-infected women in Lueyang County, China

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Abstract

Introduction: Persistent infection with high-risk human papillomavirus (hrHPV) is the main cause of cervical cancer. Thus, the effective treatment against HPV represents an opportunity to reduce the incidence of cervical cancer. Although various treatments are effective in treating HPV infection, they still provide limited benefit in reducing the rate of cervical cancer due to the lack of implementation of a standardised protocol in many low- and middle-income areas. This proposed cohort study aims to describe the status quo of treatment, attributions of the treatment decision-making process, and potential factors influencing treatment decisions.

Methods and analysis: This is a mixed method, 5-year prospective longitudinal study in Lueyang County, China, one of the areas with the highest cervical cancer incidence rates and lowest mean income in China. We will enroll hrHPV infection (at least one HPV type in the 13 high-risk subtypes) women diagnosed via a county-wide HPV infection and cervical cancer screening programme. The study procedures describe the treatment patterns and explore the potential influencing factors in treatment decision-making through questionnaires, laboratory examinations, and in-depth interviews. All participants will be evaluated at baseline and at six, 12, 24, 36, 48, and 60 months. The primary outcome is the treatment pattern, the type and duration of which will be described later. The secondary outcomes include guideline compliance and changes in the HPV infection status. The HPV impact profile, intimate relationship satisfaction, and costs within different management groups are also described and compared.

Ethics and dissemination: This study was reviewed, and all of the relevant approvals

were obtained from the Ethics Committee of the Maternity Service Centre of Lueyang Maternal and Child Health Care Hospital (2021-001). The findings from this study will be disseminated through peer-reviewed publications, conference presentations, and academic workshops.

Trial registration number: ChiCTR2100053757.

Strengths and limitations of this study

- To our knowledge, this is the first study to consider real-world data regarding the management patterns after diagnosing high-risk HPV infection among women in China.
- We will use a mixed method to explore different potential factors, revealing their internal influence mechanism on treatment decision-making options.
- Implementing this protocol will identify the gap between research and practice and determine why some patients did not receive the recommended therapies.
- It remains a challenge to sustain a high participation rate in a prospective cohort study; working outside the hometown and insufficient knowledge and awareness about the disease in Lueyang County would lead to the loss of participant follow-up.
- This is a community-based observational study of prospectively collected data from Lueyang County, China, so the study design increases the risk for the potential limitations of the presence of selection bias and a decreased generalisability of the findings to other populations.

INTRODUCTION

Cervical cancer ranks fourth among malignant tumours in females worldwide,[1] presenting a serious threat to women. Cervical cancer is a major public health concern.[2] Globally, there was an estimated incidence rate of 15.3 per 100,000 and a mortality rate of 7 per 100,000 for cervical cancer in 2018.[3] In China, the incidence rate is 10.88 per 100,000, and the mortality rate is 3.17 per 100,000.[4] Cervical cancer arises from four processes: human papillomavirus (HPV) infection, persistent HPV infection, multistage squamous intraepithelial lesions, and invasion through the basement membrane.[5] The World Health Organisation (WHO) is developing a global strategy, known as the 90–70–90 triple-intervention strategy, for eliminating cervical cancer as a public health problem by 2030.[6]

Currently, great progress has been made in the prevention of cervical cancer (e.g. HPV vaccination and cervical screening initiatives) and the development of several therapies for cervical cancer. For women who are already HPV-infected, the WHO guidelines recommend safe and effective treatment options, but these do not reach the women who need these services the most.[7-8] Several factors contribute to this failure in health service delivery, access, and utilisation, including a lack of a link between screening and treatment (compliance with treatment and follow-up), variability in service quality, and insufficient continuing education for service providers.[9-10] Thus, the implementation of the standardised management of hrHPV infection or HPV-caused precancerous lesions to reduce the prevalence of cervical cancer urgently needs to be

implemented.

Treatments for HPV infection and HPV-induced precancer lesions include conservative observation, ablative treatment (cryotherapy and thermal ablation), and excisional treatment (excision with a cold knife cone (CKC) and electrosurgical excision (LLETZ or LEEP)).[7, 11] Several studies have shown that patients with HPV infection or benign lesions can undergo tissue destruction by thermal (hot or cold), electrical, or chemical means, the success rates for which vary widely, and the variability of the inclusion criteria for each study hampers establishing a standardised management protocol.[8,12] The quality of evidence for all outcomes is low to very low, and the level of heterogeneity is high in all pooled analyses. For instance, although all currently used ablative techniques are effective in reducing cancer risk, there is a lack of data on the long term effectiveness of therapies, reasons for treatment failure, and cost-effectiveness of therapies.

For these reasons, there remains a lack of sufficient real-world evidence to support clinicians and patients in providing optimal treatment decision-making recommendations. Various factors can shape treatment decisions, including decision-maker characteristics, decision-specific criteria, and contextual factors.[13-14] The first are the decision-maker characteristics, including those for both the providers and patients, such as capabilities (i.e. knowledge of HPV), emotions (i.e. worry, anxiety, or stigma from HPV infection), and degree of expertise (i.e. benefits and limitations of

each treatment).[15-16] Second, decision-specific criteria involve classical clinical criteria, such as age, HPV type, duration of infection, sex, or expected treatment complications (i.e. adhesions or bleeding).[17] Contextual factors include the patient's socioeconomic status, healthcare system, treatment costs, and perceived support (i.e. intimate relationships).[18] Currently, it is not yet clear which patient factors affect treatment decision-making after testing positive for HPV.

The All-China Women's Federation and the Ministry of Health launched the 'Two Cancers' (cervical cancer and breast cancer) screening programme in July 2009, which implemented a free cervical cancer screening programme for rural women aged 35–64 years. This programme involved publicity, health education, and examinations.[19] In recent years, with the popularisation of cervical cancer screening, the incidence of cervical cancer in some areas of China has been effectively controlled. Lueyang County is a low-income area in China with high morbidity and mortality rates for cervical cancer. The incidence of cervical cancer has shown a decreasing trend in recent years; however, the morbidity and mortality of the disease remain high. The high prevalence rate of HPV infection (18.5%) in this region was higher than the national overall prevalence rate of HPV infection (15.54%).[20] We still do not know why morbidity or mortality is higher, and how to provide services to patients in this county. Furthermore, the standard of care for HPV and cervical lesions provided in China and how it deviates from the WHO recommendations remains unclear.

Thus, we propose to establish a prospective cohort for women infected with high-risk HPV in Lueyang, Shaanxi, aiming to (1) profile the treatment patterns and adherence to guideline-concordant management for hrHPV infection in the real-world setting, (2) identify the characteristics that associated with treatment decision-making for hrHPV infection, (3) explore the reasons for treatment choices, including initial regimen, switch, and treatment termination, and (4) evaluate the long term effects of different treatment approaches. The results will provide real-world evidence to support optimal decision-making in the treatment of hrHPV infection and, ultimately, strive to achieve the goal of '90% of women with precancer treated', which was proposed by the WHO in its Cervical Cancer Elimination Initiative.

METHODS AND ANALYSIS

Study design and setting

This mixed method, prospective cohort study with a 5-year follow-up, will take place in Lueyang County, one of the economically underdeveloped regions in Shaanxi Province, China. Lueyang County has a high prevalence of HPV infection. All women between 18-65 years old in the county are invited to participant a local government-supported cervical screening programme. The cervical screening services are managed by gynaecologists at the Maternity Service Centre of Lueyang Maternal and Child Health Care Hospital. The study was approved by the Maternity Service Centre of Lueyang Maternal and Child Health Care Hospital, and it was started on 4 November

2021 and is planned to be completed by 31 November 2026.

During the screening phase, women aged 18–65 years are recruited through a cervical screening service by gynaecologists and nurses. Basic information, hrHPV testing, and inclusion evaluations will be performed. The women diagnosed with hrHPV infection during the screening phase will be invited to participate in the study. Written informed consent will be obtained from the women regarding their participation in this prospective cohort study (including the procedures, risks, and options for dropping out of the study). Medical staff with adequate training will clearly explain the study protocol and objectives to the participants. After providing consent, each patient must sign an informed consent form. Subsequently, a participant identification (PID) number will be assigned to facilitate the study, and the other examinations will be performed. In the categorized phase, according to the outcomes of examinations and treatment decision-making, all patients will be divided into conservative observation, ablative treatment, and excisional treatment groups. Figure 1 shows the recruitment process that will be used.

Eligibility criteria

The inclusion criteria are as follows: (1) women aged 18–65 years, who had lived for 5 years in Lueyang County, (2) a diagnosis of hrHPV infection (including 13 subtypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68; participants with at least one HPV type in the high-risk group) in the screening phase, (3) non-pregnancy, (4) history of

sexual activity, (5) no history of severe immunodeficiency disease, and (6) able to understand the questions asked by the investigator.

The exclusion criteria are as follows: (1) refusal to participate in this study, (2) a diagnosis of cervical cancer, (3) other malignant tumours or serious illness, and (4) a diagnosis of mental illness or impaired consciousness.

Definition of outcomes

This study will assess the treatment patterns, compliance with guidelines, and HPV status. (For detailed information, see Supplementary Material Table S1.) [21-24] Patients in the conservative observation group will undergo routine follow-up. [25] The patients will be observed without any additional treatment. Ablative treatments include cryotherapy and thermal ablation.[6] Abnormal tissue is destroyed by heating with thermal coagulation or freezing with cryotherapy. Excisional treatment involves the surgical removal of abnormal tissue with LLETZ or CKC.[6] Switching was defined as a change to a different treatment before completing the assigned course of treatment. The switch could be to any treatment (observation, ablative, or excisional treatment). The time-to-switch was defined as the period from the date of the first treatment regimen to the date of switch to another treatment regimen during the study period.

Sampling strategy

All women meeting the inclusion criteria will be recruited for the study and followed-

up for five years. Management patterns describe using proportion and 95% two-sided exact confidence intervals (95% CI). With an estimation that among the total 40,000 women aged 18–65 years in Lueyang County, 18.5% will be diagnosed with hrHPV infection, a total of 7500 women will be eligible for the study. Considering a 20% (up to 40%) attrition rate [26], we will end up with 6000 (at least 3000) women in the cohort. Since the proportion of patients' treatment choice is unknown, varying proportions produce different actual widths as follows (see Supplementary Material Table S2), the CI width was determined by PASS (version 15) with the following parameter settings: CI formula, exact (Clopper-Pearson); confidence level (1-alpha), 0.95; proportion, 0.1 to 0.9 by 0.1. A priori, we determined that feasibility would be confirmed with (1) a recruitment rate of >60% [26]; and (2) attrition rate <40%.

Data collection

The data collection protocol will be performed according to the list outlined in Table 1. All data will be obtained by physicians at the hospital. The participants underwent a comprehensive physical examination and completed a questionnaire through face-to-face interviews. All biochemical test results (HPV testing, TCT, colposcopy, and pathological examination) and sexually transmitted diseases (syphilis and HIV) will be obtained from the hospital records. Follow-up visits will be conducted at six, 12, 24, 36, 48, and 60 months.

Table 1. Data collection schedule

Procedure	Visit 1	Visit 2	Visit 3	Visit 4-8
	Screening	Baseline	Month one	Month 6-60
Eligibility criteria	×			
Research participants consent	×			
Individual Information				
Demographic variables	×			
Menstrual history	×			
Marital history	×			
Personal hygiene behaviour	×			
Gynaecological examinations		×		
HPV knowledge	×			
HPV infection	×			
Regular examination	×			
HPV vaccination	×			
Physicians' knowledge regarding treatment		×		
Partner information	×			
Outcomes				
Primary outcome				
Treatment patterns		×		×
Secondary outcomes				

HPV testing	×			×
TCT		○		○
Colposcopy		○		○
Pathological examination		○		○
Adverse events			○	○
Other assessments				
Intimate relationship satisfaction	×			×
HIP		×		×
Costs				×

Notes: HPV, human papillomavirus. TCT, Thin-prep liquid-based cytology test. HIP, the HPV impact profile. ○, if applicable.

Measures

Baseline

The baseline data includes the individual information, characteristics, and laboratory data. Individual data will be collected through a health interview survey and medical records. Demographic variables, such as age, education level, occupation, annual income, ethnicity, and religion, will be used in the analysis, as data concerning smoking status, alcohol consumption, sexual history (total number of sexual partners, frequency of sexual life, and forms of contraception), HPV vaccination history (type of vaccine and vaccinated person-time), and hygiene habits (i.e. frequency and manner of bathing).

Other basic information, such as menstrual history (i.e. time to menarche/menopause), marital history, HPV knowledge (HPV infection, regular examination, and HPV vaccination), physicians' knowledge regarding treatment (benefits and limitations of all treatments), partner information, and gynaecological examinations (i.e. lesions of the vulva, vagina, vaginal secretions, cervix, cervical polyps, uterus, uterine accessories, vaginal cleanliness, and sexually transmitted disease type), will also be assessed. All eligible patients will undergo gynaecological examinations.

Outcomes

Laboratory data, clinical characteristics, and use of therapies will be assessed in the hospital, and all laboratory examinations will be performed during the non-menstrual period. All outcomes will be collected by gynaecological outpatient doctors, and the diagnoses will be made by a specialised gynaecologic pathologist. Treatment patterns, as the primary outcome, will be collected by receiving the available data on the history of therapies from all eligible patients. Secondary outcomes include the clinical characteristics (HPV status, cytology, colposcopy, biopsy results, and adverse events) and other assessments (HPV impact profile, intimate relationship satisfaction, and costs, see the Supplementary Material Table S2). The specific examination procedures were as follows (Figure 2) [27]:

Other assessments

The HPV impact profile (HIP), a self-reported scale, is designed to represent the full

spectrum of potential HPV-related impacts. [28-29] An intimate relationship satisfaction questionnaire, a self-made satisfaction questionnaire, is used employed to estimate the satisfaction of patients with HPV infection. Direct and indirect costs will be estimated using medical information [30] related to cervical screening, diagnosis, and treatment of HPV and cervical lesions. The details are provided in the Supplementary Material Table S3.

A semi-structured interview guide has been developed for women with hrHPV infection and service providers. The initial questions on the guide will help explore participants' perceptions and attitudes towards HPV infection. Additional questions on the guide will assess the impact of these perceptions and attitudes on treatment choices, treatment switching, and nonadherence to guidelines. All semi-structured interviews will be conducted face-to-face or via phone. Interviews will be scheduled based on the participant's convenient day and time. Interviews are anticipated to begin on 1 August 2022.

Quality control

The investigators received training on the standard operating procedure before patient recruitment was performed. A standardised operation process manual and operation video were created and distributed to all of the research assistants. There will be a question-and-answer session to solve operation problems after approximately ten patients are enrolled. In addition, the research assistants will provide feedback on a

daily basis for patients who had submitted problems within the working group.

Data management and analysis

All participants will be allocated a PID code at enrolment, which will be used in the samples and documents over the 5-year study period. All data will be collected and managed using an electronic data management platform protected by the firewall of Chongqing Medical University. The data on the platform will be accessible only by authorised researchers using private accounts and passwords. Any change will be automatically recorded in the platform log and saved as a separate file for data monitoring purposes. For the data export process, the de-identification of patient health information will be conducted following the HIPAA rule. An independent safety monitoring board will be established when the study begins, and will monitor safety throughout the study period. The data will be verified by double-checking for erroneous or missing values, and data analysis will be performed using SAS version 9.1.3 (SAS Institute, Cary, NC, USA).

The demographic and clinical characteristics of the participants will be summarised using the mean and standard deviation for continuous variables. For categorical variables, the proportion (%) will be reported. Significant associations in the contingency tables (cross-tabulations) will be assessed using standard Pearson's χ^2 test. Analysis of variance will be used to compare differences in the continuous variables among the three groups. The patient demographics, clinical characteristics, treatment

therapies (to identify the most common treatments and durations), and guideline adherence will be descriptively reported. In addition, we may apply growth mixture modelling to observe whether subsets of individuals follow distinct trajectories over time. Analyses were performed for the entire cohort and stratified by treatment patterns, occurrence of switching, and HPV types (16/18+ or other 11 subtypes +).

Management patterns will be described as the proportion and 95% exact CI (95% CI). For this method, p will be the population proportion, and r represents the number of successes from a sample of size n. Let $p\hat{}$ = r /n. Exact test (Clopper-Pearson) using a mathematical relationship.[31] between the F distribution and the cumulative binomial distribution, and the lower and upper confidence limits of a 100(1-α) % exact confidence interval for the true proportion p are given by

$$\left[\frac{r}{r+(n-r+1)F_{1-\alpha/2;2(n-r+1),2r}}, \frac{(r+1)F_{1-\alpha/2;2(r+1),2(n-r)}}{(n-r)+(r+1)F_{1-\alpha/2;2(r+1),2(n-r)}}\right]$$

Multivariate logistic regression models will be used to estimate the potential factors influencing the treatment choices, including the personal information (sexual history, HPV vaccination history (type of vaccine and vaccinated person-time)), decision-maker characteristics (patient and physician), specific criteria (13 high-risk HPV subtypes, duration of infection, and adverse events), and contextual factors (patient's socioeconomic status, treatment costs, and perceived support [i.e. intimate relationships]). Pearson's χ^2 statistics will be used to compare the treatment differences

in clearance, recurrence, and persistence rates among the groups.

Qualitative data will be transcribed verbatim and analysed using thematic analysis. [32] At this stage, a bottom-up inductive approach will be used to identify patterned meanings in the dataset within an essentialist framework to report the experiences, meanings, and realities of the participants. NVivo software (Version 11, QSR International, Doncaster, Australia) will be used to import, organise, and explore the data for analysis. An iterative process will be employed to label data and identify emerging themes. To ensure inter-rater reliability, two independent investigators will perform the coding, category creation and thematic analyses. The team will liaise several times to review themes and subthemes, resolve discrepancies, and decide on the final definitions of themes and subthemes.

At each follow-up, the proportion of patients who received guideline-concordant care will be assessed. The proportion of patients having experienced an event at specific time points (6, 12, 24, 36, 48, and 60 months) will be derived from the switching rates. Kaplan–Meier curve will be used to estimate the median time-to-switch with relevant treatment events as a treatment switch, 95% confidence intervals (CIs) for median times to event will be computed. Multivariate analysis of the switching factors (decision-maker characteristics, decision-specific criteria, and contextual factors) will be tested using Cox regression analysis.

Pearson's χ^2 statistics will be used to compare the treatment differences in clearance, recurrence, and persistence rates among the groups. The Kaplan–Meier method will be used to construct the cumulative clearance rate of HPV from the date of the first HPV diagnosis to the date of HPV clearance in each treatment group. A proportional hazards model will be fitted to evaluate the effects of treatment options and other predictors on the overall persistence and recurrence of HPV, and possible interaction terms of the main effects will be tested by comparing a reduced model with the full model. Adverse events will be compared among the different groups. Data will be reported as medians and interquartile ranges or as numbers and percentages. All comparisons will be evaluated using Wilcoxon signed rank test with continuity correction.

Missing data will be identified and reported as percentages. We will also include several other key parameters (discount rate, annual number of screened women, screening positivity rate, biopsy rate, and programmatic costs) in the one-way sensitivity analysis.

Patient and public involvement

The patients and the public were not involved in the development of the research questions or the design and analysis of the study. The extent of patient involvement in the study included answering the survey questionnaires at baseline and each follow-up. The results will be disseminated to the applicants in the form of a published article, which will be made available upon request.

Ethics and dissemination

Ethical approval for the study was obtained from the Biomedical Research Ethics Committee of the Maternity Service Centre of Lueyang Maternal and Child Health Care Hospital. All participants fulfilling the inclusion criteria will commence as full ethics approval is received from the Biomedical Research Ethics Committee. No other independent ethics reviews were conducted. The results of this study will be disseminated in peer-reviewed journals and conferences. We will provide clinicians with feedback following the peer-review process to further strategies optimal treatment decision-making.

DISCUSSION

Women are currently concerned about cervical cancer, owing to its increasing incidence and high mortality in low- and middle-income areas. Despite the availability of safe and effective methods for treating premalignant conditions, real-world evidence of treatment effects in low- and middle-income areas remains limited. To our knowledge, there are no real-world data regarding patients' treatment patterns after being diagnosed with hrHPV infection among women in these regions, and the characteristics that affect their decision-making process are rarely reported. In this study, we focus on the characteristics of clinical outcomes in different treatment groups and the relationship between decision-making and the individual's characteristics in terms of individual behaviours, psychological trajectories, and economic burden. Hence, this study is able to evaluate how these factors influence the patient's decision-making process. It will

also allow us to study the research-to-practice of discordance in greater detail with the ultimate goal of uncovering the underlying causes of discrepancies between these formal recommendations and current practices.

Decision-making has acquired crucial importance in disease management over the last 20 years since the introduction of the patient-centred principle. A variety of factors can shape treatment decisions, which include decision-maker characteristics, decision-specific criteria, and contextual factors.[13] Previous studies have stated that there are a variety of factors that influence treatment decisions in oncological diseases and other diseases, such as capabilities, emotions, age, expected treatment risk, the healthcare system, and treatment costs.[18] Little is known about the predictive factors for decision making in women undergoing hrHPV testing. This study intends to include different influencing factors to reveal their internal influence mechanism on decision-making options. The qualitative findings of this study will help us explore the perceptions and attitudes toward HPV infection and its impact on the individuals' treatment choices. Moreover, we will gain an in-depth understanding of gynaecological care needs, which will aid us in developing context-specific programmes for patients infected with hrHPV in low socioeconomic areas in future. We expect that the results can inform clinical practice with the provision of predictive algorithms that provide physicians with a clear profile of the patient at present and their probable trajectory in the long term.

This study has several strengths. First, it provides a comprehensive understanding of the therapeutic status quo in hrHPV infection and the possible underlying mechanisms involved, including the treatment patterns and disease outcomes under different treatment decisions. Second, this prospective cohort study has a long follow-up period. Therefore, this study may assist in determining causal associations between the predicted determinants of treatment decision-making and can be used to obtain trajectories of how patients' conditions influence decision-making over time.[33] Describing and analysing time-invariant and time-variant factors that predict improvement or deterioration in these trajectories will help identify potentially modifiable risk factors for future interventions, as well as patients at risk for poor outcomes. Third, this study identifies the gap between research and practice and why some patients did not receive recommended therapies. It provides an effective mechanism to ensure high compliance to treatment and also provides an opportunity to reduce cervical cancer incidence and mortality in low- and middle-income areas.

High participation rates at follow-up are critical for the validation of cohort studies. A challenge we anticipate is the loss of follow-up, which is generally a common failure in longitudinal studies. The six-month, 12-month, 24-month, 36-month, 48-month, and 60-month follow-up appointments may remain difficult to sustain for the following reasons: (1) some adults in rural areas leave their hometowns to work in cities, which means some data could not be collected promptly; (2) insufficient attention paid by patients, which might be related to the insufficient knowledge and awareness about the

disease reported in China.[34] Maintaining follow-up visits is a challenge we anticipate. A research assistant will communicate regularly with the recruited participants through WeChat, the most popular messaging and calling app, allowing one-to-one communication. The research assistant will confirm the appointment dates and send out reminders the week prior. We will offer payment to cover transport expenses and meals on the day of the visits to help increase the adherence of the participants to the protocol schedule. During the study, participants diagnosed with cervical cancer will be referred to anticancer treatments but will continue follow-up assessments, noting the change in their disease status.

Overall, we can explore treatment patterns and their association with individual characteristics and unravel the changing trajectory of potential factors that affect decision-making. Most importantly, new real-world insights will be provided regarding the role of tailored disease management in the prevention and treatment of hrHPV infections. These results imply that standardised management could help to reduce the prevalence of cervical cancer in the future. These data may help inform future clinical trial designs, highlight the need for better adherence to treatment guidelines, and inform clinical decision-making.

Authors' Contributions:

QS, SY, RZ, and WX contributed to the study design. LB, DH, RZ, SY, YN and RX performed the study. SY and LBdrafted the initial manuscript. QS and SY revised the

draft. All authors have read and approved the final manuscript.

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Competing Interests Statement:

None declared.

References:

[1] Sung H, Ferlay J, Siegel RL, *et al*. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021;71:209-249.

[2] Cohen PA, Jhingran A, Oaknin A, *et al*. Cervical cancer. *Lancet* 2019; 393:169-182.

[3] Bray F, Ferlay J, Soerjomataram I, *et al*. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68:394–424.

[4] Jie H. China cancer registration annual report 2018[M], vol. 61. Beijing: People's Publishing House; 2019. p. 63.

[5] Schiffman M, Castle PE, Jeronimo J, *et al*. *Lancet* 2007; 370:890-907.

[6] WHO. Draft global strategy towards the elimination of cervical cancer as a public

health problem. https://www.who.int/docs/default-source/documents/cervical-cancer-elimination-draft-strategy.pdf?sfvrsn=380979d6_4 (accessed Oct 9, 2019).

[7] WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention, second edition [Internet]. Geneva: World Health Organization; 2021.

[8] Basu P, Taghavi K, Hu SY, *et al*. Management of cervical premalignant lesions. *Current problems in cancer* 2018;42:129-136.

[9] Rossman AH, Reid HW, Pieters MM, *et al*. Digital Health Strategies for Cervical Cancer Control in Low- and Middle-Income Countries: Systematic Review of Current Implementations and Gaps in Research. *J Med Internet Res* 2021;23:e23350.

[10] Johnson LG, Armstrong A, Joyce CM, *et al*. Implementation strategies to improve cervical cancer prevention in sub-Saharan Africa: a systematic review. *Implementation Science* 2018;13:1-18.

[11] Hu Z, Ding WC, Zhu D, *et al*. TALEN-mediated targeting of HPV oncogenes ameliorates HPV-related cervical malignancy. *J Clin Invest* 2014;125:425–36.

[12] Castle PE, Murokora D, Perez C, *et al*. Treatment of cervical intraepithelial lesions. *International Journal of Gynecology & Obstetrics* 2017;138:20–25.

[13] Papadakis VM, Lioukas S, Chambers D. Strategic decision-making processes: the role of management and context. *Strategic management journal* 1998;19:115–147.

[14] Elbanna S. The influence of decision, environmental and firm characteristics on the rationality of strategic decision-making. *Journal of Management Studies* 2007;44:4.

[15] Mazzocco K, Masiero M, Carriero MC, *et al*. The role of emotions in cancer

patients' decision-making. *Ecancermedicalscience* 2019;13:914.

[16] Nash K, Leota J, Tran A. Neural processes in antecedent anxiety modulate risk-taking behavior. *Scientific reports* 2021;11:2637.

[17] Junius-Walker U, Wiese B, Klaaßen-Mielke R, *et al*. Older patients' perceived burdens of their health problems: a cross-sectional analysis in 74 German general practices. *Patient preference and adherence* 2015;9:811–820.

[18] Glatzer M, Panje CM, Sirén C, *et al*. Decision Making Criteria in Oncology. *Oncology* 2018;98:370–378.

[19] Wang B, He M, Chao A, *et al*. Cervical cancer screening among adult women in China, 2010. *Oncologist* 2015;20:627–634.

[20] Zhu B, Liu Y, Zuo T, *et al*. The prevalence, trends, and geographical distribution of human papillomavirus infection in China: The pooled analysis of 1.7 million women. *Cancer Medicine* 2019;8:5373–5385.

[21] Kabadi SM, Goyal RK, Nagar SP, *et al*. Treatment patterns, adverse events, and economic burden in a privately insured population of patients with chronic lymphocytic leukemia in the United States. *Cancer medicine* 2019;8:3803–3810.

[22] Twomey R, Matthews TW, Nakoneshny SC, *et al*. From Pathways to Practice: Impact of Implementing Mobilization Recommendations in Head and Neck Cancer Surgery with Free Flap Reconstruction. *Cancers* 2021;13:2890.

[23] Giuliano AR, Lee JH, Fulp W, *et al*. Incidence and clearance of genital human papillomavirus infection in men (HIM): a cohort study. *Lancet (London, England)* 2011;377:932–940.

519 [24] Follen Mitchell, M. A randomized clinical trial of cryotherapy, laser vaporization,
520 and loop electrosurgical excision for treatment of squamous intraepithelial lesions of
521 the cervix. Obstetrics & Gynecology 1998;92:737–744.
522 [25] Namikawa K, Yoshio T, Yoshimizu S, *et al*. Clinical outcomes of endoscopic
523 resection of preoperatively diagnosed non-circumferential T1a-muscularis mucosae or
524 T1b-submucosa 1 esophageal squamous cell carcinoma. *Scientific reports* 2021;11:
525 6554.
526 [26] Brahmbhatt P, Sabiston CM, Lopez C, *et al*. Feasibility of prehabilitation prior to
527 breast cancer surgery: a mixed-methods study. Frontiers in oncology 2020;10:571091.
528 [27] Specialized Committee of Human Papilloma Virus Infection Diseases of Cross-
529 Strait Association of Precision Medicine of Fujian Province. Expert consensus on HPV
530 infection and HPV-associated diseases 2017. *J Med Postgra* 2017;12:1238-1241.
531 [28] Mast TC, Zhu X, Demuro-Mercon C, *et al*. Development and psychometric
532 properties of the HPV Impact Profile (HIP) to assess the psychosocial burden of HPV.
533 *Current medical research and opinion* 2009;25:2609-2619.
534 [29] Wang KL, Jeng CJ, Yang YC, *et al*. The psychological impact of illness among
535 women experiencing human papillomavirus-related illness or screening interventions.
536 *J Psychosom Obstet Gynaecol* 2010;31:16–23.
537 [30] Ferretti C, Sarti FM, Nitrini R, *et al*. An assessment of direct and indirect costs of
538 dementia in Brazil. *PLoS One* 2018;13:e0193209.
539 [31] Fleiss JL, Levin B, Paik MC. Statistical Methods for Rates and Proportions. Third
540 Edition. John Wiley & Sons. New York., 2003. p. 25.

[32] Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol 2006;3:77–101.

[33] Guralnik JM, Kritchevsky SB. Translating research to promote healthy aging: the complementary role of longitudinal studies and clinical trials. *J Am Geriatr Soc* 2010; 58:S337-S342.

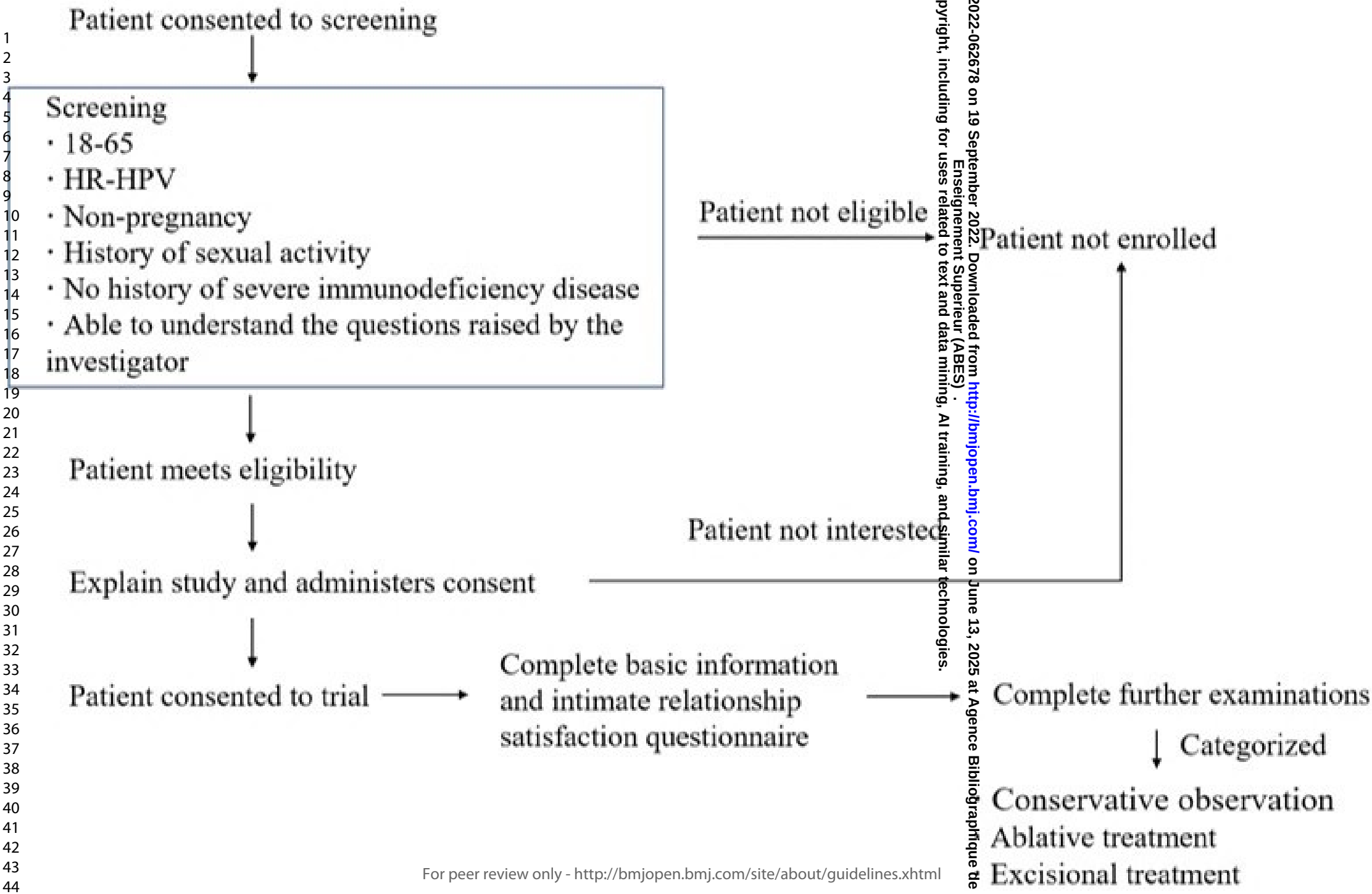
[34] Baloch Z, Yasmeen N, Li Y, et al. Knowledge and awareness of cervical cancer, human papillomavirus (HPV), and HPV vaccine among HPV-infected Chinese women. Medical science monitor: international medical journal of experimental and clinical research 2017;23:4269.

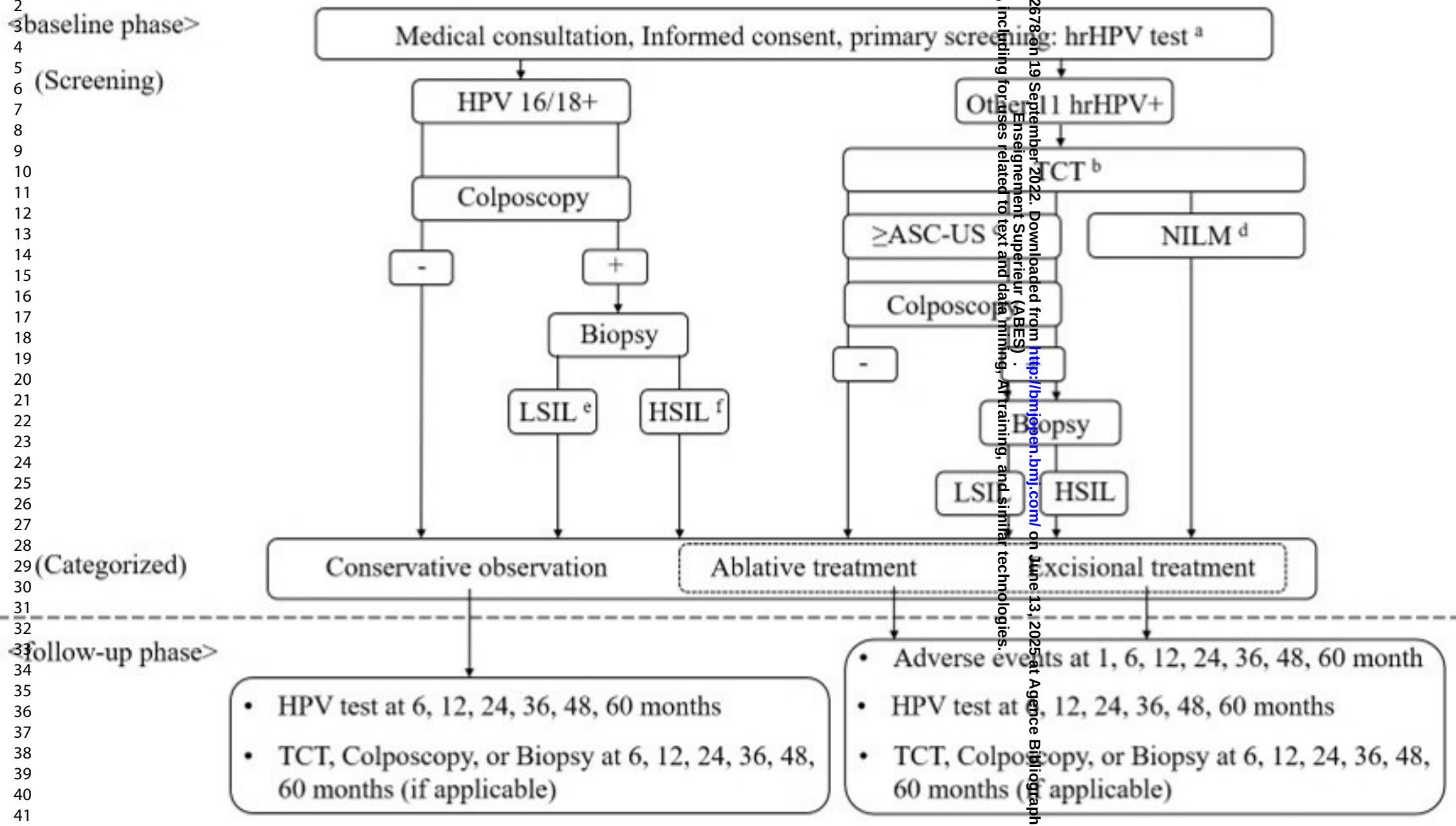
Figure Legends

Figure 1. Workflow for the recruitment procedure.

Figure 2. The specific examination procedures.[27]

Note: [a] hrHPV, high risk human papilloma virus; [b] TCT, thin-prep liquid-based cytologic test; [c] ≥*ASC-US*, atypical squamous cells of undetermined significance or above; [d] NILM, negative for intraepithelial lesions or malignancy; [e] LSIL, low-grade squamous intraepithelial lesion; [f] HSIL, high-grade squamous intraepithelial lesion.





Supplementary materials

Table S1. Definition of outcomes

Variables	Definition
Treatment patterns	(1) the number of patients who underwent conservative observation, that who underwent ablative treatment, and that who underwent excisional treatment; (2) the duration of each therapy regimen and the time to treatment initiation: The duration of treatment, the duration of each therapy regimen, and time to the initiation of treatment (the start of the initial regimen was the date of the first treatment and all treatments initiated within 90 days of that date). [6, 21]
Compliance with guidelines	Compliance with guideline, the primary outcome was the provider's adherence to the 2021 WHO guidelines for the screening, treatment, and management of patients with hrHPV infection. Compliance with guidelines refers to the proportion of patients who achieve the recommended treatment, as judged by 2 experienced gynaecological specialists. [22] Outcomes including: (1) the number of patients who received other specific treatments, including the duration of those other specific treatments; (2) the number of patients who received guideline-recommended treatment.
HPV status	The HPV clearance, persistence, and recurrence will be assessed via PCR. HPV clearance was defined as a participant testing HPV negative at two consecutive visits after testing positive. [23] The persistent disease was defined as the cytologic or histologic presence of HPV at the time of the second follow-up visit (within 6 months after treatment). Recurrent disease was defined as the cytologic or histologic presence of HPV diagnosed at a subsequent

	follow-up visit (at least 6 months after treatment) in a patient who had had at least one negative cytologic smear after treatment [24].
Adverse events	Adverse events will be recorded at 1 month, 6 months, 12 months, and 24 months after treatment onset. It including major infections or bleeding, procedure-associated pain, cervical stenosis, infertility, spontaneous abortion, perinatal deaths, premature rupture of membrane, unnecessary interventions, and increased viral shedding in women living with HIV. [7] The National Institutes of Health Common Terminology Criteria for Adverse Events (CTCAE; version 4.0) was used to grade severity of adverse events. Adverse events with CTCAE grade 3 or higher will consider to be serious.

Table S2. Numeric Results for Two-Sided CIs for One Proportion

n \ *p*	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
6000	0.015	0.020	0.023	0.025	0.025	0.025	0.023	0.020	0.015
3000	0.022	0.029	0.033	0.035	0.036	0.035	0.033	0.029	0.022

Notes: *p*, proportion of patients' treatment choices. n, sample size.

Table S3. Outcomes and other assessments

Outcomes	
HR-HPV testing	The HR-HPV subtypes were tested using the 21 HPV GenoArray Diagnostic Kit (Yaneng Biosciences, Shenzhen, China) from the Tianbo Biomedical Laboratory (Xian, China). This included testing on 13 high-risk subtypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68).
Thin-prep liquid-based cytology test (TCT)	Exfoliated cervical cells from women attending the gynaecological outpatient clinic were collected using a specialised cervical brush by a clinician. The cervical cells were detected using TCT, and the results of cytological pathology were diagnosed by senior physicians according to the Bethesda System of cervical cytology.
Cytological test	Standard colposcopic assessment will be performed when a cytological test is abnormal at the threshold of atypical squamous cells of an undetermined significance (or borderline dyskaryosis) or when the HPV 16/18 test result is positive. The colposcopic findings will be reported according to ASCCP terminology for colposcopic practice.
Pathological examination	For the pathological examination of the women who undergoing colposcopy, a biopsy will be performed only in cases with abnormal cervical findings, and if the colposcopy is unsatisfactory, a cervical curettage sample will be obtained.
Other assessments	
HIP	It consists of 29 items measuring worries and concerns, emotional impact, sexual impact, self-image, partner issues and transmission, interactions with doctors, and control/life impact.[28] The HIP item scales were linearly transformed to a scale of 0–100, and each item was a 0–10 point discretised analogue scale. The Mandarin Chinese version of the HIP questionnaire was generated through a

	standardised process and has been previously used in Taiwan.[29]
Intimate relationship satisfaction questionnaire	It contains two self-reported questions related to partner and sexual satisfaction. The scoring for each item ranges from very dissatisfied (0) to very satisfied (10).
Costs	The direct costs included patients' medication, health care, and other resources (such as time in seeking/receiving care and post-treatment recovery time). The costs of medication and health service utilisation will be calculated from the medical records using market prices. The indirect cost estimates of economic losses due to spending time on screening, examinations, and treatment are based on hourly wages per capita. [30]

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Profiling the real-world management status of high-risk human papillomavirus infection: A protocol to establish a prospective cohort of high-risk human papillomavirus-infected women in Lueyang County, China

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Profiling the real-world management status of high-risk human papillomavirus infection: A protocol to establish a prospective cohort of high-risk human papillomavirus-infected women in Lueyang County, China

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Abstract

Introduction: Persistent infection with high-risk human papillomavirus (hrHPV) is the main cause of cervical cancer. Thus, the effective treatment against HPV represents an opportunity to reduce the incidence of cervical cancer. Although various treatments are effective in treating HPV infection, they still provide limited benefit in reducing the rate of cervical cancer due to the lack of implementation of a standardised protocol in many low- and middle-income areas. This proposed cohort study aims to describe the status quo of treatment, attributions of the treatment decision-making process, and potential factors influencing treatment decisions.

Methods and analysis: This is a mixed method, 5-year prospective longitudinal study in Lueyang County, China, one of the areas with the highest cervical cancer incidence rates and lowest mean income in China. We will enroll hrHPV infection (at least one HPV type in the 13 high-risk subtypes) women diagnosed via a county-wide HPV infection and cervical cancer screening programme. The study procedures describe the treatment patterns and explore the potential influencing factors in treatment decision-making through questionnaires, laboratory examinations, and in-depth interviews. All participants will be evaluated at baseline and at six, 12, 24, 36, 48, and 60 months. The primary outcome is the treatment pattern, the type and duration of which will be described later. The secondary outcomes include guideline compliance and changes in the HPV infection status. The HPV impact profile, intimate relationship satisfaction, and costs within different management groups are also described and compared.

Ethics and dissemination: This study was reviewed, and all of the relevant approvals

were obtained from the Ethics Committee of the Maternity Service Centre of Lueyang Maternal and Child Health Care Hospital (2021-001). The findings from this study will be disseminated through peer-reviewed publications, conference presentations, and academic workshops.

Trial registration number: ChiCTR2100053757.

Strengths and limitations of this study

- To our knowledge, this is the first study to consider real-world data regarding the management patterns after diagnosing high-risk HPV infection among women in China.
- We will use a mixed method to explore different potential factors, revealing their internal influence mechanism on treatment decision-making options.
- Implementing this protocol will identify the gap between research and practice and determine why some patients did not receive the recommended therapies.
- It remains a challenge to sustain a high participation rate in a prospective cohort study; working outside the hometown and insufficient knowledge and awareness about the disease in Lueyang County would lead to the loss of participant follow-up.
- This is a community-based observational study of prospectively collected data from Lueyang County, China, so the study design increases the risk for the potential limitations of the presence of selection bias and a decreased generalisability of the findings to other populations.

INTRODUCTION

Cervical cancer ranks fourth among malignant tumours in females worldwide,[1] presenting a serious threat to women. Cervical cancer is a major public health concern.[2] Globally, there was an estimated incidence rate of 15.3 per 100,000 and a mortality rate of 7 per 100,000 for cervical cancer in 2018.[3] In China, the incidence rate is 10.88 per 100,000, and the mortality rate is 3.17 per 100,000.[4] Cervical cancer arises from four processes: human papillomavirus (HPV) infection, persistent HPV infection, multistage squamous intraepithelial lesions, and invasion through the basement membrane.[5] The World Health Organisation (WHO) is developing a global strategy, known as the 90–70–90 triple-intervention strategy, for eliminating cervical cancer as a public health problem by 2030.[6]

Currently, great progress has been made in the prevention of cervical cancer (e.g. HPV vaccination and cervical screening initiatives) and the development of several therapies for cervical cancer. For women who are already HPV-infected, the WHO guidelines recommend safe and effective treatment options, but these do not reach the women who need these services the most.[7-8] Several factors contribute to this failure in health service delivery, access, and utilisation, including a lack of a link between screening and treatment (compliance with treatment and follow-up), variability in service quality, and insufficient continuing education for service providers.[9-10] Thus, the implementation of the standardised management of hrHPV infection or HPV-caused precancerous lesions to reduce the prevalence of cervical cancer urgently needs to be

implemented.

Treatments for HPV infection and HPV-induced precancer lesions include conservative observation, ablative treatment (cryotherapy and thermal ablation), and excisional treatment (excision with a cold knife cone (CKC) and electrosurgical excision (LLETZ or LEEP)).[7, 11] Several studies have shown that patients with HPV infection or benign lesions can undergo tissue destruction by thermal (hot or cold), electrical, or chemical means, the success rates for which vary widely, and the variability of the inclusion criteria for each study hampers establishing a standardised management protocol.[8,12] The quality of evidence for all outcomes is low to very low, and the level of heterogeneity is high in all pooled analyses. For instance, although all currently used ablative techniques are effective in reducing cancer risk, there is a lack of data on the long term effectiveness of therapies, reasons for treatment failure, and cost-effectiveness of therapies.

For these reasons, there remains a lack of sufficient real-world evidence to support clinicians and patients in providing optimal treatment decision-making recommendations. Various factors can shape treatment decisions, including decision-maker characteristics, decision-specific criteria, and contextual factors.[13-14] The first are the decision-maker characteristics, including those for both the providers and patients, such as capabilities (i.e. knowledge of HPV), emotions (i.e. worry, anxiety, or stigma from HPV infection), and degree of expertise (i.e. benefits and limitations of

each treatment).[15-16] Second, decision-specific criteria involve classical clinical criteria, such as age, HPV type, duration of infection, sex, or expected treatment complications (i.e. adhesions or bleeding).[17] Contextual factors include the patient's socioeconomic status, healthcare system, treatment costs, and perceived support (i.e. intimate relationships).[18] Currently, it is not yet clear which patient factors affect treatment decision-making after testing positive for HPV.

The All-China Women's Federation and the Ministry of Health launched the 'Two Cancers' (cervical cancer and breast cancer) screening programme in July 2009, which implemented a free cervical cancer screening programme for rural women aged 35–64 years. This programme involved publicity, health education, and examinations.[19] In recent years, with the popularisation of cervical cancer screening, the incidence of cervical cancer in some areas of China has been effectively controlled. Lueyang County is a low-income area in China with high morbidity and mortality rates for cervical cancer. The incidence of cervical cancer has shown a decreasing trend in recent years; however, the morbidity and mortality of the disease remain high. The high prevalence rate of HPV infection (18.5%) in this region was higher than the national overall prevalence rate of HPV infection (15.54%).[20] We still do not know why morbidity or mortality is higher, and how to provide services to patients in this county. Furthermore, the standard of care for HPV and cervical lesions provided in China and how it deviates from the WHO recommendations remains unclear.

Thus, we propose to establish a prospective cohort for women infected with high-risk HPV in Lueyang, Shaanxi, aiming to (1) profile the treatment patterns and adherence to guideline-concordant management for hrHPV infection in the real-world setting, (2) identify the characteristics that associated with treatment decision-making for hrHPV infection, (3) explore the reasons for treatment choices, including initial regimen, switch, and treatment termination, and (4) evaluate the long term effects of different treatment approaches. The results will provide real-world evidence to support optimal decision-making in the treatment of hrHPV infection and, ultimately, strive to achieve the goal of '90% of women with precancer treated', which was proposed by the WHO in its Cervical Cancer Elimination Initiative.

METHODS AND ANALYSIS

Study design and setting

This mixed method, prospective cohort study with a 5-year follow-up, will take place in Lueyang County, one of the economically underdeveloped regions in Shaanxi Province, China. Lueyang County has a high prevalence of HPV infection. All women between 18-65 years old in the county are invited to participant a local government-supported cervical screening programme. The cervical screening services are managed by gynaecologists at the Maternity Service Centre of Lueyang Maternal and Child Health Care Hospital. The study was approved by the Maternity Service Centre of Lueyang Maternal and Child Health Care Hospital, and it was started on 4 November

2021 and is planned to be completed by 31 November 2026.

During the screening phase, women aged 18–65 years are recruited through a cervical screening service by gynaecologists and nurses. Basic information, hrHPV testing, and inclusion evaluations will be performed. The women diagnosed with hrHPV infection during the screening phase will be invited to participate in the study. Written informed consent will be obtained from the women regarding their participation in this prospective cohort study (including the procedures, risks, and options for dropping out of the study). Medical staff with adequate training will clearly explain the study protocol and objectives to the participants. After providing consent, each patient must sign an informed consent form. Subsequently, a participant identification (PID) number will be assigned to facilitate the study, and the other examinations will be performed. In the categorized phase, according to the outcomes of examinations and treatment decision-making, all patients will be divided into conservative observation, ablative treatment, and excisional treatment groups. Figure 1 shows the recruitment process that will be used.

Eligibility criteria

The inclusion criteria are as follows: (1) women aged 18–65 years, who had lived for 5 years in Lueyang County, (2) a diagnosis of hrHPV infection (including 13 subtypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68; participants with at least one HPV type in the high-risk group) in the screening phase, (3) non-pregnancy, (4) history of

sexual activity, (5) no history of severe immunodeficiency disease, and (6) able to understand the questions asked by the investigator.

The exclusion criteria are as follows: (1) refusal to participate in this study, (2) a diagnosis of cervical cancer, (3) other malignant tumours or serious illness, and (4) a diagnosis of mental illness or impaired consciousness.

Definition of outcomes

This study will assess the treatment patterns, compliance with guidelines, and HPV status. (For detailed information, see Supplementary Material Table S1.) [21-24] Patients in the conservative observation group will undergo routine follow-up. [25] The patients will be observed without any additional treatment. Ablative treatments include cryotherapy and thermal ablation.[6] Abnormal tissue is destroyed by heating with thermal coagulation or freezing with cryotherapy. Excisional treatment involves the surgical removal of abnormal tissue with LLETZ or CKC.[6] Switching was defined as a change to a different treatment before completing the assigned course of treatment. The switch could be to any treatment (observation, ablative, or excisional treatment). The time-to-switch was defined as the period from the date of the first treatment regimen to the date of switch to another treatment regimen during the study period.

Sampling strategy

All women meeting the inclusion criteria will be recruited for the study and followed-

up for five years. Management patterns describe using proportion and 95% two-sided exact confidence intervals (95% CI). With an estimation that among the total 40,000 women aged 18–65 years in Lueyang County, 18.5% will be diagnosed with hrHPV infection, a total of 7500 women will be eligible for the study. Considering a 20% (up to 40%) attrition rate [26], we will end up with 6000 (at least 3000) women in the cohort. Since the proportion of patients' treatment choice is unknown, varying proportions produce different actual widths as follows (see Supplementary Material Table S2), the CI width was determined by PASS (version 15) with the following parameter settings: CI formula, exact (Clopper-Pearson); confidence level (1-alpha), 0.95; proportion, 0.1 to 0.9 by 0.1. A priori, we determined that feasibility would be confirmed with (1) a recruitment rate of >60% [26]; and (2) attrition rate <40%.

Data collection

The data collection protocol will be performed according to the list outlined in Table 1. All data will be obtained by physicians at the hospital. The participants underwent a comprehensive physical examination and completed a questionnaire through face-to-face interviews. All biochemical test results (HPV testing, TCT, colposcopy, and pathological examination) and sexually transmitted diseases (syphilis and HIV) will be obtained from the hospital records. Follow-up visits will be conducted at six, 12, 24, 36, 48, and 60 months.

Table 1. Data collection schedule

Procedure	Visit 1	Visit 2	Visit 3	Visit 4-8
	Screening	Baseline	Month one	Month 6-60
Eligibility criteria	×			
Research participants consent	×			
Individual Information				
Demographic variables	×			
Menstrual history	×			
Marital history	×			
Personal hygiene behaviour	×			
Gynaecological examinations		×		
HPV knowledge	×			
HPV infection	×			
Regular examination	×			
HPV vaccination	×			
Physicians' knowledge regarding treatment		×		
Partner information	×			
Outcomes				
Primary outcome				
Treatment patterns		×		×
Secondary outcomes				

HPV testing	×			×
TCT		○		○
Colposcopy		○		○
Pathological examination		○		○
Adverse events			○	○
Other assessments				
Intimate relationship satisfaction	×			×
HIP		×		×
Costs				×

Notes: HPV, human papillomavirus. TCT, Thin-prep liquid-based cytology test. HIP, the HPV impact profile. ○, if applicable.

Measures

Baseline

The baseline data includes the individual information, characteristics, and laboratory data. Individual data will be collected through a health interview survey and medical records. Demographic variables, such as age, education level, occupation, annual income, ethnicity, and religion, will be used in the analysis, as data concerning smoking status, alcohol consumption, sexual history (total number of sexual partners, frequency of sexual life, and forms of contraception), HPV vaccination history (type of vaccine and vaccinated person-time), and hygiene habits (i.e. frequency and manner of bathing).

Other basic information, such as menstrual history (i.e. time to menarche/menopause), marital history, HPV knowledge (HPV infection, regular examination, and HPV vaccination), physicians' knowledge regarding treatment (benefits and limitations of all treatments), partner information, and gynaecological examinations (i.e. lesions of the vulva, vagina, vaginal secretions, cervix, cervical polyps, uterus, uterine accessories, vaginal cleanliness, and sexually transmitted disease type), will also be assessed. All eligible patients will undergo gynaecological examinations.

Outcomes

Laboratory data, clinical characteristics, and use of therapies will be assessed in the hospital, and all laboratory examinations will be performed during the non-menstrual period. All outcomes will be collected by gynaecological outpatient doctors, and the diagnoses will be made by a specialised gynaecologic pathologist. Treatment patterns, as the primary outcome, will be collected by receiving the available data on the history of therapies from all eligible patients. Secondary outcomes include the clinical characteristics (HPV status, cytology, colposcopy, biopsy results, and adverse events) and other assessments (HPV impact profile, intimate relationship satisfaction, and costs, see the Supplementary Material Table S2). The specific examination procedures were as follows (Figure 2) [27]:

Other assessments

The HPV impact profile (HIP), a self-reported scale, is designed to represent the full

spectrum of potential HPV-related impacts. [28-29] An intimate relationship satisfaction questionnaire, a self-made satisfaction questionnaire, is used employed to estimate the satisfaction of patients with HPV infection. Direct and indirect costs will be estimated using medical information [30] related to cervical screening, diagnosis, and treatment of HPV and cervical lesions. The details are provided in the Supplementary Material Table S3.

A semi-structured interview guide (see Supplementary Material Table S4) has been developed for women with hrHPV infection and service providers. The initial questions on the guide will help explore participants' perceptions and attitudes towards HPV infection. Additional questions on the guide will assess the impact of these perceptions and attitudes on treatment choices, treatment switching, and nonadherence to guidelines. All semi-structured interviews will be conducted face-to-face or via phone. Interviews will be scheduled based on the participant's convenient day and time. Interviews are anticipated to begin on 1 August 2022.

Quality control

The investigators received training on the standard operating procedure before patient recruitment was performed. A standardised operation process manual and operation video were created and distributed to all of the research assistants. There will be a question-and-answer session to solve operation problems after approximately ten patients are enrolled. In addition, the research assistants will provide feedback on a

daily basis for patients who had submitted problems within the working group.

Data management and analysis

All participants will be allocated a PID code at enrolment, which will be used in the samples and documents over the 5-year study period. All data will be collected and managed using an electronic data management platform protected by the firewall of Chongqing Medical University. The data on the platform will be accessible only by authorised researchers using private accounts and passwords. Any change will be automatically recorded in the platform log and saved as a separate file for data monitoring purposes. For the data export process, the de-identification of patient health information will be conducted following the HIPAA rule. An independent safety monitoring board will be established when the study begins, and will monitor safety throughout the study period. The data will be verified by double-checking for erroneous or missing values, and data analysis will be performed using SAS version 9.1.3 (SAS Institute, Cary, NC, USA).

The demographic and clinical characteristics of the participants will be summarised using the mean and standard deviation for continuous variables. For categorical variables, the proportion (%) will be reported. Significant associations in the contingency tables (cross-tabulations) will be assessed using standard Pearson's χ^2 test. Analysis of variance will be used to compare differences in the continuous variables among the three groups. The patient demographics, clinical characteristics, treatment

therapies (to identify the most common treatments and durations), and guideline adherence will be descriptively reported. In addition, we may apply growth mixture modelling to observe whether subsets of individuals follow distinct trajectories over time. Analyses were performed for the entire cohort and stratified by treatment patterns, occurrence of switching, and HPV types (16/18+ or other 11 subtypes +).

Management patterns will be described as the proportion and 95% exact CI (95% CI). For this method, p will be the population proportion, and r represents the number of successes from a sample of size n. Let $p\hat{}$ = r /n. Exact test (Clopper-Pearson) using a mathematical relationship.[31] between the F distribution and the cumulative binomial distribution, and the lower and upper confidence limits of a 100(1-α) % exact confidence interval for the true proportion p are given by

$$\left[\frac{r}{r+(n-r+1)F_{1-\alpha/2;2(n-r+1),2r}}, \frac{(r+1)F_{1-\alpha/2;2(r+1),2(n-r)}}{(n-r)+(r+1)F_{1-\alpha/2;2(r+1),2(n-r)}}\right]$$

Multivariate logistic regression models will be used to estimate the potential factors influencing the treatment choices, including the personal information (sexual history, HPV vaccination history (type of vaccine and vaccinated person-time)), decision-maker characteristics (patient and physician), specific criteria (13 high-risk HPV subtypes, duration of infection, and adverse events), and contextual factors (patient's socioeconomic status, treatment costs, and perceived support [i.e. intimate relationships]). Pearson's χ^2 statistics will be used to compare the treatment differences

in clearance, recurrence, and persistence rates among the groups.

Qualitative data will be transcribed verbatim and analysed using thematic analysis. [32] At this stage, a bottom-up inductive approach will be used to identify patterned meanings in the dataset within an essentialist framework to report the experiences, meanings, and realities of the participants. NVivo software (Version 11, QSR International, Doncaster, Australia) will be used to import, organise, and explore the data for analysis. An iterative process will be employed to label data and identify emerging themes. To ensure inter-rater reliability, two independent investigators will perform the coding, category creation and thematic analyses. The team will liaise several times to review themes and subthemes, resolve discrepancies, and decide on the final definitions of themes and subthemes.

At each follow-up, the proportion of patients who received guideline-concordant care will be assessed. The proportion of patients having experienced an event at specific time points (6, 12, 24, 36, 48, and 60 months) will be derived from the switching rates. Kaplan–Meier curve will be used to estimate the median time-to-switch with relevant treatment events as a treatment switch, 95% confidence intervals (CIs) for median times to event will be computed. Multivariate analysis of the switching factors (decision-maker characteristics, decision-specific criteria, and contextual factors) will be tested using Cox regression analysis.

Pearson's χ^2 statistics will be used to compare the treatment differences in clearance, recurrence, and persistence rates among the groups. The Kaplan–Meier method will be used to construct the cumulative clearance rate of HPV from the date of the first HPV diagnosis to the date of HPV clearance in each treatment group. A proportional hazards model will be fitted to evaluate the effects of treatment options and other predictors on the overall persistence and recurrence of HPV, and possible interaction terms of the main effects will be tested by comparing a reduced model with the full model. Adverse events will be compared among the different groups. Data will be reported as medians and interquartile ranges or as numbers and percentages. All comparisons will be evaluated using Wilcoxon signed rank test with continuity correction.

Missing data will be identified and reported as percentages. We will also include several other key parameters (discount rate, annual number of screened women, screening positivity rate, biopsy rate, and programmatic costs) in the one-way sensitivity analysis.

Patient and public involvement

The patients and the public were not involved in the development of the research questions or the design and analysis of the study. The extent of patient involvement in the study included answering the survey questionnaires at baseline and each follow-up. The results will be disseminated to the applicants in the form of a published article, which will be made available upon request.

Ethics and dissemination

Ethical approval for the study was obtained from the Biomedical Research Ethics Committee of the Maternity Service Centre of Lueyang Maternal and Child Health Care Hospital. All participants fulfilling the inclusion criteria will commence as full ethics approval is received from the Biomedical Research Ethics Committee. No other independent ethics reviews were conducted. The results of this study will be disseminated in peer-reviewed journals and conferences. We will provide clinicians with feedback following the peer-review process to further strategies optimal treatment decision-making.

DISCUSSION

Women are currently concerned about cervical cancer, owing to its increasing incidence and high mortality in low- and middle-income areas. Despite the availability of safe and effective methods for treating premalignant conditions, real-world evidence of treatment effects in low- and middle-income areas remains limited. To our knowledge, there are no real-world data regarding patients' treatment patterns after being diagnosed with hrHPV infection among women in these regions, and the characteristics that affect their decision-making process are rarely reported. In this study, we focus on the characteristics of clinical outcomes in different treatment groups and the relationship between decision-making and the individual's characteristics in terms of individual behaviours, psychological trajectories, and economic burden. Hence, this study is able to evaluate how these factors influence the patient's decision-making process. It will

also allow us to study the research-to-practice of discordance in greater detail with the ultimate goal of uncovering the underlying causes of discrepancies between these formal recommendations and current practices.

Decision-making has acquired crucial importance in disease management over the last 20 years since the introduction of the patient-centred principle. A variety of factors can shape treatment decisions, which include decision-maker characteristics, decision-specific criteria, and contextual factors.[13] Previous studies have stated that there are a variety of factors that influence treatment decisions in oncological diseases and other diseases, such as capabilities, emotions, age, expected treatment risk, the healthcare system, and treatment costs.[18] Little is known about the predictive factors for decision making in women undergoing hrHPV testing. This study intends to include different influencing factors to reveal their internal influence mechanism on decision-making options. The qualitative findings of this study will help us explore the perceptions and attitudes toward HPV infection and its impact on the individuals' treatment choices. Moreover, we will gain an in-depth understanding of gynaecological care needs, which will aid us in developing context-specific programmes for patients infected with hrHPV in low socioeconomic areas in future. We expect that the results can inform clinical practice with the provision of predictive algorithms that provide physicians with a clear profile of the patient at present and their probable trajectory in the long term.

This study has several strengths. First, it provides a comprehensive understanding of the therapeutic status quo in hrHPV infection and the possible underlying mechanisms involved, including the treatment patterns and disease outcomes under different treatment decisions. Second, this prospective cohort study has a long follow-up period. Therefore, this study may assist in determining causal associations between the predicted determinants of treatment decision-making and can be used to obtain trajectories of how patients' conditions influence decision-making over time.[33] Describing and analysing time-invariant and time-variant factors that predict improvement or deterioration in these trajectories will help identify potentially modifiable risk factors for future interventions, as well as patients at risk for poor outcomes. Third, this study identifies the gap between research and practice and why some patients did not receive recommended therapies. It provides an effective mechanism to ensure high compliance to treatment and also provides an opportunity to reduce cervical cancer incidence and mortality in low- and middle-income areas.

High participation rates at follow-up are critical for the validation of cohort studies. A challenge we anticipate is the loss of follow-up, which is generally a common failure in longitudinal studies. The six-month, 12-month, 24-month, 36-month, 48-month, and 60-month follow-up appointments may remain difficult to sustain for the following reasons: (1) some adults in rural areas leave their hometowns to work in cities, which means some data could not be collected promptly; (2) insufficient attention paid by patients, which might be related to the insufficient knowledge and awareness about the

disease reported in China.[34] Maintaining follow-up visits is a challenge we anticipate. A research assistant will communicate regularly with the recruited participants through WeChat, the most popular messaging and calling app, allowing one-to-one communication. The research assistant will confirm the appointment dates and send out reminders the week prior. We will offer payment to cover transport expenses and meals on the day of the visits to help increase the adherence of the participants to the protocol schedule. During the study, participants diagnosed with cervical cancer will be referred to anticancer treatments but will continue follow-up assessments, noting the change in their disease status.

Overall, we can explore treatment patterns and their association with individual characteristics and unravel the changing trajectory of potential factors that affect decision-making. Most importantly, new real-world insights will be provided regarding the role of tailored disease management in the prevention and treatment of hrHPV infections. These results imply that standardised management could help to reduce the prevalence of cervical cancer in the future. These data may help inform future clinical trial designs, highlight the need for better adherence to treatment guidelines, and inform clinical decision-making.

Authors' Contributions:

QS, SY, RZ, and WX contributed to the study design. LB, DH, RZ, SY, YN and RX performed the study. SY and LBdrafted the initial manuscript. QS and SY revised the

draft. All authors have read and approved the final manuscript.

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None declared.

References:

[1] Sung H, Ferlay J, Siegel RL, *et al*. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021;71:209-249.

[2] Cohen PA, Jhingran A, Oaknin A, *et al*. Cervical cancer. *Lancet* 2019; 393:169-182.

[3] Bray F, Ferlay J, Soerjomataram I, *et al*. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68:394–424.

[4] Jie H. China cancer registration annual report 2018[M], vol. 61. Beijing: People's Publishing House; 2019. p. 63.

[5] Schiffman M, Castle PE, Jeronimo J, *et al*. *Lancet* 2007; 370:890-907.

[6] WHO. Draft global strategy towards the elimination of cervical cancer as a public

health problem. https://www.who.int/docs/default-source/documents/cervical-cancer-elimination-draft-strategy.pdf?sfvrsn=380979d6_4 (accessed Oct 9, 2019).

[7] WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention, second edition [Internet]. Geneva: World Health Organization; 2021.

[8] Basu P, Taghavi K, Hu SY, *et al*. Management of cervical premalignant lesions. *Current problems in cancer* 2018;42:129-136.

[9] Rossman AH, Reid HW, Pieters MM, *et al*. Digital Health Strategies for Cervical Cancer Control in Low- and Middle-Income Countries: Systematic Review of Current Implementations and Gaps in Research. *J Med Internet Res* 2021;23:e23350.

[10] Johnson LG, Armstrong A, Joyce CM, *et al*. Implementation strategies to improve cervical cancer prevention in sub-Saharan Africa: a systematic review. *Implementation Science* 2018;13:1-18.

[11] Hu Z, Ding WC, Zhu D, *et al*. TALEN-mediated targeting of HPV oncogenes ameliorates HPV-related cervical malignancy. *J Clin Invest* 2014;125:425–36.

[12] Castle PE, Murokora D, Perez C, *et al*. Treatment of cervical intraepithelial lesions. *International Journal of Gynecology & Obstetrics* 2017;138:20–25.

[13] Papadakis VM, Lioukas S, Chambers D. Strategic decision-making processes: the role of management and context. *Strategic management journal* 1998;19:115–147.

[14] Elbanna S. The influence of decision, environmental and firm characteristics on the rationality of strategic decision-making. *Journal of Management Studies* 2007;44:4.

[15] Mazzocco K, Masiero M, Carriero MC, *et al*. The role of emotions in cancer

patients' decision-making. *Ecancermedicalscience* 2019;13:914.

[16] Nash K, Leota J, Tran A. Neural processes in antecedent anxiety modulate risk-taking behavior. *Scientific reports* 2021;11:2637.

[17] Junius-Walker U, Wiese B, Klaaßen-Mielke R, *et al*. Older patients' perceived burdens of their health problems: a cross-sectional analysis in 74 German general practices. *Patient preference and adherence* 2015;9:811–820.

[18] Glatzer M, Panje CM, Sirén C, *et al*. Decision Making Criteria in Oncology. *Oncology* 2018;98:370–378.

[19] Wang B, He M, Chao A, *et al*. Cervical cancer screening among adult women in China, 2010. *Oncologist* 2015;20:627–634.

[20] Zhu B, Liu Y, Zuo T, *et al*. The prevalence, trends, and geographical distribution of human papillomavirus infection in China: The pooled analysis of 1.7 million women. *Cancer Medicine* 2019;8:5373–5385.

[21] Kabadi SM, Goyal RK, Nagar SP, *et al*. Treatment patterns, adverse events, and economic burden in a privately insured population of patients with chronic lymphocytic leukemia in the United States. *Cancer medicine* 2019;8:3803–3810.

[22] Twomey R, Matthews TW, Nakoneshny SC, *et al*. From Pathways to Practice: Impact of Implementing Mobilization Recommendations in Head and Neck Cancer Surgery with Free Flap Reconstruction. *Cancers* 2021;13:2890.

[23] Giuliano AR, Lee JH, Fulp W, *et al*. Incidence and clearance of genital human papillomavirus infection in men (HIM): a cohort study. *Lancet (London, England)* 2011;377:932–940.

519 [24] Follen Mitchell, M. A randomized clinical trial of cryotherapy, laser vaporization,
520 and loop electrosurgical excision for treatment of squamous intraepithelial lesions of
521 the cervix. Obstetrics & Gynecology 1998;92:737–744.
522 [25] Namikawa K, Yoshio T, Yoshimizu S, *et al*. Clinical outcomes of endoscopic
523 resection of preoperatively diagnosed non-circumferential T1a-muscularis mucosae or
524 T1b-submucosa 1 esophageal squamous cell carcinoma. *Scientific reports* 2021;11:
525 6554.
526 [26] Brahmbhatt P, Sabiston CM, Lopez C, *et al*. Feasibility of prehabilitation prior to
527 breast cancer surgery: a mixed-methods study. Frontiers in oncology 2020;10:571091.
528 [27] Specialized Committee of Human Papilloma Virus Infection Diseases of Cross-
529 Strait Association of Precision Medicine of Fujian Province. Expert consensus on HPV
530 infection and HPV-associated diseases 2017. *J Med Postgra* 2017;12:1238-1241.
531 [28] Mast TC, Zhu X, Demuro-Mercon C, *et al*. Development and psychometric
532 properties of the HPV Impact Profile (HIP) to assess the psychosocial burden of HPV.
533 *Current medical research and opinion* 2009;25:2609-2619.
534 [29] Wang KL, Jeng CJ, Yang YC, *et al*. The psychological impact of illness among
535 women experiencing human papillomavirus-related illness or screening interventions.
536 *J Psychosom Obstet Gynaecol* 2010;31:16–23.
537 [30] Ferretti C, Sarti FM, Nitrini R, *et al*. An assessment of direct and indirect costs of
538 dementia in Brazil. *PLoS One* 2018;13:e0193209.
539 [31] Fleiss JL, Levin B, Paik MC. Statistical Methods for Rates and Proportions. Third
540 Edition. John Wiley & Sons. New York., 2003. p. 25.

[32] Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol 2006;3:77–101.

[33] Guralnik JM, Kritchevsky SB. Translating research to promote healthy aging: the complementary role of longitudinal studies and clinical trials. *J Am Geriatr Soc* 2010; 58:S337-S342.

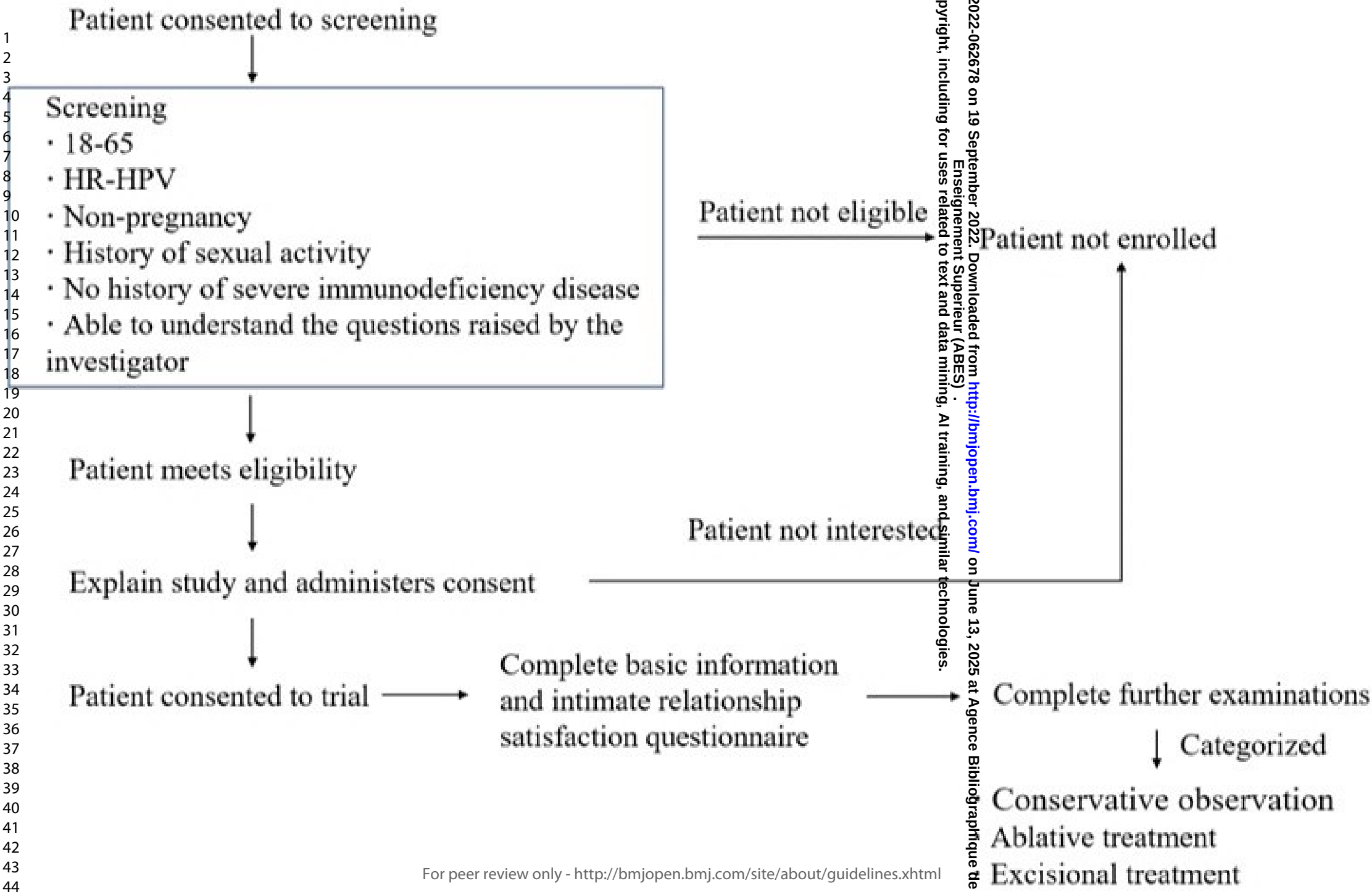
[34] Baloch Z, Yasmeen N, Li Y, et al. Knowledge and awareness of cervical cancer, human papillomavirus (HPV), and HPV vaccine among HPV-infected Chinese women. Medical science monitor: international medical journal of experimental and clinical research 2017;23:4269.

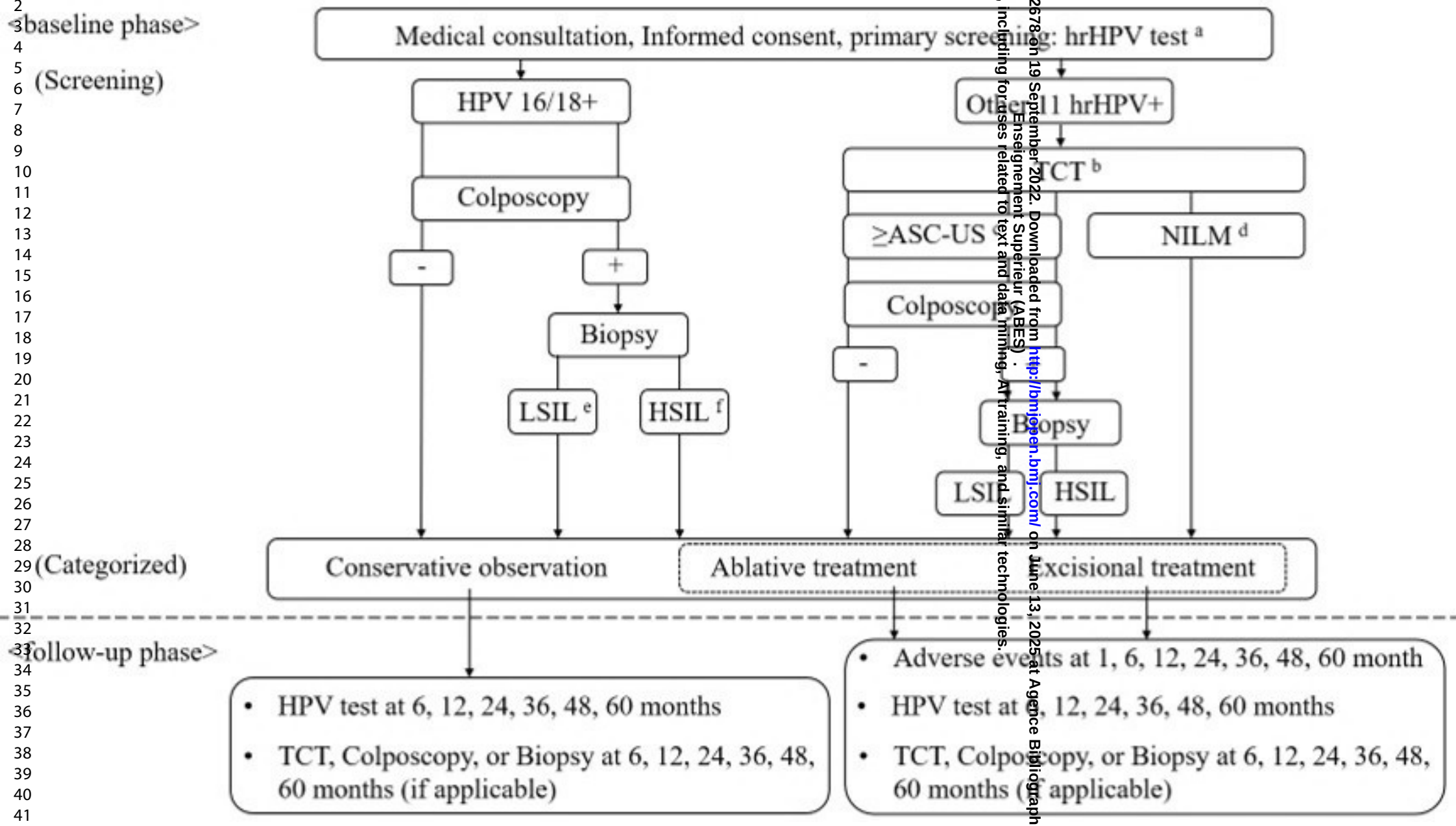
Figure Legends

Figure 1. Workflow for the recruitment procedure.

Figure 2. The specific examination procedures.[27]

Note: [a] hrHPV, high risk human papilloma virus; [b] TCT, thin-prep liquid-based cytologic test; [c] ≥*ASC-US*, atypical squamous cells of undetermined significance or above; [d] NILM, negative for intraepithelial lesions or malignancy; [e] LSIL, low-grade squamous intraepithelial lesion; [f] HSIL, high-grade squamous intraepithelial lesion.





Supplementary materials

Table S1. Definition of outcomes

Variables	Definition
Treatment patterns	(1) the number of patients who underwent conservative observation, that who underwent ablative treatment, and that who underwent excisional treatment; (2) the duration of each therapy regimen and the time to treatment initiation: The duration of treatment, the duration of each therapy regimen, and time to the initiation of treatment (the start of the initial regimen was the date of the first treatment and all treatments initiated within 90 days of that date). [6, 21]
Compliance with guidelines	Compliance with guideline, the primary outcome was the provider's adherence to the 2021 WHO guidelines for the screening, treatment, and management of patients with hrHPV infection. Compliance with guidelines refers to the proportion of patients who achieve the recommended treatment, as judged by 2 experienced gynaecological specialists. [22] Outcomes including: (1) the number of patients who received other specific treatments, including the duration of those other specific treatments; (2) the number of patients who received guideline-recommended treatment.
HPV status	The HPV clearance, persistence, and recurrence will be assessed via PCR. HPV clearance was defined as a participant testing HPV negative at two consecutive visits after testing positive. [23] The persistent disease was defined as the cytologic or histologic presence of HPV at the time of the second follow-up visit (within 6 months after treatment). Recurrent disease was defined as the cytologic or histologic presence of HPV diagnosed at a subsequent

	follow-up visit (at least 6 months after treatment) in a patient who had had at least one negative cytologic smear after treatment [24].
Adverse events	Adverse events will be recorded at 1 month, 6 months, 12 months, and 24 months after treatment onset. It including major infections or bleeding, procedure-associated pain, cervical stenosis, infertility, spontaneous abortion, perinatal deaths, premature rupture of membrane, unnecessary interventions, and increased viral shedding in women living with HIV. [7] The National Institutes of Health Common Terminology Criteria for Adverse Events (CTCAE; version 4.0) was used to grade severity of adverse events. Adverse events with CTCAE grade 3 or higher will consider to be serious.

Table S2. Numeric Results for Two-Sided CIs for One Proportion

n \ *p*	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
6000	0.015	0.020	0.023	0.025	0.025	0.025	0.023	0.020	0.015
3000	0.022	0.029	0.033	0.035	0.036	0.035	0.033	0.029	0.022

Notes: *p*, proportion of patients' treatment choices. n, sample size.

Table S3. Outcomes and other assessments

Outcomes	
HR-HPV testing	The HR-HPV subtypes were tested using the 21 HPV GenoArray Diagnostic Kit (Yaneng Biosciences, Shenzhen, China) from the Tianbo Biomedical Laboratory (Xian, China). This included testing on 13 high-risk subtypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68).
Thin-prep liquid-based cytology test (TCT)	Exfoliated cervical cells from women attending the gynaecological outpatient clinic were collected using a specialised cervical brush by a clinician. The cervical cells were detected using TCT, and the results of cytological pathology were diagnosed by senior physicians according to the Bethesda System of cervical cytology.
Cytological test	Standard colposcopic assessment will be performed when a cytological test is abnormal at the threshold of atypical squamous cells of an undetermined significance (or borderline dyskaryosis) or when the HPV 16/18 test result is positive. The colposcopic findings will be reported according to ASCCP terminology for colposcopic practice.
Pathological examination	For the pathological examination of the women who undergoing colposcopy, a biopsy will be performed only in cases with abnormal cervical findings, and if the colposcopy is unsatisfactory, a cervical curettage sample will be obtained.
Other assessments	
HIP	It consists of 29 items measuring worries and concerns, emotional impact, sexual impact, self-image, partner issues and transmission, interactions with doctors, and control/life impact.[28] The HIP item scales were linearly transformed to a scale of 0–100, and each item was a 0–10 point discretised analogue scale. The Mandarin Chinese version of the HIP questionnaire was generated through a

	standardised process and has been previously used in Taiwan.[29]
Intimate relationship satisfaction questionnaire	It contains two self-reported questions related to partner and sexual satisfaction. The scoring for each item ranges from very dissatisfied (0) to very satisfied (10).
Costs	The direct costs included patients' medication, health care, and other resources (such as time in seeking/receiving care and post-treatment recovery time). The costs of medication and health service utilisation will be calculated from the medical records using market prices. The indirect cost estimates of economic losses due to spending time on screening, examinations, and treatment are based on hourly wages per capita. [30]

Table S4. Interview guide

Roles	Research questions	Main topics	Probing questions
Patients	Can you talk about how you felt when you heard this diagnosis?	Attitudes to HPV	How would you prioritize goals as it relates to your HPV treatment? Do you have any concerns regarding your treatment? If so, what are they?
	Could you tell me about your experience of the treatment you received?	Treatment choices	Can you name the initial treatment you received? Did you have any other treatment? Can you tell me a little bit about the conversation you had with your doctor about your treatment? What were the reasons for choosing the treatment you did?
	What made you decide to change your treatment?	Nonadherence to treatment	What do you think the main reason is for these changes? Could you give some examples? Procedures? Something else?
Service providers	What do you know about the screen-and-treat approach guidelines recently issued by WHO?	Familiarity with guideline	What did you do when you got the most recently updated guideline? How did the screen-and-treat approach differ from that in the previous ones?
	Can you talk about how you make treatment decisions?	Treatment choices	What information has helped the treatment decision-making? Can you tell me a little bit about the conversation you had with your patients about their treatment decisions?
	What are the reasons for treatment deviation from the current WHO guidelines?	Nonadherence to guideline	Could you tell me why you didn't follow the WHO guidelines? What barriers have you encountered when you implementing the WHO guideline in your hospital?

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Profiling the real-world management status of high-risk human papillomavirus infection: A protocol to establish a prospective cohort of high-risk human papillomavirus-infected women in Lueyang County, China

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Profiling the real-world management status of high-risk human papillomavirus infection: A protocol to establish a prospective cohort of high-risk human papillomavirus-infected women in Lueyang County, China

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Abstract

Introduction: Persistent infection with high-risk human papillomavirus (hrHPV) is the main cause of cervical cancer. Thus, the effective treatment against HPV represents an opportunity to reduce the incidence of cervical cancer. Although various treatments are effective in treating HPV infection, they still provide limited benefit in reducing the rate of cervical cancer due to the lack of implementation of a standardised protocol in many low- and middle-income areas. This proposed cohort study aims to describe the status quo of treatment, attributions of the treatment decision-making process, and potential factors influencing treatment decisions.

Methods and analysis: This is a mixed method, 5-year prospective longitudinal study in Lueyang County, China, one of the areas with the highest cervical cancer incidence rates and lowest mean income in China. We will enroll hrHPV infection (at least one HPV type in the 13 high-risk subtypes) women diagnosed via a county-wide HPV infection and cervical cancer screening programme. The study procedures describe the treatment patterns and explore the potential influencing factors in treatment decision-making through questionnaires, laboratory examinations, and in-depth interviews. All participants will be evaluated at baseline and at six, 12, 24, 36, 48, and 60 months. The primary outcome is the treatment pattern, the type and duration of which will be described later. The secondary outcomes include guideline compliance and changes in the HPV infection status. The HPV impact profile, intimate relationship satisfaction, and costs within different management groups are also described and compared.

Ethics and dissemination: This study was reviewed, and all of the relevant approvals

were obtained from the Ethics Committee of the Maternity Service Centre of Lueyang Maternal and Child Health Care Hospital (2021-001). The findings from this study will be disseminated through peer-reviewed publications, conference presentations, and academic workshops.

Trial registration number: ChiCTR2100053757.

Strengths and limitations of this study

- To our knowledge, this is the first study to consider real-world data regarding the management patterns after diagnosing high-risk HPV infection among women in China.
- We will use a mixed method to explore different potential factors, revealing their internal influence mechanism on treatment decision-making options.
- Implementing this protocol will identify the gap between research and practice and determine why some patients did not receive the recommended therapies.
- It remains a challenge to sustain a high participation rate in a prospective cohort study; working outside the hometown and insufficient knowledge and awareness about the disease in Lueyang County would lead to the loss of participant follow-up.
- This is a community-based observational study of prospectively collected data from Lueyang County, China, so the study design increases the risk for the potential limitations of the presence of selection bias and a decreased generalisability of the findings to other populations.

INTRODUCTION

Cervical cancer ranks fourth among malignant tumours in females worldwide,[1] presenting a serious threat to women. Cervical cancer is a major public health concern.[2] Globally, there was an estimated incidence rate of 15.3 per 100,000 and a mortality rate of 7 per 100,000 for cervical cancer in 2018.[3] In China, the incidence rate is 10.88 per 100,000, and the mortality rate is 3.17 per 100,000.[4] Cervical cancer arises from four processes: human papillomavirus (HPV) infection, persistent HPV infection, multistage squamous intraepithelial lesions, and invasion through the basement membrane.[5] The World Health Organisation (WHO) is developing a global strategy, known as the 90–70–90 triple-intervention strategy, for eliminating cervical cancer as a public health problem by 2030.[6]

Currently, great progress has been made in the prevention of cervical cancer (e.g. HPV vaccination and cervical screening initiatives) and the development of several therapies for cervical cancer. For women who are already HPV-infected, the WHO guidelines recommend safe and effective treatment options, but these do not reach the women who need these services the most.[7-8] Several factors contribute to this failure in health service delivery, access, and utilisation, including a lack of a link between screening and treatment (compliance with treatment and follow-up), variability in service quality, and insufficient continuing education for service providers.[9-10] Thus, the implementation of the standardised management of hrHPV infection or HPV-caused precancerous lesions to reduce the prevalence of cervical cancer urgently needs to be

implemented.

Treatments for HPV infection and HPV-induced precancer lesions include conservative observation, ablative treatment (cryotherapy and thermal ablation), and excisional treatment (excision with a cold knife cone (CKC) and electrosurgical excision (LLETZ or LEEP)).[7, 11] Several studies have shown that patients with HPV infection or benign lesions can undergo tissue destruction by thermal (hot or cold), electrical, or chemical means, the success rates for which vary widely, and the variability of the inclusion criteria for each study hampers establishing a standardised management protocol.[8,12] The quality of evidence for all outcomes is low to very low, and the level of heterogeneity is high in all pooled analyses. For instance, although all currently used ablative techniques are effective in reducing cancer risk, there is a lack of data on the long term effectiveness of therapies, reasons for treatment failure, and cost-effectiveness of therapies.

For these reasons, there remains a lack of sufficient real-world evidence to support clinicians and patients in providing optimal treatment decision-making recommendations. Various factors can shape treatment decisions, including decision-maker characteristics, decision-specific criteria, and contextual factors.[13-14] The first are the decision-maker characteristics, including those for both the providers and patients, such as capabilities (i.e. knowledge of HPV), emotions (i.e. worry, anxiety, or stigma from HPV infection), and degree of expertise (i.e. benefits and limitations of

each treatment).[15-16] Second, decision-specific criteria involve classical clinical criteria, such as age, HPV type, duration of infection, sex, or expected treatment complications (i.e. adhesions or bleeding).[17] Contextual factors include the patient's socioeconomic status, healthcare system, treatment costs, and perceived support (i.e. intimate relationships).[18] Currently, it is not yet clear which patient factors affect treatment decision-making after testing positive for HPV.

The All-China Women's Federation and the Ministry of Health launched the 'Two Cancers' (cervical cancer and breast cancer) screening programme in July 2009, which implemented a free cervical cancer screening programme for rural women aged 35–64 years. This programme involved publicity, health education, and examinations.[19] In recent years, with the popularisation of cervical cancer screening, the incidence of cervical cancer in some areas of China has been effectively controlled. Lueyang County is a low-income area in China with high morbidity and mortality rates for cervical cancer. The incidence of cervical cancer has shown a decreasing trend in recent years; however, the morbidity and mortality of the disease remain high. The high prevalence rate of HPV infection (18.5%) in this region was higher than the national overall prevalence rate of HPV infection (15.54%).[20] We still do not know why morbidity or mortality is higher, and how to provide services to patients in this county. Furthermore, the standard of care for HPV and cervical lesions provided in China and how it deviates from the WHO recommendations remains unclear.

Thus, we propose to establish a prospective cohort for women infected with high-risk HPV in Lueyang, Shaanxi, aiming to (1) profile the treatment patterns and adherence to guideline-concordant management for hrHPV infection in the real-world setting, (2) identify the characteristics that associated with treatment decision-making for hrHPV infection, (3) explore the reasons for treatment choices, including initial regimen, switch, and treatment termination, and (4) evaluate the long term effects of different treatment approaches. The results will provide real-world evidence to support optimal decision-making in the treatment of hrHPV infection and, ultimately, strive to achieve the goal of '90% of women with precancer treated', which was proposed by the WHO in its Cervical Cancer Elimination Initiative.

METHODS AND ANALYSIS

Study design and setting

This mixed method, prospective cohort study with a 5-year follow-up, will take place in Lueyang County, one of the economically underdeveloped regions in Shaanxi Province, China. Lueyang County has a high prevalence of HPV infection. All women between 18-65 years old in the county are invited to participant a local government-supported cervical screening programme. The cervical screening services are managed by gynaecologists at the Maternity Service Centre of Lueyang Maternal and Child Health Care Hospital. The study was approved by the Maternity Service Centre of Lueyang Maternal and Child Health Care Hospital, and it was started on 4 November

2021 and is planned to be completed by 31 November 2026.

During the screening phase, women aged 18–65 years are recruited through a cervical screening service by gynaecologists and nurses. Basic information, hrHPV testing, and inclusion evaluations will be performed. The women diagnosed with hrHPV infection during the screening phase will be invited to participate in the study. Written informed consent will be obtained from the women regarding their participation in this prospective cohort study (including the procedures, risks, and options for dropping out of the study). Medical staff with adequate training will clearly explain the study protocol and objectives to the participants. After providing consent, each patient must sign an informed consent form. Subsequently, a participant identification (PID) number will be assigned to facilitate the study, and the other examinations will be performed. In the categorized phase, according to the outcomes of examinations and treatment decision-making, all patients will be divided into conservative observation, ablative treatment, and excisional treatment groups. Figure 1 shows the recruitment process that will be used.

Eligibility criteria

The inclusion criteria are as follows: (1) women aged 18–65 years, who had lived for 5 years in Lueyang County, (2) a diagnosis of hrHPV infection (including 13 subtypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68; participants with at least one HPV type in the high-risk group) in the screening phase, (3) non-pregnancy, (4) history of

sexual activity, (5) no history of severe immunodeficiency disease, and (6) able to understand the questions asked by the investigator.

The exclusion criteria are as follows: (1) refusal to participate in this study, (2) a diagnosis of cervical cancer, (3) other malignant tumours or serious illness, and (4) a diagnosis of mental illness or impaired consciousness.

Definition of outcomes

This study will assess the treatment patterns, compliance with guidelines, and HPV status. (For detailed information, see Supplementary Material Table S1.) [21-24] Patients in the conservative observation group will undergo routine follow-up. [25] The patients will be observed without any additional treatment. Ablative treatments include cryotherapy and thermal ablation.[6] Abnormal tissue is destroyed by heating with thermal coagulation or freezing with cryotherapy. Excisional treatment involves the surgical removal of abnormal tissue with LLETZ or CKC.[6] Switching was defined as a change to a different treatment before completing the assigned course of treatment. The switch could be to any treatment (observation, ablative, or excisional treatment). The time-to-switch was defined as the period from the date of the first treatment regimen to the date of switch to another treatment regimen during the study period.

Sampling strategy

All women meeting the inclusion criteria will be recruited for the study and followed-

up for five years. Management patterns describe using proportion and 95% two-sided exact confidence intervals (95% CI). With an estimation that among the total 40,000 women aged 18–65 years in Lueyang County, 18.5% will be diagnosed with hrHPV infection, a total of 7500 women will be eligible for the study. Considering a 20% (up to 40%) attrition rate [26], we will end up with 6000 (at least 3000) women in the cohort. Since the proportion of patients' treatment choice is unknown, varying proportions produce different actual widths as follows (see Supplementary Material Table S2), the CI width was determined by PASS (version 15) with the following parameter settings: CI formula, exact (Clopper-Pearson); confidence level (1-alpha), 0.95; proportion, 0.1 to 0.9 by 0.1. A priori, we determined that feasibility would be confirmed with (1) a recruitment rate of >60% [26]; and (2) attrition rate <40%.

Data collection

The data collection protocol will be performed according to the list outlined in Table 1. All data will be obtained by physicians at the hospital. The participants underwent a comprehensive physical examination and completed a questionnaire through face-to-face interviews. All biochemical test results (HPV testing, TCT, colposcopy, and pathological examination) and sexually transmitted diseases (syphilis and HIV) will be obtained from the hospital records. Follow-up visits will be conducted at six, 12, 24, 36, 48, and 60 months.

Table 1. Data collection schedule

Procedure	Visit 1	Visit 2	Visit 3	Visit 4-8
	Screening	Baseline	Month one	Month 6-60
Eligibility criteria	×			
Research participants consent	×			
Individual Information				
Demographic variables	×			
Menstrual history	×			
Marital history	×			
Personal hygiene behaviour	×			
Gynaecological examinations		×		
HPV knowledge	×			
HPV infection	×			
Regular examination	×			
HPV vaccination	×			
Physicians' knowledge regarding treatment		×		
Partner information	×			
Outcomes				
Primary outcome				
Treatment patterns		×		×
Secondary outcomes				

HPV testing	×			×
TCT		○		○
Colposcopy		○		○
Pathological examination		○		○
Adverse events			○	○
Other assessments				
Intimate relationship satisfaction	×			×
HIP		×		×
Costs				×

Notes: HPV, human papillomavirus. TCT, Thin-prep liquid-based cytology test. HIP, the HPV impact profile. ○, if applicable.

Measures

Baseline

The baseline data includes the individual information, characteristics, and laboratory data. Individual data will be collected through a health interview survey and medical records. Demographic variables, such as age, education level, occupation, annual income, ethnicity, and religion, will be used in the analysis, as data concerning smoking status, alcohol consumption, sexual history (total number of sexual partners, frequency of sexual life, and forms of contraception), HPV vaccination history (type of vaccine and vaccinated person-time), and hygiene habits (i.e. frequency and manner of bathing).

Other basic information, such as menstrual history (i.e. time to menarche/menopause), marital history, HPV knowledge (HPV infection, regular examination, and HPV vaccination), physicians' knowledge regarding treatment (benefits and limitations of all treatments), partner information, and gynaecological examinations (i.e. lesions of the vulva, vagina, vaginal secretions, cervix, cervical polyps, uterus, uterine accessories, vaginal cleanliness, and sexually transmitted disease type), will also be assessed. All eligible patients will undergo gynaecological examinations.

Outcomes

Laboratory data, clinical characteristics, and use of therapies will be assessed in the hospital, and all laboratory examinations will be performed during the non-menstrual period. All outcomes will be collected by gynaecological outpatient doctors, and the diagnoses will be made by a specialised gynaecologic pathologist. Treatment patterns, as the primary outcome, will be collected by receiving the available data on the history of therapies from all eligible patients. Secondary outcomes include the clinical characteristics (HPV status, cytology, colposcopy, biopsy results, and adverse events) and other assessments (HPV impact profile, intimate relationship satisfaction, and costs, see the Supplementary Material Table S2). The specific examination procedures were as follows (Figure 2) [27]:

Other assessments

The HPV impact profile (HIP), a self-reported scale, is designed to represent the full

spectrum of potential HPV-related impacts. [28-29] An intimate relationship satisfaction questionnaire, a self-made satisfaction questionnaire, is used employed to estimate the satisfaction of patients with HPV infection. Direct and indirect costs will be estimated using medical information [30] related to cervical screening, diagnosis, and treatment of HPV and cervical lesions. The details are provided in the Supplementary Material Table S3.

A semi-structured interview guide (see Supplementary Material Table S4) has been developed for women with hrHPV infection and service providers. The initial questions on the guide will help explore participants' perceptions and attitudes towards HPV infection. Additional questions on the guide will assess the impact of these perceptions and attitudes on treatment choices, treatment switching, and nonadherence to guidelines. All semi-structured interviews will be conducted face-to-face or via phone. Interviews will be scheduled based on the participant's convenient day and time. Interviews are anticipated to begin on 1 August 2022.

Quality control

The investigators received training on the standard operating procedure before patient recruitment was performed. A standardised operation process manual and operation video were created and distributed to all of the research assistants. There will be a question-and-answer session to solve operation problems after approximately ten patients are enrolled. In addition, the research assistants will provide feedback on a

daily basis for patients who had submitted problems within the working group.

Data management and analysis

All participants will be allocated a PID code at enrolment, which will be used in the samples and documents over the 5-year study period. All data will be collected and managed using an electronic data management platform protected by the firewall of Chongqing Medical University. The data on the platform will be accessible only by authorised researchers using private accounts and passwords. Any change will be automatically recorded in the platform log and saved as a separate file for data monitoring purposes. For the data export process, the de-identification of patient health information will be conducted following the HIPAA rule. An independent safety monitoring board will be established when the study begins, and will monitor safety throughout the study period. The data will be verified by double-checking for erroneous or missing values, and data analysis will be performed using SAS version 9.1.3 (SAS Institute, Cary, NC, USA).

The demographic and clinical characteristics of the participants will be summarised using the mean and standard deviation for continuous variables. For categorical variables, the proportion (%) will be reported. Significant associations in the contingency tables (cross-tabulations) will be assessed using standard Pearson's χ^2 test. Analysis of variance will be used to compare differences in the continuous variables among the three groups. The patient demographics, clinical characteristics, treatment

therapies (to identify the most common treatments and durations), and guideline adherence will be descriptively reported. In addition, we may apply growth mixture modelling to observe whether subsets of individuals follow distinct trajectories over time. Analyses were performed for the entire cohort and stratified by treatment patterns, occurrence of switching, and HPV types (16/18+ or other 11 subtypes +).

Management patterns will be described as the proportion and 95% exact CI (95% CI). For this method, p will be the population proportion, and r represents the number of successes from a sample of size n. Let $p\hat{}$ = r /n. Exact test (Clopper-Pearson) using a mathematical relationship.[31] between the F distribution and the cumulative binomial distribution, and the lower and upper confidence limits of a 100(1-α) % exact confidence interval for the true proportion p are given by

$$\left[\frac{r}{r+(n-r+1)F_{1-\alpha/2;2(n-r+1),2r}}, \frac{(r+1)F_{1-\alpha/2;2(r+1),2(n-r)}}{(n-r)+(r+1)F_{1-\alpha/2;2(r+1),2(n-r)}}\right]$$

Multivariate logistic regression models will be used to estimate the potential factors influencing the treatment choices, including the personal information (sexual history, HPV vaccination history (type of vaccine and vaccinated person-time)), decision-maker characteristics (patient and physician), specific criteria (13 high-risk HPV subtypes, duration of infection, and adverse events), and contextual factors (patient's socioeconomic status, treatment costs, and perceived support [i.e. intimate relationships]). Pearson's χ^2 statistics will be used to compare the treatment differences

in clearance, recurrence, and persistence rates among the groups.

Qualitative data will be transcribed verbatim and analysed using thematic analysis. [32] At this stage, a bottom-up inductive approach will be used to identify patterned meanings in the dataset within an essentialist framework to report the experiences, meanings, and realities of the participants. NVivo software (Version 11, QSR International, Doncaster, Australia) will be used to import, organise, and explore the data for analysis. An iterative process will be employed to label data and identify emerging themes. To ensure inter-rater reliability, two independent investigators will perform the coding, category creation and thematic analyses. The team will liaise several times to review themes and subthemes, resolve discrepancies, and decide on the final definitions of themes and subthemes.

At each follow-up, the proportion of patients who received guideline-concordant care will be assessed. The proportion of patients having experienced an event at specific time points (6, 12, 24, 36, 48, and 60 months) will be derived from the switching rates. Kaplan–Meier curve will be used to estimate the median time-to-switch with relevant treatment events as a treatment switch, 95% confidence intervals (CIs) for median times to event will be computed. Multivariate analysis of the switching factors (decision-maker characteristics, decision-specific criteria, and contextual factors) will be tested using Cox regression analysis.

Pearson's χ^2 statistics will be used to compare the treatment differences in clearance, recurrence, and persistence rates among the groups. The Kaplan–Meier method will be used to construct the cumulative clearance rate of HPV from the date of the first HPV diagnosis to the date of HPV clearance in each treatment group. A proportional hazards model will be fitted to evaluate the effects of treatment options and other predictors on the overall persistence and recurrence of HPV, and possible interaction terms of the main effects will be tested by comparing a reduced model with the full model. Adverse events will be compared among the different groups. Data will be reported as medians and interquartile ranges or as numbers and percentages. All comparisons will be evaluated using Wilcoxon signed rank test with continuity correction.

Missing data will be identified and reported as percentages. We will also include several other key parameters (discount rate, annual number of screened women, screening positivity rate, biopsy rate, and programmatic costs) in the one-way sensitivity analysis.

Patient and public involvement

The patients and the public were not involved in the development of the research questions or the design and analysis of the study. The extent of patient involvement in the study included answering the survey questionnaires at baseline and each follow-up. The results will be disseminated to the applicants in the form of a published article, which will be made available upon request.

Ethics and dissemination

Ethical approval for the study was obtained from the Biomedical Research Ethics Committee of the Maternity Service Centre of Lueyang Maternal and Child Health Care Hospital. All participants fulfilling the inclusion criteria will commence as full ethics approval is received from the Biomedical Research Ethics Committee. No other independent ethics reviews were conducted. The results of this study will be disseminated in peer-reviewed journals and conferences. We will provide clinicians with feedback following the peer-review process to further strategies optimal treatment decision-making.

DISCUSSION

Women are currently concerned about cervical cancer, owing to its increasing incidence and high mortality in low- and middle-income areas. Despite the availability of safe and effective methods for treating premalignant conditions, real-world evidence of treatment effects in low- and middle-income areas remains limited. To our knowledge, there are no real-world data regarding patients' treatment patterns after being diagnosed with hrHPV infection among women in these regions, and the characteristics that affect their decision-making process are rarely reported. In this study, we focus on the characteristics of clinical outcomes in different treatment groups and the relationship between decision-making and the individual's characteristics in terms of individual behaviours, psychological trajectories, and economic burden. Hence, this study is able to evaluate how these factors influence the patient's decision-making process. It will

also allow us to study the research-to-practice of discordance in greater detail with the ultimate goal of uncovering the underlying causes of discrepancies between these formal recommendations and current practices.

Decision-making has acquired crucial importance in disease management over the last 20 years since the introduction of the patient-centred principle. A variety of factors can shape treatment decisions, which include decision-maker characteristics, decision-specific criteria, and contextual factors.[13] Previous studies have stated that there are a variety of factors that influence treatment decisions in oncological diseases and other diseases, such as capabilities, emotions, age, expected treatment risk, the healthcare system, and treatment costs.[18] Little is known about the predictive factors for decision making in women undergoing hrHPV testing. This study intends to include different influencing factors to reveal their internal influence mechanism on decision-making options. The qualitative findings of this study will help us explore the perceptions and attitudes toward HPV infection and its impact on the individuals' treatment choices. Moreover, we will gain an in-depth understanding of gynaecological care needs, which will aid us in developing context-specific programmes for patients infected with hrHPV in low socioeconomic areas in future. We expect that the results can inform clinical practice with the provision of predictive algorithms that provide physicians with a clear profile of the patient at present and their probable trajectory in the long term.

This study has several strengths. First, it provides a comprehensive understanding of the therapeutic status quo in hrHPV infection and the possible underlying mechanisms involved, including the treatment patterns and disease outcomes under different treatment decisions. Second, this prospective cohort study has a long follow-up period. Therefore, this study may assist in determining causal associations between the predicted determinants of treatment decision-making and can be used to obtain trajectories of how patients' conditions influence decision-making over time.[33] Describing and analysing time-invariant and time-variant factors that predict improvement or deterioration in these trajectories will help identify potentially modifiable risk factors for future interventions, as well as patients at risk for poor outcomes. Third, this study identifies the gap between research and practice and why some patients did not receive recommended therapies. It provides an effective mechanism to ensure high compliance to treatment and also provides an opportunity to reduce cervical cancer incidence and mortality in low- and middle-income areas.

High participation rates at follow-up are critical for the validation of cohort studies. A challenge we anticipate is the loss of follow-up, which is generally a common failure in longitudinal studies. The six-month, 12-month, 24-month, 36-month, 48-month, and 60-month follow-up appointments may remain difficult to sustain for the following reasons: (1) some adults in rural areas leave their hometowns to work in cities, which means some data could not be collected promptly; (2) insufficient attention paid by patients, which might be related to the insufficient knowledge and awareness about the

disease reported in China.[34] Maintaining follow-up visits is a challenge we anticipate. A research assistant will communicate regularly with the recruited participants through WeChat, the most popular messaging and calling app, allowing one-to-one communication. The research assistant will confirm the appointment dates and send out reminders the week prior. We will offer payment to cover transport expenses and meals on the day of the visits to help increase the adherence of the participants to the protocol schedule. Discordant results and previous treatments will be recorded, and their treatment regimen will depend solely on their behaviours. After this descriptive study, we will provide health education to raise women's treatment adherence and clinician's guideline adherence. During the study, participants diagnosed with cervical cancer will be referred to anticancer treatments but will continue follow-up assessments, noting the change in their disease status.

Overall, we can explore treatment patterns and their association with individual characteristics and unravel the changing trajectory of potential factors that affect decision-making. Most importantly, new real-world insights will be provided regarding the role of tailored disease management in the prevention and treatment of hrHPV infections. These results imply that standardised management could help to reduce the prevalence of cervical cancer in the future. These data may help inform future clinical trial designs, highlight the need for better adherence to treatment guidelines, and inform clinical decision-making.

Authors' Contributions:

QS, SY, RZ, and WX contributed to the study design. LB, DH, RZ, SY, YN and RX performed the study. SY and LBdrafted the initial manuscript. QS and SY revised the draft. All authors have read and approved the final manuscript.

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Competing Interests Statement:

None declared.

References:

[1] Sung H, Ferlay J, Siegel RL, *et al*. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021;71:209-249.

[2] Cohen PA, Jhingran A, Oaknin A, *et al*. Cervical cancer. *Lancet* 2019; 393:169-182.

[3] Bray F, Ferlay J, Soerjomataram I, *et al*. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68:394–424.

[4] Jie H. China cancer registration annual report 2018[M], vol. 61. Beijing: People's

Publishing House; 2019. p. 63.

[5] Schiffman M, Castle PE, Jeronimo J, *et al*. *Lancet* 2007; 370:890-907.

[6] WHO. Draft global strategy towards the elimination of cervical cancer as a public health problem. https://www.who.int/docs/default-source/documents/cervical-cancer-elimination-draft-strategy.pdf?sfvrsn=380979d6_4 (accessed Oct 9, 2019).

[7] WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention, second edition [Internet]. Geneva: World Health Organization; 2021.

[8] Basu P, Taghavi K, Hu SY, *et al*. Management of cervical premalignant lesions. *Current problems in cancer* 2018;42:129-136.

[9] Rossman AH, Reid HW, Pieters MM, *et al*. Digital Health Strategies for Cervical Cancer Control in Low- and Middle-Income Countries: Systematic Review of Current Implementations and Gaps in Research. *J Med Internet Res* 2021;23:e23350.

[10] Johnson LG, Armstrong A, Joyce CM, *et al*. Implementation strategies to improve cervical cancer prevention in sub-Saharan Africa: a systematic review. *Implementation Science* 2018;13:1-18.

[11] Hu Z, Ding WC, Zhu D, *et al*. TALEN-mediated targeting of HPV oncogenes ameliorates HPV-related cervical malignancy. *J Clin Invest* 2014;125:425–36.

[12] Castle PE, Murokora D, Perez C, *et al*. Treatment of cervical intraepithelial lesions. *International Journal of Gynecology & Obstetrics* 2017;138:20–25.

[13] Papadakis VM, Lioukas S, Chambers D. Strategic decision-making processes: the role of management and context. *Strategic management journal* 1998;19:115–147.

[14] Elbanna S. The influence of decision, environmental and firm characteristics on the rationality of strategic decision-making. *Journal of Management Studies* 2007;44:4.

[15] Mazzocco K, Masiero M, Carriero MC, *et al*. The role of emotions in cancer patients' decision-making. *Ecancermedicalscience* 2019;13:914.

[16] Nash K, Leota J, Tran A. Neural processes in antecedent anxiety modulate risk-taking behavior. *Scientific reports* 2021;11:2637.

[17] Junius-Walker U, Wiese B, Klaaßen-Mielke R, *et al*. Older patients' perceived burdens of their health problems: a cross-sectional analysis in 74 German general practices. *Patient preference and adherence* 2015;9:811–820.

[18] Glatzer M, Panje CM, Sirén C, *et al*. Decision Making Criteria in Oncology. *Oncology* 2018;98:370–378.

[19] Wang B, He M, Chao A, *et al*. Cervical cancer screening among adult women in China, 2010. *Oncologist* 2015;20:627–634.

[20] Zhu B, Liu Y, Zuo T, *et al*. The prevalence, trends, and geographical distribution of human papillomavirus infection in China: The pooled analysis of 1.7 million women. *Cancer Medicine* 2019;8:5373–5385.

[21] Kabadi SM, Goyal RK, Nagar SP, *et al*. Treatment patterns, adverse events, and economic burden in a privately insured population of patients with chronic lymphocytic leukemia in the United States. *Cancer medicine* 2019;8:3803–3810.

[22] Twomey R, Matthews TW, Nakoneshny SC, *et al*. From Pathways to Practice: Impact of Implementing Mobilization Recommendations in Head and Neck Cancer Surgery with Free Flap Reconstruction. *Cancers* 2021;13:2890.

519 [23] Giuliano AR, Lee JH, Fulp W, *et al*. Incidence and clearance of genital human
520 papillomavirus infection in men (HIM): a cohort study. *Lancet (London, England)*
521 2011;377:932–940.
522 [24] Follen Mitchell, M. A randomized clinical trial of cryotherapy, laser vaporization,
523 and loop electrosurgical excision for treatment of squamous intraepithelial lesions of
524 the cervix. Obstetrics & Gynecology 1998;92:737–744.
525 [25] Namikawa K, Yoshio T, Yoshimizu S, *et al*. Clinical outcomes of endoscopic
526 resection of preoperatively diagnosed non-circumferential T1a-muscularis mucosae or
527 T1b-submucosa 1 esophageal squamous cell carcinoma. *Scientific reports* 2021;11:
528 6554.
529 [26] Brahmbhatt P, Sabiston CM, Lopez C, *et al*. Feasibility of prehabilitation prior to
530 breast cancer surgery: a mixed-methods study. Frontiers in oncology 2020;10:571091.
531 [27] Specialized Committee of Human Papilloma Virus Infection Diseases of Cross-
532 Strait Association of Precision Medicine of Fujian Province. Expert consensus on HPV
533 infection and HPV-associated diseases 2017. *J Med Postgra* 2017;12:1238-1241.
534 [28] Mast TC, Zhu X, Demuro-Mercon C, *et al*. Development and psychometric
535 properties of the HPV Impact Profile (HIP) to assess the psychosocial burden of HPV.
536 *Current medical research and opinion* 2009;25:2609-2619.
537 [29] Wang KL, Jeng CJ, Yang YC, *et al*. The psychological impact of illness among
538 women experiencing human papillomavirus-related illness or screening interventions.
539 *J Psychosom Obstet Gynaecol* 2010;31:16–23.
540 [30] Ferretti C, Sarti FM, Nitrini R, *et al*. An assessment of direct and indirect costs of

dementia in Brazil. *PLoS One* 2018;13:e0193209.

[31] Fleiss JL, Levin B, Paik MC. Statistical Methods for Rates and Proportions. Third Edition. John Wiley & Sons. New York., 2003. p. 25.

[32] Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol 2006;3:77–101.

[33] Guralnik JM, Kritchevsky SB. Translating research to promote healthy aging: the complementary role of longitudinal studies and clinical trials. *J Am Geriatr Soc* 2010; 58:S337-S342.

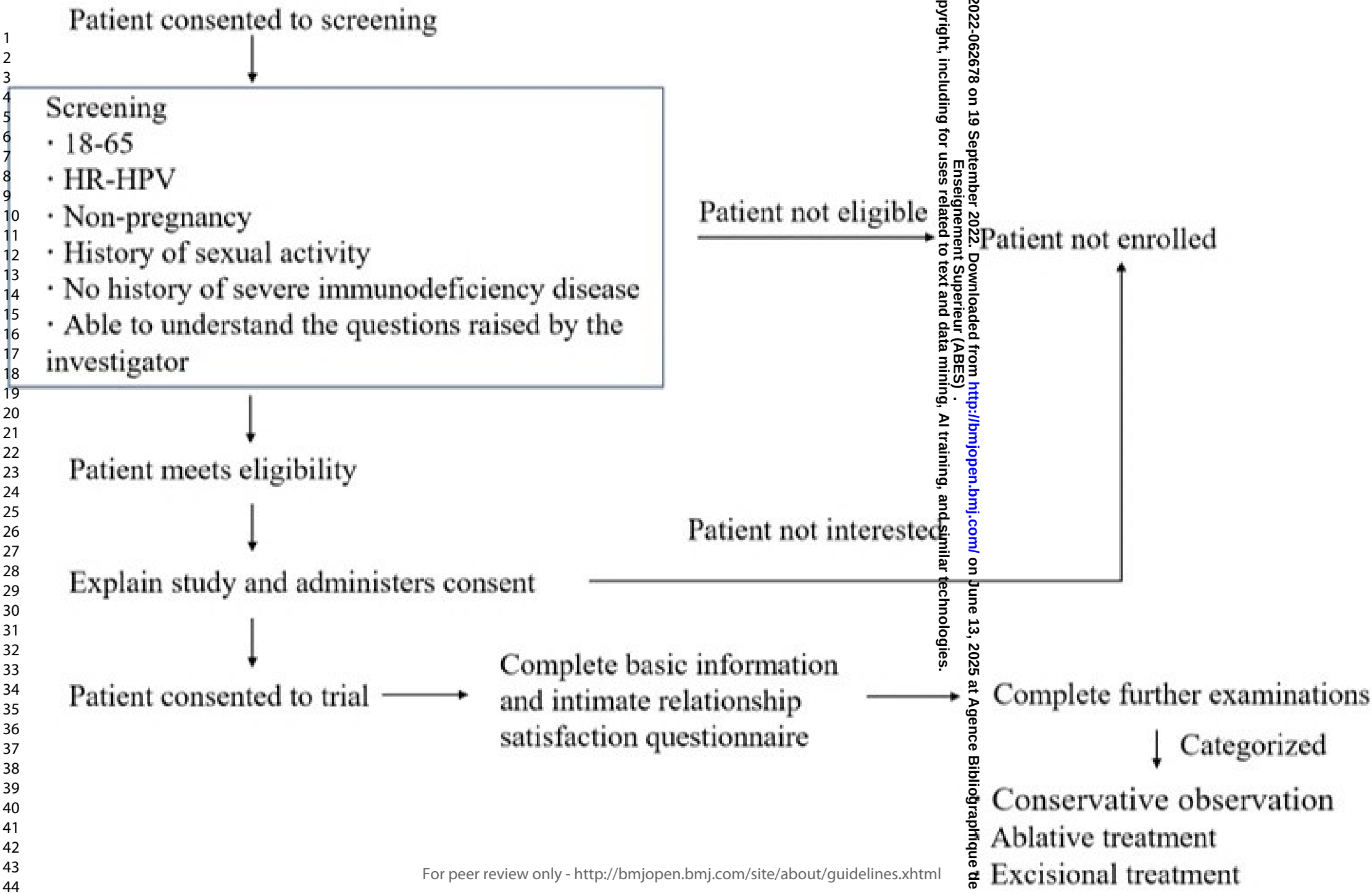
[34] Baloch Z, Yasmeen N, Li Y, et al. Knowledge and awareness of cervical cancer, human papillomavirus (HPV), and HPV vaccine among HPV-infected Chinese women. Medical science monitor: international medical journal of experimental and clinical research 2017;23:4269.

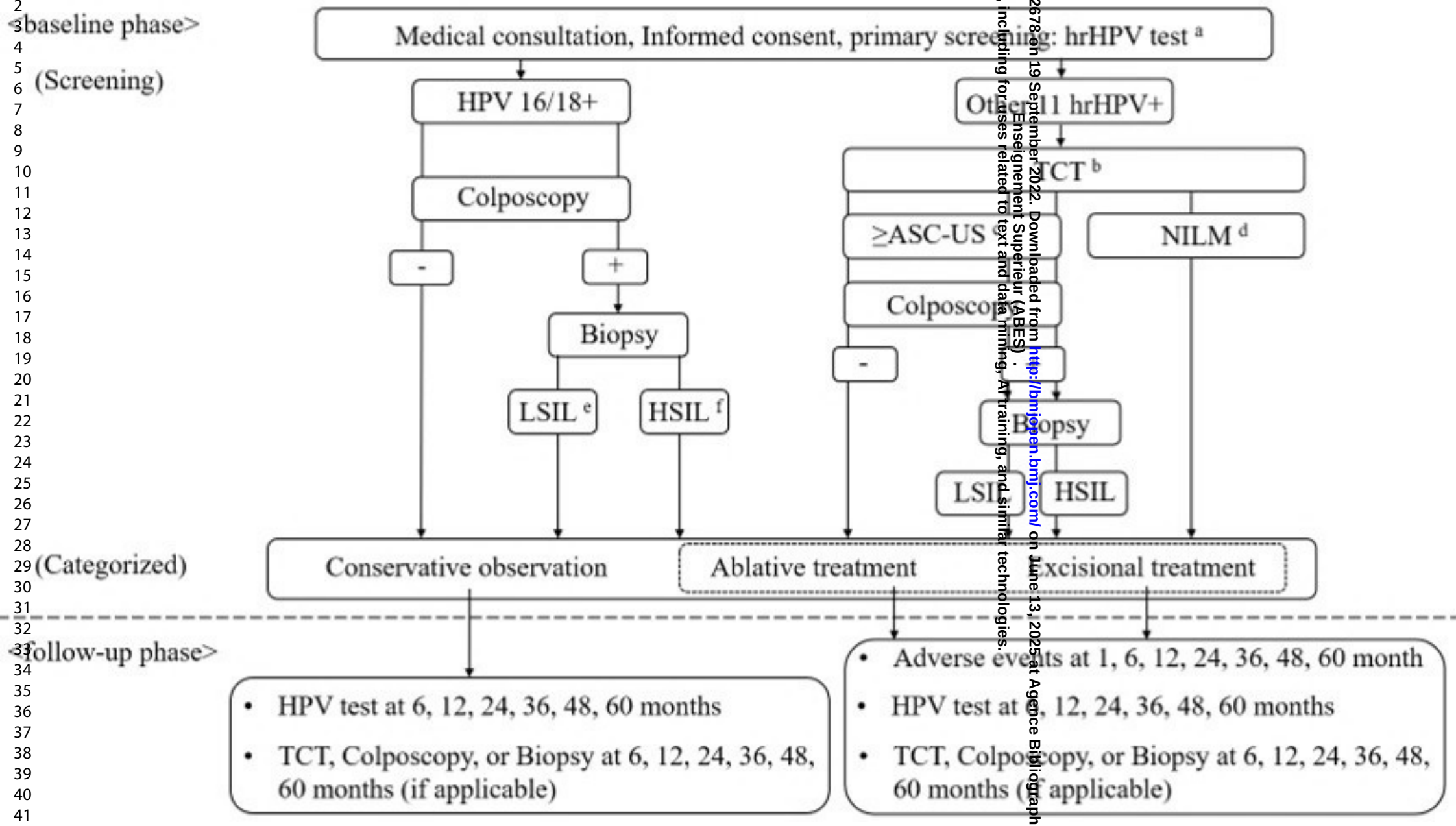
Figure Legends

Figure 1. Workflow for the recruitment procedure.

Figure 2. The specific examination procedures.[27]

Note: [a] hrHPV, high risk human papilloma virus; [b] TCT, thin-prep liquid-based cytologic test; [c] ≥*ASC-US*, atypical squamous cells of undetermined significance or above; [d] NILM, negative for intraepithelial lesions or malignancy; [e] LSIL, low-grade squamous intraepithelial lesion; [f] HSIL, high-grade squamous intraepithelial lesion.





Supplementary materials

Table S1. Definition of outcomes

Variables	Definition
Treatment patterns	(1) the number of patients who underwent conservative observation, that who underwent ablative treatment, and that who underwent excisional treatment; (2) the duration of each therapy regimen and the time to treatment initiation: The duration of treatment, the duration of each therapy regimen, and time to the initiation of treatment (the start of the initial regimen was the date of the first treatment and all treatments initiated within 90 days of that date). [6, 21] If the previous treatment has finished before 90 days of screening date, it will only be recorded and we will treat new option as the initial regimen. If the previous treatment has not finished within 90 days of screening date, we will treat it as the initial regimen to follow-up.
Compliance with guidelines	Compliance with guideline, the primary outcome was the provider's adherence to the 2021 WHO guidelines for the screening, treatment, and management of patients with hrHPV infection. Compliance with guidelines refers to the proportion of patients who achieve the recommended treatment, as judged by 2 experienced gynaecological specialists. [22] Outcomes including: (1) the number of patients who received other specific treatments, including the duration of those other specific treatments; (2) the number of patients who received guideline-recommended treatment.
HPV status	The HPV clearance, persistence, and recurrence will be assessed via PCR. HPV clearance was defined as a participant testing HPV negative at two consecutive visits after testing positive. [23] The

	persistent disease was defined as the cytologic or histologic presence of HPV at the time of the second follow-up visit (within 6 months after treatment). Recurrent disease was defined as the cytologic or histologic presence of HPV diagnosed at a subsequent follow-up visit (at least 6 months after treatment) in a patient who had had at least one negative cytologic smear after treatment [24].
Adverse events	Adverse events will be recorded at 1 month, 6 months, 12 months, and 24 months after treatment onset. It including major infections or bleeding, procedure-associated pain, cervical stenosis, infertility, spontaneous abortion, perinatal deaths, premature rupture of membrane, unnecessary interventions, and increased viral shedding in women living with HIV. [7] The National Institutes of Health Common Terminology Criteria for Adverse Events (CTCAE; version 4.0) was used to grade severity of adverse events. Adverse events with CTCAE grade 3 or higher will consider to be serious.

Table S2. Numeric Results for Two-Sided CIs for One Proportion

n \ *p*	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
6000	0.015	0.020	0.023	0.025	0.025	0.025	0.023	0.020	0.015
3000	0.022	0.029	0.033	0.035	0.036	0.035	0.033	0.029	0.022

Notes: *p*, proportion of patients' treatment choices. n, sample size.

Table S3. Outcomes and other assessments

Outcomes	
HR-HPV testing	The HR-HPV subtypes were tested using the 21 HPV GenoArray Diagnostic Kit (Yaneng Biosciences, Shenzhen, China) from the Tianbo Biomedical Laboratory (Xian, China). This included testing on 13 high-risk subtypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68).
Thin-prep liquid-based cytology test (TCT)	Exfoliated cervical cells from women attending the gynaecological outpatient clinic were collected using a specialised cervical brush by a clinician. The cervical cells were detected using TCT, and the results of cytological pathology were diagnosed by senior physicians according to the Bethesda System of cervical cytology.
Cytological test	Standard colposcopic assessment will be performed when a cytological test is abnormal at the threshold of atypical squamous cells of an undetermined significance (or borderline dyskaryosis) or when the HPV 16/18 test result is positive. The colposcopic findings will be reported according to ASCCP terminology for colposcopic practice.
Pathological examination	For the pathological examination of the women who undergoing colposcopy, a biopsy will be performed only in cases with abnormal cervical findings, and if the colposcopy is unsatisfactory, a cervical curettage sample will be obtained.
Other assessments	
HIP	It consists of 29 items measuring worries and concerns, emotional impact, sexual impact, self-image, partner issues and transmission, interactions with doctors, and control/life impact.[28] The HIP item scales were linearly transformed to a scale of 0–100, and each item was a 0–10 point discretised analogue scale. The Mandarin Chinese version of the HIP questionnaire was generated through a

	standardised process and has been previously used in Taiwan.[29]
Intimate relationship satisfaction questionnaire	It contains two self-reported questions related to partner and sexual satisfaction. The scoring for each item ranges from very dissatisfied (0) to very satisfied (10).
Costs	The direct costs included patients' medication, health care, and other resources (such as time in seeking/receiving care and post-treatment recovery time). The costs of medication and health service utilisation will be calculated from the medical records using market prices. The indirect cost estimates of economic losses due to spending time on screening, examinations, and treatment are based on hourly wages per capita. [30]

Table S4. Interview guide

Roles	Research questions	Main topics	Probing questions
Patients	Can you talk about how you felt when you heard this diagnosis?	Attitudes to HPV	How would you prioritize goals as it relates to your HPV treatment? Do you have any concerns regarding your treatment? If so, what are they?
	Could you tell me about your experience of the treatment you received?	Treatment choices	Can you name the initial treatment you received? Did you have any other treatment? Can you tell me a little bit about the conversation you had with your doctor about your treatment? What were the reasons for choosing the treatment you did?
	What made you decide to change your treatment?	Nonadherence to treatment	What do you think the main reason is for these changes? Could you give some examples? Procedures? Something else?
Service providers	What do you know about the screen-and-treat approach guidelines recently issued by WHO?	Familiarity with guideline	What did you do when you got the most recently updated guideline? How did the screen-and-treat approach differ from that in the previous ones?
	Can you talk about how you make treatment decisions?	Treatment choices	What information has helped the treatment decision-making? Can you tell me a little bit about the conversation you had with your patients about their treatment decisions?
	What are the reasons for treatment deviation from the current WHO guidelines?	Nonadherence to guideline	Could you tell me why you didn't follow the WHO guidelines? What barriers have you encountered when you implementing the WHO guideline in your hospital?