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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 papillomavirusinfected 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
Siyuan Yang ¹ , Li Bai ² , Wei Xu ³ , Ruoyi Zhang ³ , Dehua Hu ² , Yuxian Nie ¹ , Rumei
Xiang ³ , Qiuling Shi ^{1,3*}
1 State Key Laboratory of Ultrasound in Medicine and Engineering, Chongqing
Medical University, 1 Yixueyuan Road, Yuzhong District, Chongqing ,400016, China
2 The Maternity Service Centre of Lueyang Maternal and Child Health Care Hospital,
Zhongxue Road, Lueyang, Shaanxi, 724300, China
3 School of Public Health and Management, Chongqing Medical University, 1
Yixueyuan Road, Yuzhong District, Chongqing ,400016, China
Siyuan Yang and Li Bai are co-first authors of the article.
Corresponding Author Information
Qiuling Shi, Ph.D. MD, School of Public Health and Management, Chongqing Medical
University, 1 Yixueyuan Road, Yuzhong District, Chongqing ,400016, China. Tel: +86-
23-63303353; Fax: +86-23-63303353; 400016; Email: qshi@cqmu.edu.cn.
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23	Abstrac

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.

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

Page 3 of 29

BMJ Open

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67 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 HPVcaused precancerous lesions to reduce the prevalence of cervical cancer urgently needs

 89 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 patients providing treatment and in optimal 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

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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

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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.

140 METHODS AND ANALYSIS

142 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

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> 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 Lien 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

177 diagnosis of mental illness or impaired consciousness.

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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 guidelinerecommended 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 **BMJ** Open

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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]

- 205 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.

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

Personal hygiene behaviour

Gynaecological examinations

HPV knowledge

HPV infection

219 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-toface 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 4 Visit 5 Visit 3 Screening Baseline Month six Month 12 Month 24 Eligibility criteria Х Research participants consent \times Individual Information Demographic variables × Menstrual history × Marital history \times

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Regular examination	×				
HPV vaccination	×				
Physicians' knowledge regarding		~			
treatment		×			
Partner information	×				
Outcomes					
Primary outcome					
Treatment patterns	6	×	×	×	×
Secondary outcomes	0				
HPV testing	×		×	×	×
ТСТ		°,	0	0	0
Colposcopy		0	0	0	0
Pathological examination		0	0	0	0
Other assessments					
Intimate relationship satisfaction	×		×	×	×
HIP		×	×	×	×
Costs			×	×	×
229 Notes: HPV, human papil	lomavirus. To	CT, Thin-prep	b liquid-based	cytology tes	t. HIP,

230 the HPV impact profile. \circ , if applicable.

232 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.

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249 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

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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.

277 Other assessments

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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). Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

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.

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Quality control 301

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302 The investigators received training on the standard operating procedure before patient 303 recruitment was performed. A standardised operation process manual and operation 304 video were created and distributed to all of the research assistants. Group training was 305 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 306 307 to begin their official work. There will be a question-and-answer session to solve 308 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 309 problems within the working group. 310 CUR

311

Data management and analysis 312

All participants will be allocated a PID code at enrolment, which will be used in the 313 samples and documents over the 24-month study period. All data will be collected and 314 managed using an electronic data management platform protected by the firewall of 315 316 Chongqing Medical University. The data on the platform will be accessible only by authorised researchers using private accounts and passwords. Any change will be 317 automatically recorded in the platform log and saved as a separate file for data 318 monitoring purposes. For the data export process, the de-identification of patient health 319 320 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 321

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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 4.0 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 $p^{-} = r / n$. 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 $100(1-\alpha)$ % exact confidence interval for the true proportion *p* are given by

341
$$\left[\frac{r}{r+(n-r+1)F_{1-\alpha/2;2(n-r+1),2r}},\frac{(r+1)F_{1-\alpha/2;2(r+1),2(n-r)}}{(n-r)+(r+1)F_{1-\alpha/2;2(r+1),2(n-r)}}\right]$$

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

Page 18 of 29

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> 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.

357 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.

364 Ethics and dissemination

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

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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

372 decision-making.

374 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

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388 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 followup 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]

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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.

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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. **Funding Statement:** This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. **Competing Interests Statement:** None declared. References [1] Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN

BMJ Open

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456 Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA*457 *Cancer J Clin* 2021;71:209-249.

- 458 [2] Cohen PA, Jhingran A, Oaknin A, *et al.* Cervical cancer. *Lancet* 2019; 393:169459 182.
- 460 [3] Bray F, Ferlay J, Soerjomataram I, *et al.* Global cancer statistics 2018: GLOBOCAN
 461 estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA*462 *Cancer J Clin* 2018;68:394–424.

463 [4] Jie H. China cancer registration annual report 2018[M], vol. 61. Beijing: People's
464 Publishing House; 2019. p. 63.

465 [5] Schiffman M, Castle PE, Jeronimo J, *et al. Lancet* 2007; 370:890-907.

466 [6] WHO. Draft global strategy towards the elimination of cervical cancer as a public

467 health problem. https://www.who.int/docs/default-source/documents/cervical-cancer-

468 elimination-draft-strategy.pdf?sfvrsn=380979d6_4 (accessed Oct 9, 2019).

469 [7] WHO guideline for screening and treatment of cervical pre-cancer lesions for
470 cervical cancer prevention, second edition [Internet]. Geneva: World Health
471 Organization; 2021.

472 [8] Basu P, Taghavi K, Hu SY, *et al.* Management of cervical premalignant lesions.

- 473 *Current problems in cancer* 2018;42:129-136.
- 474 [9] Rossman AH, Reid HW, Pieters MM, et al. Digital Health Strategies for Cervical
- 475 Cancer Control in Low- and Middle-Income Countries: Systematic Review of Current
- 476 Implementations and Gaps in Research. *J Med Internet Res* 2021;23:e23350.
- 477 [10] Johnson LG, Armstrong A, Joyce CM, et al. Implementation strategies to improve

BMJ Open

478	cervical cancer prevention in sub-Saharan Africa: a systematic review. Implementation
479	<i>Science</i> 2018;13:1-18.
480	[11] Hu Z, Ding WC, Zhu D, et al. TALEN-mediated targeting of HPV oncogenes
481	ameliorates HPV-related cervical malignancy. J Clin Invest 2014;125:425-36.
482	[12] Castle PE, Murokora D, Perez C, et al. Treatment of cervical intraepithelial lesions.
483	International Journal of Gynecology & Obstetrics 2017;138:20–25.
484	[13] Papadakis VM, Lioukas S, Chambers D. Strategic decision-making processes: the
485	role of management and context. Strategic management journal 1998;19:115–147.
486	[14] Elbanna S. The influence of decision, environmental and firm characteristics on
487	the rationality of strategic decision-making. Journal of Management Studies 2007;44:4.
488	[15] Mazzocco K, Masiero M, Carriero MC, et al. The role of emotions in cancer
489	patients' decision-making. Ecancermedicalscience 2019;13:914.
490	[16] Nash K, Leota J, Tran A. Neural processes in antecedent anxiety modulate risk-
491	taking behavior. Scientific reports 2021;11:2637.
492	[17] Junius-Walker U, Wiese B, Klaaßen-Mielke R, et al. Older patients' perceived
493	burdens of their health problems: a cross-sectional analysis in 74 German general
494	practices. Patient preference and adherence 2015;9:811-820.
495	[18] Glatzer M, Panje CM, Sirén C, et al. Decision Making Criteria in Oncology.
496	Oncology 2018;98:370–378.
497	[19] Wang B, He M, Chao A, et al. Cervical cancer screening among adult women in
498	China, 2010. Oncologist 2015;20:627-634.

499 [20] Zhu B, Liu Y, Zuo T, et al. The prevalence, trends, and geographical distribution

BMJ Open

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.

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

BMJ Open

[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.

542 Figure Legends

- 543 Figure 1. Workflow for the recruitment procedure.
- 544 Figure 2. The specific examination procedures.[27]
- 545 Note: ^a TCT, thin-prep liquid-based cytologic test; ^b ≥ASC-US, atypical squamous cells
- 546 of undetermined significance or above.

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	Patient consented to screening		
	↓ BM.	J Open	Page 28 of 29
5	Screening		
•	18-65		
1٠	HR-HPV	~	
2 ·	Non-pregnancy	Patient not eligible	Patient not enrolled
3 '	History of sexual activity		t attent not emotied
4	No history of severe immunodeficiency disease		
5	Able to understand the questions raised by the		
6	nvestigator		
7	Ļ		
8	Patient meets eligibility		
9	1	Patient not interested	
10	÷	I attent not interested	
11	Explain study and administers consent		
12			
13	Complete bas	ic information	
11	Patient consented to trial	relationship	Complete further examinations
14	satisfaction q	uestionnaire	Allocated
15	For peer review only - http://bmjope	n.bmj.com/site/abou	: Conservative observation
16			Ablative treatment
17			Fxcisional treatment
10			Excisional availabilit



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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 papillomavirusinfected women in Lueyang County, China

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Primary Subject Heading :	Obstetrics and gynaecology
Secondary Subject Heading:	Obstetrics and gynaecology, Medical management
Keywords:	Public health < INFECTIOUS DISEASES, EPIDEMIOLOGY, Infection control < INFECTIOUS DISEASES

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1	Profiling the real-world management status of high-risk human papillomavirus
2	infection: A protocol to establish a prospective cohort of high-risk human
3	papillomavirus-infected women in Lueyang County, China
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5	Siyuan Yang ¹ , Li Bai ² , Wei Xu ³ , Ruoyi Zhang ³ , Dehua Hu ² , Yuxian Nie ¹ , Rumei
6	Xiang ³ , Qiuling Shi ^{1,3*}
7	
8	1 State Key Laboratory of Ultrasound in Medicine and Engineering, Chongqing
9	Medical University, 1 Yixueyuan Road, Yuzhong District, Chongqing ,400016, China
10	2 The Maternity Service Centre of Lueyang Maternal and Child Health Care Hospital,
11	Zhongxue Road, Lueyang, Shaanxi, 724300, China
12	3 School of Public Health and Management, Chongqing Medical University, 1
13	Yixueyuan Road, Yuzhong District, Chongqing ,400016, China
14	
15	Siyuan Yang and Li Bai are co-first authors of the article.
16	
17	Corresponding Author Information
18	Qiuling Shi, Ph.D. MD, School of Public Health, Chongqing Medical University, 1
19	Yixueyuan Road, Yuzhong District, Chongqing ,400016, China. Tel: +86-23-63303353;
20	Fax: +86-23-63303353; 400016; Email: qshi@cqmu.edu.cn.
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22	Word count: abstract (n=295), main text (n=3959).
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23	Abstract
20	Austraci

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

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7	46	Maternal and Child Health Care Hospital (2021-001). The findings from this study will
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9	47	be discominated through near reviewed nublications, conference presentations, and
10	47	be disseminated through peer-reviewed publications, conference presentations, and
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12	48	academic workshops.
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14	49	Trial registration number: ChiCTR2100053757
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25	53	the management patterns after diagnosing high-risk HPV infection among
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27	54	women in China.
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30	55	• we will use a mixed method to explore different potential factors, revealing
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33	56	their internal influence mechanism on treatment decision-making options.
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36	0.	imprementing and protocol will recharg the gap octive of resource and practice
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38	58	and determine why some patients and not receive the recommended therapies.
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40 41	59	• It remains a challenge to sustain a high participation rate in a prospective cohort
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54	64	from Lueyang County, China, so the study design increases the risk for the
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67 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
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89 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 patients providing treatment and in optimal 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

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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.

Page 7 of 35

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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. review

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

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155 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.

172 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

177 sexual activity, (5) no history of severe immunodeficiency disease, and (6) able to178 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.

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

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> 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%. 12.0

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 6-6	
Eligibility criteria	×				
Research participants consent	×				
Individual Information					
Demographic variables	×				
Menstrual history	×				
Marital history	×				
Personal hygiene behaviour	×				
Gynaecological examinations	C	×			
HPV knowledge	×				
HPV infection	×				
Regular examination	×	0			
HPV vaccination	×	7			
Physicians' knowledge regarding			5.		
treatment		*	1		
Partner information	×				
Outcomes					
Primary outcome					
Treatment patterns		×		×	
Secondary outcomes					

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HPV testing	×			×
ТСТ		0		0
Colposcopy		0		0
Pathological examination		0		0
Adverse events			0	0
Other assessments				
Intimate relationship satisfaction	×			×
HIP	6	×		×
Costs	C			×

Notes: HPV, human papillomavirus. TCT, Thin-prep liquid-based cytology test. HIP,

the HPV impact profile. \circ , if applicable.

Measures

Baseline

ι-pι 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).

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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.

242 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]:

254 Other assessments

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

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> 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.

272 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

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

280 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).

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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

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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 $p^{2} = r / n$. 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

312
$$\left[\frac{r}{r+(n-r+1)F_{1-\alpha/2;2(n-r+1),2r}},\frac{(r+1)F_{1-\alpha/2;2(r+1),2(n-r)}}{(n-r)+(r+1)F_{1-\alpha/2;2(r+1),2(n-r)}}\right]$$

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

321 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.

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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.

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> 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.

358 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.

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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

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Page 20 of 35

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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.

Page 21 of 35

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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.

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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

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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.

450 Authors' Contributions:

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

453	draft. All authors have read and approved the final manuscript.
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459	Competing Interests Statement:
460	None declared.
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462	References:
463	[1] Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN
464	Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA
465	<i>Cancer J Clin</i> 2021;71:209-249.
466	[2] Cohen PA, Jhingran A, Oaknin A, et al. Cervical cancer. Lancet 2019; 393:169-
467	182.
468	[3] Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN
469	estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA
470	<i>Cancer J Clin</i> 2018;68:394–424.
471	[4] Jie H. China cancer registration annual report 2018[M], vol. 61. Beijing: People's
472	Publishing House; 2019. p. 63.
473	[5] Schiffman M, Castle PE, Jeronimo J, et al. Lancet 2007; 370:890-907.
474	[6] WHO. Draft global strategy towards the elimination of cervical cancer as a public
	23

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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

BMJ Open

497	patients' decision-making. Ecancermedicalscience 2019;13:914.
498	[16] Nash K, Leota J, Tran A. Neural processes in antecedent anxiety modulate risk-
499	taking behavior. Scientific reports 2021;11:2637.
500	[17] Junius-Walker U, Wiese B, Klaaßen-Mielke R, et al. Older patients' perceived
501	burdens of their health problems: a cross-sectional analysis in 74 German general
502	practices. Patient preference and adherence 2015;9:811-820.
503	[18] Glatzer M, Panje CM, Sirén C, et al. Decision Making Criteria in Oncology.
504	Oncology 2018;98:370–378.
505	[19] Wang B, He M, Chao A, et al. Cervical cancer screening among adult women in
506	China, 2010. Oncologist 2015;20:627–634.
507	[20] Zhu B, Liu Y, Zuo T, et al. The prevalence, trends, and geographical distribution
508	of human papillomavirus infection in China: The pooled analysis of 1.7 million women.
509	Cancer Medicine 2019;8:5373–5385.
510	[21] Kabadi SM, Goyal RK, Nagar SP, et al. Treatment patterns, adverse events, and
511	economic burden in a privately insured population of patients with chronic lymphocytic
512	leukemia in the United States. Cancer medicine 2019;8:3803-3810.
513	[22] Twomey R, Matthews TW, Nakoneshny SC, et al. From Pathways to Practice:
514	Impact of Implementing Mobilization Recommendations in Head and Neck Cancer
515	Surgery with Free Flap Reconstruction. Cancers 2021;13:2890.
516	[23] Giuliano AR, Lee JH, Fulp W, et al. Incidence and clearance of genital human
517	papillomavirus infection in men (HIM): a cohort study. Lancet (London, England)
518	2011;377:932–940.
	25

Page 26 of 35

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- 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
- resection of preoperatively diagnosed non-circumferential T1a-muscularis mucosae or
 T1b-submucosa 1 esophageal squamous cell carcinoma. *Scientific reports* 2021;11:
 6554.

[26] Brahmbhatt P, Sabiston CM, Lopez C, et al. Feasibility of prehabilitation prior to

- breast cancer surgery: a mixed-methods study. Frontiers in oncology 2020;10:571091. [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.
 - 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.

 541 [32] Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol
542 2006;3:77–101.

543 [33] Guralnik JM, Kritchevsky SB. Translating research to promote healthy aging: the
544 complementary role of longitudinal studies and clinical trials. *J Am Geriatr Soc* 2010;
545 58:S337-S342.

546 [34] Baloch Z, Yasmeen N, Li Y, et al. Knowledge and awareness of cervical cancer,
547 human papillomavirus (HPV), and HPV vaccine among HPV-infected Chinese women.
548 Medical science monitor: international medical journal of experimental and clinical

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549 research 2017;23:4269.

550 Figure Legends

- 551 Figure 1. Workflow for the recruitment procedure.
- 552 Figure 2. The specific examination procedures.[27]
- 553 Note: a hrHPV, high risk human papilloma virus; b TCT, thin-prep liquid-based
- 554 cytologic test; $c \ge ASC-US$, atypical squamous cells of undetermined significance or
 - above; ^d NILM, negative for intraepithelial lesions or malignancy; ^e LSIL, low-grade
- 556 squamous intraepithelial lesion; ^f HSIL, high-grade squamous intraepithelial lesion.

Patient consented to screening Screening 18-65 HR-HPV Non-pregnancy History of sexual activity No history of sexual activity Able to understand the questions raised by the investigator Patient meets eligibility Patient meets eligibility Patient not interested to trial Patient consented to trial Complete basic information and intimate relationship satisfaction questionnaire Conservative observation Ablative treatment	Pag	e 29 of 35 B	MJ Open	iopen-
Screening 18-65 HR-HPV Non-pregnancy History of sexual activity No history of severe immunodeficiency disease Able to understand the questions raised by the investigator Patient meets eligibility Patient meets eligibility Patient meets eligibility Patient consented to trial \longrightarrow Complete basic information Patient consented to trial \longrightarrow Complete basic information and intimate relationship satisfaction questionnaire Conservative observation Ablative treatment	1 2 3	Patient consented to screening	pyright, inc	2022-062678
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43 For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 	Patient consented to trial \longrightarrow Complete bas and intimate satisfaction q	sic information relationship juestionnaire pen.bmj.com/site/about/guidelines.xhtml	Complete further examination: Categorized Conservative observation Ablative treatment Excisional treatment



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	Compliance with guideline, the primary outcome was the provider's				
guidelines	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				

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	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.

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n p	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
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3000	0.022	0.029	0.033	0.035	0.036	0.035	0.033	0.029	0.022

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

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

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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-	Exfoliated cervical cells from women attending the gynaecological
based cytology test	outpatient clinic were collected using a specialised cervical brush
(TCT)	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	For the pathological examination of the women who undergoing
examination	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

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standardised process and has been previously used in Taiwan.[29]
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).
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]

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

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1	Profiling the real-world management status of high-risk human papillomavirus
2	infection: A protocol to establish a prospective cohort of high-risk human
3	papillomavirus-infected women in Lueyang County, China
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5	Siyuan Yang ¹ , Li Bai ² , Wei Xu ³ , Ruoyi Zhang ³ , Dehua Hu ² , Yuxian Nie ¹ , Rumei
6	Xiang ³ , Qiuling Shi ^{1,3*}
7	
8	1 State Key Laboratory of Ultrasound in Medicine and Engineering, Chongqing
9	Medical University, 1 Yixueyuan Road, Yuzhong District, Chongqing ,400016, China
10	2 The Maternity Service Centre of Lueyang Maternal and Child Health Care Hospital,
11	Zhongxue Road, Lueyang, Shaanxi, 724300, China
12	3 School of Public Health and Management, Chongqing Medical University, 1
13	Yixueyuan Road, Yuzhong District, Chongqing ,400016, China
14	
15	Siyuan Yang and Li Bai are co-first authors of the article.
16	
17	Corresponding Author Information
18	Qiuling Shi, Ph.D. MD, School of Public Health, Chongqing Medical University, 1
19	Yixueyuan Road, Yuzhong District, Chongqing ,400016, China. Tel: +86-23-63303353;
20	Fax: +86-23-63303353; 400016; Email: qshi@cqmu.edu.cn.
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23	Abstract
20	Austraci

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

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12	40	academic workshops.
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67 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
89 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 patients providing treatment and in optimal 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

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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.

Page 7 of 36

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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. review

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

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155 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.

172 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

177 sexual activity, (5) no history of severe immunodeficiency disease, and (6) able to178 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.

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

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> 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%. 12.0

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 6-6	
Eligibility criteria	×				
Research participants consent	×				
Individual Information					
Demographic variables	×				
Menstrual history	×				
Marital history	×				
Personal hygiene behaviour	×				
Gynaecological examinations	2	×			
HPV knowledge	×				
HPV infection	×				
Regular examination	×	0			
HPV vaccination	×	7			
Physicians' knowledge regarding		Q	5.		
treatment		×	1		
Partner information	×				
Outcomes					
Primary outcome					
Treatment patterns		×		×	
Secondary outcomes					

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HPV testing	×			×
ТСТ		0		0
Colposcopy		0		0
Pathological examination		0		0
Adverse events			0	0
Other assessments				
Intimate relationship satisfaction	×			×
HIP	6	×		×
Costs	9			×

Notes: HPV, human papillomavirus. TCT, Thin-prep liquid-based cytology test. HIP,

eliez oj the HPV impact profile. \circ , 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).

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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.

242 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]:

254 Other assessments

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

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> 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.

272 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

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

280 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).

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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

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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 $p^{2} = r / n$. 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

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

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

321 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.

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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.

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> 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.

358 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.

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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

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Page 20 of 36

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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.

Page 21 of 36

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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.

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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

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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.

450 Authors' Contributions:

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

453	draft. All authors have read and approved the final manuscript.
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461	
462	References:
463	[1] Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN
464	Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA
465	<i>Cancer J Clin</i> 2021;71:209-249.
466	[2] Cohen PA, Jhingran A, Oaknin A, et al. Cervical cancer. Lancet 2019; 393:169-
467	182.
468	[3] Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN
469	estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA
470	<i>Cancer J Clin</i> 2018;68:394–424.
471	[4] Jie H. China cancer registration annual report 2018[M], vol. 61. Beijing: People's
472	Publishing House; 2019. p. 63.
473	[5] Schiffman M, Castle PE, Jeronimo J, et al. Lancet 2007; 370:890-907.
474	[6] WHO. Draft global strategy towards the elimination of cervical cancer as a public
	23

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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

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3 4 5	497	patients' decision-making. Ecancermedicalscience 2019;13:914.
6 7	498	[16] Nash K, Leota J, Tran A. Neural processes in antecedent anxiety modulate risk-
8 9 10	499	taking behavior. Scientific reports 2021;11:2637.
11 12 13	500	[17] Junius-Walker U, Wiese B, Klaaßen-Mielke R, et al. Older patients' perceived
14 15	501	burdens of their health problems: a cross-sectional analysis in 74 German general
17 18	502	practices. Patient preference and adherence 2015;9:811-820.
19 20 21	503	[18] Glatzer M, Panje CM, Sirén C, et al. Decision Making Criteria in Oncology.
22 23	504	Oncology 2018;98:370–378.
24 25 26	505	[19] Wang B, He M, Chao A, et al. Cervical cancer screening among adult women in
27 28 29	506	China, 2010. Oncologist 2015;20:627–634.
30 31	507	[20] Zhu B, Liu Y, Zuo T, et al. The prevalence, trends, and geographical distribution
32 33 34	508	of human papillomavirus infection in China: The pooled analysis of 1.7 million women.
35 36 27	509	Cancer Medicine 2019;8:5373–5385.
37 38 39	510	[21] Kabadi SM, Goyal RK, Nagar SP, et al. Treatment patterns, adverse events, and
40 41 42	511	economic burden in a privately insured population of patients with chronic lymphocytic
43 44	512	leukemia in the United States. Cancer medicine 2019;8:3803–3810.
45 46 47	513	[22] Twomey R, Matthews TW, Nakoneshny SC, et al. From Pathways to Practice:
48 49	514	Impact of Implementing Mobilization Recommendations in Head and Neck Cancer
50 51 52	515	Surgery with Free Flap Reconstruction. Cancers 2021;13:2890.
53 54	516	[23] Giuliano AR, Lee JH, Fulp W, et al. Incidence and clearance of genital human
56 57	517	papillomavirus infection in men (HIM): a cohort study. Lancet (London, England)
58 59 60	518	2011;377:932–940.
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Page 26 of 36

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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.

[25] 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.

[26] Brahmbhatt P, Sabiston CM, Lopez C, et al. Feasibility of prehabilitation prior to breast cancer surgery: a mixed-methods study. Frontiers in oncology 2020;10:571091. [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.

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.

 541 [32] Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol
542 2006;3:77–101.

543 [33] Guralnik JM, Kritchevsky SB. Translating research to promote healthy aging: the
544 complementary role of longitudinal studies and clinical trials. *J Am Geriatr Soc* 2010;
545 58:S337-S342.

546 [34] Baloch Z, Yasmeen N, Li Y, et al. Knowledge and awareness of cervical cancer,
547 human papillomavirus (HPV), and HPV vaccine among HPV-infected Chinese women.
548 Medical science monitor: international medical journal of experimental and clinical

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549 research 2017;23:4269.

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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; $^{\circ} \geq ASC-US$, atypical squamous cells of undetermined significance or

above; ^d NILM, negative for intraepithelial lesions or malignancy; ^e LSIL, low-grade

d lesion; ¹ . squamous intraepithelial lesion; ^f HSIL, high-grade squamous intraepithelial lesion.

Pag	e 29 of 36 BN	/J Open		
1 2 3	Patient consented to screening	pyright, inc		
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25	Screening • 18-65 • HR-HPV • Non-pregnancy • History of sexual activity • No history of severe immunodeficiency disease • Able to understand the questions raised by the investigator Patient meets eligibility	Patient not eligible	Patient not	enrolled
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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	Compliance with guideline, the primary outcome was the provider's			
guidelines	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			

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	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.

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3000	0.022	0.029	0.033	0.035	0.036	0.035	0.033	0.029	0.022

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

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

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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-	Exfoliated cervical cells from women attending the gynaecological
based cytology test	outpatient clinic were collected using a specialised cervical brush
(TCT)	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	For the pathological examination of the women who undergoing
examination	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]It contains two self-reported questions related to partner and sexual
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).
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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Table S4. Interview guide

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6 Roles	Research questions	Main topics	Probing questions
7 Patients 8 9 10	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?
11 12 13	-		Do you have any concerns regarding your treatment? If so, what are they?
14 15 16 17	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?
18 19 20 21 22 23			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?
24 25 26 27 28 29	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?
30			Something else?
 Service providers a a	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?
36 37 38 39 40 41	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
42 43 44 45 46 47 48 49	What are the reasons for treatment deviation from the current WHO guidelines?	Nonadherence to guideline	decisions? 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 papillomavirusinfected women in Lueyang County, China

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1	Profiling the real-world management status of high-risk human papillomavirus
2	infection: A protocol to establish a prospective cohort of high-risk human
3	papillomavirus-infected women in Lueyang County, China
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5	Siyuan Yang ¹ , Li Bai ² , Wei Xu ³ , Ruoyi Zhang ³ , Dehua Hu ² , Yuxian Nie ¹ , Rumei
6	Xiang ³ , Qiuling Shi ^{1,3*}
7	
8	1 State Key Laboratory of Ultrasound in Medicine and Engineering, Chongqing
9	Medical University, 1 Yixueyuan Road, Yuzhong District, Chongqing ,400016, China
10	2 The Maternity Service Centre of Lueyang Maternal and Child Health Care Hospital,
11	Zhongxue Road, Lueyang, Shaanxi, 724300, China
12	3 School of Public Health and Management, Chongqing Medical University, 1
13	Yixueyuan Road, Yuzhong District, Chongqing ,400016, China
14	
15	Siyuan Yang and Li Bai are co-first authors of the article.
16	
17	Corresponding Author Information
18	Qiuling Shi, Ph.D. MD, School of Public Health, Chongqing Medical University, 1
19	Yixueyuan Road, Yuzhong District, Chongqing, 400016, China. Tel: +86-23-63303353;
20	Fax: +86-23-63303353; 400016; Email: qshi@cqmu.edu.cn.
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23	Abstract
20	Austraci

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

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4 5	45	were obtained from the Ethics Committee of the Maternity Service Centre of Lueyang
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15	49	Trial registration number: ChiCTR2100053757.
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20	51	Strengths and minitations of this study
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25	53	the management patterns after diagnosing high-risk HPV infection among
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30	55	• We will use a mixed method to explore different potential factors, revealing
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35	57	• Implementing this protocol will identify the gap between research and practice
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38	58	and determine why some patients did not receive the recommended therapies.
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67 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

 89 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 patients providing treatment and in optimal 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

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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.

Page 7 of 36

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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. review

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

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155 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.

172 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

177 sexual activity, (5) no history of severe immunodeficiency disease, and (6) able to178 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.

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

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> 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%. 12.0

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 6-6
Eligibility criteria	×			
Research participants consent	×			
Individual Information				
Demographic variables	×			
Menstrual history	×			
Marital history	×			
Personal hygiene behaviour	×			
Gynaecological examinations	2	×		
HPV knowledge	×			
HPV infection	×			
Regular examination	×	0		
HPV vaccination	×	7		
Physicians' knowledge regarding		0	5.	
treatment		×	1	
Partner information	×			
Outcomes				
Primary outcome				
Treatment patterns		×		×
Secondary outcomes				

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HPV testing	×			×
ТСТ		0		0
Colposcopy		0		0
Pathological examination		0		0
Adverse events			0	0
Other assessments				
Intimate relationship satisfaction	×			×
HIP	6	×		×
Costs	9			×

Notes: HPV, human papillomavirus. TCT, Thin-prep liquid-based cytology test. HIP,

eliez oj the HPV impact profile. \circ , 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).

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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.

242 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]:

254 Other assessments

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

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> 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.

272 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

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

280 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).

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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

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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 $p^{2} = r / n$. 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

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

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

321 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.

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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.

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> 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.

358 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.

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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

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Page 20 of 36

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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.

Page 21 of 36

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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.

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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

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> 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.

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453	Authors' Contributions:
454	QS, SY, RZ, and WX contributed to the study design. LB, DH, RZ, SY, YN and RX
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465	References:
466	[1] Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN
467	Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA
468	<i>Cancer J Clin</i> 2021;71:209-249.
469	[2] Cohen PA, Jhingran A, Oaknin A, et al. Cervical cancer. Lancet 2019; 393:169-
470	182.
471	[3] Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN
472	estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA
473	<i>Cancer J Clin</i> 2018;68:394–424.
474	[4] Jie H. China cancer registration annual report 2018[M], vol. 61. Beijing: People's

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

BMJ Open

475	Publishing House; 2019. p. 63.
476	[5] Schiffman M, Castle PE, Jeronimo J, et al. Lancet 2007; 370:890-907.
477	[6] WHO. Draft global strategy towards the elimination of cervical cancer as a public
478	health problem. https://www.who.int/docs/default-source/documents/cervical-cancer-
479	elimination-draft-strategy.pdf?sfvrsn=380979d6_4 (accessed Oct 9, 2019).
480	[7] WHO guideline for screening and treatment of cervical pre-cancer lesions for
481	cervical cancer prevention, second edition [Internet]. Geneva: World Health
482	Organization; 2021.
483	[8] Basu P, Taghavi K, Hu SY, et al. Management of cervical premalignant lesions.
484	Current problems in cancer 2018;42:129-136.
485	[9] Rossman AH, Reid HW, Pieters MM, et al. Digital Health Strategies for Cervical
486	Cancer Control in Low- and Middle-Income Countries: Systematic Review of Current
487	Implementations and Gaps in Research. J Med Internet Res 2021;23:e23350.
488	[10] Johnson LG, Armstrong A, Joyce CM, et al. Implementation strategies to improve
489	cervical cancer prevention in sub-Saharan Africa: a systematic review. Implementation
490	<i>Science</i> 2018;13:1-18.
491	[11] Hu Z, Ding WC, Zhu D, et al. TALEN-mediated targeting of HPV oncogenes
492	ameliorates HPV-related cervical malignancy. J Clin Invest 2014;125:425-36.
493	[12] Castle PE, Murokora D, Perez C, et al. Treatment of cervical intraepithelial lesions.
494	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.

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т.) Л6
40
47
48
49
50
51
52
52
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54
55
56
57
58
50
72
60

497	[14] Elbanna S. The influence of decision, environmental and firm characteristics on
498	the rationality of strategic decision-making. Journal of Management Studies 2007;44:4.
499	[15] Mazzocco K, Masiero M, Carriero MC, et al. The role of emotions in cancer
500	patients' decision-making. Ecancermedicalscience 2019;13:914.
501	[16] Nash K, Leota J, Tran A. Neural processes in antecedent anxiety modulate risk-
502	taking behavior. Scientific reports 2021;11:2637.
503	[17] Junius-Walker U, Wiese B, Klaaßen-Mielke R, et al. Older patients' perceived
504	burdens of their health problems: a cross-sectional analysis in 74 German general
505	practices. Patient preference and adherence 2015;9:811-820.
506	[18] Glatzer M, Panje CM, Sirén C, et al. Decision Making Criteria in Oncology.
507	Oncology 2018;98:370–378.
508	[19] Wang B, He M, Chao A, et al. Cervical cancer screening among adult women in
509	China, 2010. Oncologist 2015;20:627–634.
510	[20] Zhu B, Liu Y, Zuo T, et al. The prevalence, trends, and geographical distribution
511	of human papillomavirus infection in China: The pooled analysis of 1.7 million women.
512	<i>Cancer Medicine</i> 2019;8:5373–5385.
513	[21] Kabadi SM, Goyal RK, Nagar SP, et al. Treatment patterns, adverse events, and
514	economic burden in a privately insured population of patients with chronic lymphocytic
515	leukemia in the United States. Cancer medicine 2019;8:3803-3810.
516	[22] Twomey R, Matthews TW, Nakoneshny SC, et al. From Pathways to Practice:
517	Impact of Implementing Mobilization Recommendations in Head and Neck Cancer
518	Surgery with Free Flap Reconstruction. Cancers 2021;13:2890.

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

BMJ Open

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.

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

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9
10
10
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44
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48
49
50
51
52
53
54
55
56
57
50
20
59

- 541 dementia in Brazil. PLoS One 2018;13:e0193209.
- 542 [31] Fleiss JL, Levin B, Paik MC. Statistical Methods for Rates and Proportions. Third
- 543 Edition. John Wiley & Sons. New York., 2003. p. 25.
- [32] Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol 544 545 2006;3:77-101.
- 546 [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; 547 58:S337-S342. 548
 - [34] Baloch Z, Yasmeen N, Li Y, et al. Knowledge and awareness of cervical cancer, 549
- 550 human papillomavirus (HPV), and HPV vaccine among HPV-infected Chinese women.
- 551 Medical science monitor: international medical journal of experimental and clinical ,ic.
 - 552 research 2017;23:4269.

- 554 Figure 1. Workflow for the recruitment procedure.
- 555 Figure 2. The specific examination procedures.[27]
- 556 Note: ^a hrHPV, high risk human papilloma virus; ^b TCT, thin-prep liquid-based
- 557 cytologic test; $c \ge ASC-US$, atypical squamous cells of undetermined significance or

above; ^d NILM, negative for intraepithelial lesions or malignancy; ^e LSIL, low-grade

559 squamous intraepithelial lesion; ^f HSIL, high-grade squamous intraepithelial lesion.

Pag	e 29 of 36 BN	/J Open		
1 2 3	Patient consented to screening	pyright, inc		
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25	Screening • 18-65 • HR-HPV • Non-pregnancy • History of sexual activity • No history of severe immunodeficiency disease • Able to understand the questions raised by the investigator Patient meets eligibility	Patient not eligible	Patient not	enrolled
26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42	Explain study and administers consent Patient consented to trial Complete bas and intimate r satisfaction que	Patient not interested	Complete Conserva Ablative tr	further examinations ↓ Categorized tive observation eatment
43 44 45 46	For peer review only - http://bmjop	en.bmj.com/site/about/guidelines.xhtml	Excisional	treatment



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	Compliance with guideline, the primary outcome was the provider's
guidelines	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

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	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.			
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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

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

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

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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-	Exfoliated cervical cells from women attending the gynaecological			
based cytology test	outpatient clinic were collected using a specialised cervical brush			
(TCT)	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	For the pathological examination of the women who undergoing			
examination	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			

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	standardised process and has been previously used in Taiwan.[29]
Intimate relationship	It contains two self-reported questions related to partner and sexual
satisfaction	satisfaction. The scoring for each item ranges from very dissatisfied
questionnaire	(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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Table S4. Interview guide

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6	Roles	Research questions	Main topics	Probing questions	_
7 0	Patients	Can you talk about how you	Attitudes to HPV	How would you prioritize goals as it	
0 9		felt when you heard this		relates to your HPV treatment?	
10		diagnosis?			
11		C		Do you have any concerns regarding	
12				your treatment? If so what are they?	
13		Could you tall ma about your	Treatment choices	Con you name the initial treatment you	
14		could you tell me about you	Treatment choices	can you hame the initial treatment you	Pro
16		· 10		received? Did you have any other	tec
17		you received?		treatment?	ted ,
18				Can you tell me a little bit about the	by .
19 20				conversation you had with your doctor	cop
20 21				about your treatment?	oy ri
21				What were the reasons for choosing the	ght
23				treatment you did?	, in
24		What made you decide to	Nonadherence to treatment	What do you think the main reason is	cluc
25		change your treatment?		for these changes?	ling
26 27		change your treatment?		Could you give some eventuals?	fo
27 28				Could you give some examples?	Бп
29				Procedures?	nse es i
30				Something else?	ign -
31	Service	What do you know about the	Familiarity with guideline	What did you do when you got the most	ted
32	providers	screen-and-treat approach		recently updated guideline?	to t
33		guidelines recently issued by		How did the screen-and-treat approach	iext Sul
35		WHO?		differ from that in the previous ones?	an
36		Can you talk about how you	Treatment choices	What information has helped the	d da
37		make treatment decisions?		treatment decision-making?	ata (A
38		make treatment decisions.		Con you tall ma a little bit about the	min
39 40				Can you ten me a nute on about the	ing
41				conversation you had with your	, ≥I
42				patients about their treatment	tra
43				decisions?	inin ·
44		What are the reasons for	Nonadherence to guideline	Could you tell me why you didn't	, ĝ
45 46		treatment deviation from the		follow the WHO guidelines?	Ind
47		current WHO guidelines?		What barriers have you encountered	sin
48		-		when you implementing the WHO	ıilaı
49				guideline in your hospital?	r teo
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