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Efficacy of different surgical approaches in the clinical and survival outcomes of patients with early-stage cervical cancer: protocol of a phase III multicentre randomised controlled trial in China

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ABSTRACT

Introduction In the last three decades, minimally invasive surgery (MIS) for radical hysterectomy (RH) has become a popular treatment option for early-stage cervical cancer. However, a recently published randomised controlled trial (LACC trial) and an epidemiological study in the USA revealed strong evidence against the survival advantage of MIS for RH. However, the influencing factors of research centres and the learning curves of surgeons in these studies lacked sufficient evaluation. The efficacy of different surgical approaches for early-stage cervical cancer in the clinical and survival outcomes remains to be validated.

Methods and analysis Patients diagnosed with FIGO (2009) stage IA1 (with lymphovascular space invasion), IA2 or IB1 cervical cancer with histological subtype of squamous cell carcinoma, adenocarcinoma or adenosquamous carcinoma will be recruited in this multicentre randomised controlled study. Patients will be randomly assigned to undergo MIS (robot-assisted or laparoscopic RH) or abdominal RH. Within 2 years, 1448 patients in 28 centres in China will be recruited to meet the criteria of a non-inferiority threshold of HR of 1.6 with bilateral nominal α <0.05 and power of 0.8. All surgeries will be performed by the indicated experienced surgeons. At least 100 RH cases in the individual past one decade of practice will be analysed as proof of learning curves. The primary objective of this study is 5-year disease-free survival. The secondary objectives include the overall survival rate, progression-free survival rate, disease-free survival rate, cost-effectiveness and quality of life.

Ethics and dissemination This study has been approved by the Institutional Review Board of Peking Union Medical College Hospital and is filed on record by all other centres. Written informed consent will be obtained from all eligible participants before enrolment. The results will be disseminated through community events, academic conferences, student theses and peer-reviewed journals.

Trial registration number NCT03739944.

INTRODUCTION

Uterine cervical cancer is the fourth most common malignancy in women worldwide, and 85% of cases occur in developing countries as the second leading cause of cancer mortality for women.1 The incidence of cervical cancer is also increasing in China, with 98,900 new cases and 30,500 deaths in 2015.2 Current guidelines3 4 indicate that either laparotomy or minimally invasive surgery (MIS) is an acceptable approach to radical hysterectomy (RH) in patients with early-stage (IA2 to IIA) cervical cancer. These recommendations have led to widespread use of a minimally invasive approach. Numerous retrospective studies5–7 and a meta-analysis8 have shown that MIS is associated with less intraoperative blood loss, shorter length of hospital stay and lower risk of postoperative complications than abdominal RH (ARH). Moreover, MIS has not been associated with lower 5-year rates of disease-free survival (DFS) or overall survival (OS) than ARH has.5 6 9–14 However, there is a paucity of adequately powered, prospective, randomised trials evaluating survival outcomes, surgical safety, quality of life (QoL) and other important

Strength and limitations of this study

- With the advantage of multiple patients with cervical cancer in China, this study can be implemented very soon.
- This study, in contrast with the LACC trial, considers surgeons as one of the important parameters for the survival analysis.
- This study will use uniform reports of pathologi
cal outcomes. The comprehensive and meticulous pathological data will support information about the prognosis.
- The emphasis on the individual surgeon’s experience and skill most likely will limit generalisation of the findings of this study.

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factors. Recently, Ramirez et al\textsuperscript{15} reported a multicentre randomised controlled trial (RCT), namely, the LACC trial, the results of which showed that MIS for RH had a lower 4.5-year DFS, progression-free survival (PFS), OS and disease-specific survival rates and a higher local recurrence rate than the laparotomic approach. A retrospective study by Melamed et al\textsuperscript{16} showed that the MIS group had higher mortality than the abdominal surgery group. In addition, based on the SEER database, the adoption of MIS coincided with a decline in the 4-year relative survival rate of 0.8% per year after 2006.\textsuperscript{16} The results of both studies aroused great controversy over the surgical approaches to cervical cancer worldwide. It seems that MIS was responsible for this trend, which was significantly different from the situation in early-stage uterine, colorectal or gastric cancer.\textsuperscript{17–20}

However, the causes of the inferior survival outcomes in the MIS group were still unknown. The RCT enrolled 631 cases from 33 centres, with an average of 2 cases recruited per year in each centre, and patients with recurrent disease were focused mainly in 14 centres. Furthermore, too much is unknown about the patient’s pathological data in both the RCT and retrospective studies. Regarding the retrospective study, there were only year 2000–2010 data from the SEER database and year 2010–2013 data from the cohort analysis in the USA. The impact of learning curves of individual surgeons on the survival outcomes of early-stage cervical cancer was not considered an important factor. According to published data, 2006 was the year in which surgeons in the USA began to adopt minimally invasive RH for the treatment of cervical cancer.\textsuperscript{21} Conrad et al\textsuperscript{22} evaluated the current patterns in the use of MIS procedures by Society of Gynecologic Oncology members and compared the results against those of their 2004 and 2007 surveys. There was an increase in conversion from MIS to laparotomy. Mastery of laparoscopic RH (LRH) required experience in at least 25 and up to 50 cases.\textsuperscript{23} To fully clarify the potential disadvantage of MIS and the possible reasons, we will prospectively enrol and assess patients receiving different surgical approaches in 28 Chinese domestic centres (online supplementary table 1). To reduce or even eliminate potential bias caused by the factors of study centres and/or individual surgeons, all the major RH procedures (resection of the parametrium and lymph nodes) will be performed by the indicated surgeons with sufficient experience and skills. A retrospective analysis of the surgical cases of these surgeons will be provided as evidence of learning curves.

**Aims and objectives**

**Primary objective**

1. The primary aim of this RCT is to analyse the 5-year DFS of patients with early-stage cervical cancer receiving different surgical approaches, including MIS (robot-assisted RH (RRH) or LRH) versus ARH.

**Secondary objectives**

1. To assess the OS at the 5-year follow-up in the MIS and ARH groups.
2. To compare the RRH/LRH and ARH, with respect to general QoL, pelvic floor dysfunction (function of the bladder and intestines, sexual function) and cost-effectiveness of health economics.
3. To determine the survival outcomes, general QoL and pelvic floor dysfunction in patients receiving nerve-sparing radical hysterectomy and RH without nerve sparing through the same surgical approach.
4. To investigate the value of cytological testing of peritoneal washes before and after the surgery.
5. To explore the effects of energy devices during the operation on QoL and survival outcomes.
6. To assess the predictive value of the follow-up scheme (physical examination, cervical Pap smear, HPV testing, imaging) in the recurrence of cervical cancer.
7. To assess the potential effects of uterine manipulation and manner of vaginal resection on survival outcomes.
8. To assess the specific recurrent site in the MIS and ARH groups.

**METHODS AND ANALYSIS**

**Study design**

This study is a randomised, controlled, non-inferiority, two-arm trial comparing the efficacy of different surgical approaches on survival and clinical outcomes in Chinese patients with early-stage cervical cancer. A total of 28 domestic centres will recruit 1448 patients (724 per group) from 31 December 2018 through 31 December 2020. A biphasic RCT will be performed to test the feasibility of recruitment and equivalence with regard to DFS and some other outcomes of patients with early-stage cervical cancer. The primary outcomes variable in phase I will be feasibility of recruitment as determined by overall trial recruitment and the analysis of secondary objectives (except the survival outcomes) in 100 patients. During phase II, survival outcomes (OS, DFS) as well as the secondary objectives will be analysed comprehensively. All of these data will be reported to the Data Security Committee (online supplementary table 2) at different time points. The decisions from the Data Security Committee about whether to go on the trial or not will be implemented by the researchers. The CONSORT flow diagram refers to figure 1.

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Recruitment and eligibility
Recruitment began on 31 December 2018. Patients will be enrolled based on the following eligibility criteria:

Inclusion criteria
1. Patients with FIGO (2009) stage IA1 (with lympho-vascular space invasion (LVSI)), IA2 or IB1 cervical cancer and Eastern Cooperative Oncology Group performance status of 0 to 1.
2. Patients with a histological subtype of squamous cell carcinoma, adenocarcinoma or adenosquamous carcinoma.
3. Patients aged 18 years or older.
4. Patients providing informed written consent for participation in this study.
5. Patients scheduled to undergo class B or C surgery of modified Querleu-Morrow (Q-M) surgery classification for IA1 (with LVSI)/IA2 and IB1, respectively.
6. Patients with surgery primarily performed by the surgeons designated in the research centres.

Exclusion criteria
1. Patients with a histological subtype of neuroendocrine, clear cell, serous cell type or metastatic carcinoma rather than squamous cell carcinoma, adenocarcinoma or adenosquamous carcinoma.
2. Patients with stage IA1 without LVSI or clinically advanced disease (stages IB2–IV).
3. Patients with a uterine size larger than 12 cm.
4. Pregnant women.
5. Patients receiving neoadjuvant chemotherapy or radiotherapy.
6. Patients with an estimated life expectancy of less than 6 months.
7. Patients who cannot remain for a long time in the lithotomy and steep Trendelenburg position.
8. Patients with obvious abnormal bladder function before the operation as confirmed by a urodynamic study.
9. Patients with previous pelvic radiotherapy, previous pelvic reconstruction and brain/spinal cord diseases.
10. Patients younger than 18 years old.
11. Patients without a systematic preoperative imaging evaluation (CT, MRI, PET/CT).
12. Patients who are HIV or hepatitis B/C positive, have autoimmune disorders and systemic diseases (such as diabetes mellitus, hormone-treatment diseases, severe liver and kidney dysfunction), or have severe mental illness or a pre-existing cancer diagnosis.

Randomisation
In this study, block competition in the randomisation will be adopted. Once eligible patients are recruited, a randomised number will be allocated by the Central Randomization Management Information System for Clinical Trial (http://random.your-data.cn:8095/random/login.jsp) according to the applying centres.

Interventions
Study centres and surgeon selection
The selection and determination of study centres and surgeons were discussed in the proposal meeting on 23 December 2018. All the surgeons (ie, the principal investigators) from all study centres in online supplementary table 1 have approved the study protocol by a signed research agreement. They are all well-known, experienced surgeons of gynaecological oncology in China who are experienced in both MIS and abdominal RH. To qualify the skills and learning curves of these surgeons, at least 100 unselected, consecutive RH cases for early-stage cervical cancer in their past decade of practice will be retrospectively collected for the analysis of surgical and survival outcomes. These data will be used to verify the learning curves of MIS and ARH in these surgeons in a retrospective cohort study (registration no. NCT03738969, SACCC, ClinicalTrials.gov).

Surgical treatment
Patients eligible for enrolment with early-stage cervical cancer will be randomly assigned to the MIS group and ARH group. Patients diagnosed with stage IA1 with positive LVSI and stage IA2 will undergo Q-M type B2, and stage IB1 patients will be treated with Q-M type C1 or C2 according to the surgeon’s preference. Salpingo-oophorectomy will be performed at the same time for post-menopausal women. Pelvic lymphadenectomy will be performed in all patients, and para-aortic lymphadenectomy will be performed in selected patients of stage IB1
who are suspected to have metastasis to para-aortic lymph nodes during the intraoperative inspection according to the guideline.\textsuperscript{3} Resection of the sentinel lymph node is acceptable but requires clear notification.

1. MIS consists of laparoscopic and robotic RH, which depends on the surgeon’s preference and the setting of study centres.

2. Q-M types follow the criteria of reports from Querleu and Morrow\textsuperscript{20} and Gibula \textit{et al.}\textsuperscript{30} Type B corresponds to the modified radical hysterectomy. Identification of autonomic nerves is not required, and the hypogastric plexus remains fully preserved. Type C1 requires separation of the medial part, which entails recto-uterine and recto-vaginal ligaments, and the lateral laminar structure. Furthermore, type C1 requires only a partial dissection of the ureter from the ventral parametria, which is usually asymmetric towards more extensive resection of the medial leaf of the cranial (above the ureter) part of the ventral parametria. In the C2 type, the ureter is completely dissected from the ventral parametria up to the urinary bladder wall.\textsuperscript{30}

3. Pelvic lymphadenectomy consists of resection of lymph nodes along the bilateral iliac vessels, around the obturator nerve and in the parametrium. However, lymph nodes of the parametrium should be recorded separately.

4. Para-aortic lymphadenectomy consists of four levels: the bifurcate of iliac vessels, the common iliac vessels, inferior mesenteric artery and renal veins.

5. Whether or not a uterine manipulator is used should be clearly stated, and the method of vaginal excision should be clarified as (a) excision after sealing the vagina, (b) excision without sealing the vagina or (c) excision under vaginal exposure.

6. Peritoneal washing for cytology analysis will be collected before and after all the procedures in the MIS and ARH groups.

**Sample size calculation**

The estimations of sample size are listed in table 1. The primary objective of this study is to explore if there are differences between MIS and ARH with respect to DFS. We assume that the rate of DFS at 5 years is approximately 85%, and the non-inferiority threshold of 8% is clinically acceptable. The corresponding HR is set at 1.60 with a significance level, and the power is set at 0.8. A total of 1158 patients with 336 recurrences are needed. Considering the possible 20% rate of loss to follow-up, 1448 patients are needed to accomplish the study goal. The bilateral \(\alpha\) value will be adjusted by the Pocock method to ensure that the total type I errors are controlled within 0.05.\textsuperscript{31} To evaluate patient safety, three rounds of analysis will be carried out at the 1/3, 2/3 and final information points when 112, 224 and 336 recurrences, respectively, occur (the bilateral \(\alpha\) values are 0.02, 0.02 and 0.02; the power values are 0.3, 0.6 and 0.8, respectively). The proportional hazards assumption will be tested at the 1/3 information point as to adjust the following recruiting sample size.

**Measurement**

Clinical assessments at different time points are listed in online supplementary table 3. The patients’ detailed clinicopathological records and surgical details will be collected by medical staff, as well as the complications, disease recurrence and survival information, postoperative adjuvant chemotherapy and/or radiotherapy, and the relevant morbidity. Pathological data will be reported according to a uniform standard.\textsuperscript{32} All data from domestic research centres will be input into the database by trained medical staff, facilitating the real-time assessment of data completeness and patients’ follow-up centrally. Details are as follows:

1. Surgical outcomes include estimated blood loss, transfusion, surgical duration and hospital stay after RH.

2. Pathological outcomes include the measurement of critical parameters of the width or length of the resected parametrium, vagina and uterosacral ligaments under their natural conditions; numbers and locations of harvested lymph nodes; and feasibility of sentinel lymph node biopsy. An independent pathological centre will be set to review all the samples from all the study centres. A standardised FIGO staging system of 2009\textsuperscript{33} should be executed in all study centres since this version of staging is based on the preoperative evaluations. In this system, IA1 has measured stromal invasion of \(\leq 3.0\) mm in depth and extension of \(\leq 7.0\) mm, IA2 has measured stromal invasion of \(>3.0\) mm and not \(>5.0\) mm with an extension of not \(>7.0\) mm, and IB1 had clinically visible lesions \(\leq 4.0\) cm in greatest dimension limited to the cervix uteri or preclinical cancers greater than stage IA.

3. Survival outcomes: The time to recurrence means the duration from the date of surgery to the time the patient is diagnosed with disease recurrence. Disease-specific survival refers to the time from diagnosis to the date of death from cervical cancer–associated complications and/or cancer progression. The OS time is the time from the date of surgery to the date of death (or the last follow-up date if the patient is alive).

4. An authorised Chinese edition of QLQ-C30\textsuperscript{34} and its cervical cancer module QLQ-CX24\textsuperscript{35} will be used to assess the QoL. Sexual function will be assessed using the 19-item Female Sexual Function Index.\textsuperscript{36} Pelvic floor disorders will be assessed using the PFIQ-7 questionnaire.\textsuperscript{37}

5. In the urodynamic study, the residual urine (RU) within 14 days after the RH and a period of RU less than 50 mL from the date of RH will be recorded. Comprehensive urodynamic testing will be performed 4 weeks before the RH, 4 months after the RH and annually after the RH.

6. Anorectal manometry will be performed 4 weeks before the RH, 4 months after the RH and annually after the RH.
**Table 1** Sample size calculations for phase II

| Laparotomic group | Non-inferiority threshold value | 5-year DFS rate | Power | Number of cases required | Times of analysis | Time points of analysis | Threshold value | Nominal α (bilateral) | Cumulative power | Total cases assuming 20% missing follow-up rate |
|------------------|---------------------------------|-----------------|-------|--------------------------|------------------|------------------------|-----------------|----------------------|-----------------|-----------------------------------------------|
|                  |                                 | Non-inferiority threshold value HR |       |                          |                  |                        |                 |                      |                 |                                |
|                  |                                 | 1.6082          | 0.9   | 1529 443                 | 1                | 148                    | 2.27943         | 0.022642 0.394137 | 0.394137 1912 |
|                  |                                 |                 |       |                          | 2                | 296                    | 2.29488         | 0.02174 0.731679 |                    |                                |
| 0.85             | −0.08                           |                 |       |                          | Final            | 443                    | 2.29588         | 0.021683 0.900083 |                    |                                |
|                  |                                 |                 |       |                          | 1                | 112                    | 2.27943         | 0.022642 0.298272 | 0.298272 1448 |
|                  |                                 |                 |       |                          | 2                | 224                    | 2.29488         | 0.02174 0.601534 |                    |                                |
| 0.8              | −0.08                           |                 | 0.8   | 1158 336                 | Final            | 336                    | 2.29588         | 0.021683 0.800055 |                    |                                |
|                  |                                 |                 |       |                          |                  |                        |                 |                      |                 |                                |
|                  |                                 |                 |       |                          | Final            | 324                    | 2.29588         | 0.021683 0.900132 |                    |                                |
|                  |                                 |                 |       |                          | 1                | 104                    | 2.27943         | 0.022642 0.3942   | 0.3942 1692 |
|                  |                                 |                 |       |                          | 2                | 216                    | 2.29488         | 0.02174 0.731754 |                    |                                |
| 0.8              | −0.08                           |                 |       |                          | Final            | 246                    | 2.29588         | 0.021683 0.800144 |                    |                                |
|                  |                                 |                 |       |                          |                  |                        |                 |                      |                 |                                |
|                  |                                 |                 |       |                          | Final            | 246                    | 2.29588         | 0.021683 0.800144 |                    |                                |
|                  |                                 |                 |       |                          | 1                | 82                     | 2.27943         | 0.022642 0.298337 | 0.298337 1280 |
| 0.75             | −0.08                           |                 | 0.8   | 1024 246                 | Final            | 246                    | 2.29588         | 0.021683 0.601635 |                    |                                |
|                  |                                 |                 |       |                          |                  |                        |                 |                      |                 |                                |
|                  |                                 |                 |       |                          | Final            | 215                    | 2.29588         | 0.021683 0.900004 |                    |                                |
|                  |                                 |                 |       |                          | 1                | 72                     | 2.27943         | 0.022642 0.394035 | 0.394035 1416 |
|                  |                                 |                 |       |                          | 2                | 144                    | 2.29488         | 0.02174 0.731558 |                    |                                |
| 0.75             | −0.08                           |                 | 0.9   | 1131 215                 | Final            | 215                    | 2.29588         | 0.021683 0.900004 |                    |                                |
|                  |                                 |                 |       |                          |                  |                        |                 |                      |                 |                                |
|                  |                                 |                 |       |                          | Final            | 215                    | 2.29588         | 0.021683 0.900004 |                    |                                |
|                  |                                 | 1.3921          | 0.9   | 1131 215                 | 1                | 72                     | 2.27943         | 0.022642 0.394035 | 0.394035 1416 |
| 0.75             | −0.08                           |                 | 0.8   | 857 163                  | 2                | 144                    | 2.29488         | 0.02174 0.731558 |                    |                                |
|                  |                                 |                 |       |                          | Final            | 163                    | 2.29588         | 0.021683 0.800153 |                    |                                |
|                  |                                 |                 |       |                          |                  |                        |                 |                      |                 |                                |

DFS, disease-free survival.
7. Complications will be recorded as intraoperative, perioperative, early (<4 weeks) postoperative and delayed postoperative (4 weeks to 6 months after the RH) complications according to the protocol of LACC trial, and the severity will be judged by the Common Terminology Criteria for Adverse Events V.4.03.

8. Health economic data, such as hospitalisation expenses for admission surgery, direct costs of radiotherapy, total costs of chemotherapy and hospitalisation expenses due to complications within 4 weeks after surgery, will be collected. Total hospital costs include procedure-specific costs, blood transfusions and costs for readmissions and re-interventions until 3 months after surgery. The hospital internal charges and purchase costs will be used for estimation.

**Safety and adverse events**

After the accrual of 100 patients in phase I, data will be analysed to allow the determination of several key components of the study, which are not the primary end points specified in the protocol. These components will include the rate of accrual and compliance with randomised treatment allocation and the analysis of secondary objectives (except the survival outcomes). If the rate of surgical complications in the MIS group is greater than 8% or if 100 patients are enrolled for more than 6 months, the study will be terminated.

This trial will be conducted in compliance with this study protocol. The Data Safety Monitoring Committee receives study data regularly, including complications and survival outcomes. The committee will investigate the data and decide whether to continue the study at indicated check points of the recurrent patients when reaching 112, 224 and 336 cases.

**Statistical analysis**

Continuous variables conformed to the normal distribution will be described with means and SD, and discrete variables not conformed to the normal distribution will be summarised with medians, ranges and IQRs. The t-test and non-parametric analysis will be used for continuous variables with and without normal distribution, and the χ² test or Fisher’s exact test will be used for categorical variables. Mixed-effects model or repeated ANOVA analysis, and multilevel model would be carried out to improve the statistical performance for the comparisons carried out in every key point of this study. To evaluate the strength of associations, bivariate and multivariable logistic regression analyses will be used, and the strength of associations will be expressed as HRs with 95% CIs. Kaplan-Meier plots will be generated for recurrence and death rates between the groups, and the log-rank test will be applied for the eventual significant differences. The survival outcomes will be compared according to intention-to-treat and per-protocol basis. Unless otherwise stated, all analyses will be performed with a two-sided significance level of 0.05 and conducted with the use of SPSS V.23.0 software.

**Cost-effectiveness analysis**

The cost-effectiveness is measured as the incremental cost/unit of improvement in functional outcome and is measured in terms of the primary outcome plus using quality-adjusted life years to undertake a cost–use analysis. Three separate models can be used to compare the costs associated with MIS and ARH for the treatment of early-stage cervical cancer: (1) a societal perspective model, which includes inpatient hospital costs, MIS expenses, lost wages and caregiver costs; (2) a hospital perspective plus MIS costs model, which is identical to the societal perspective model but excludes lost wages and caregiver costs; (3) a hospital perspective without MIS costs model, which is identical to the hospital perspective plus the MIS costs model except that it excludes the initial cost of the MIS.

**Limitations**

There are two main shortcomings in this study. First, the emphasis on the individual surgeon’s experience and skill will probably limit generalisation of the conclusions of this study. Second, it will probably be difficult to explain the study design to the patients and obtain informed consent because of the existing conclusions of the LACC trial and other studies.

**Patient and public involvement**

Participants who are interviewed will be informed that they have the right to freely withdraw from the study, for any reason, at any time prior to their data being integrated into the database. In the current trial, no patients were involved in the design of the study or in the selection of outcome measures. Furthermore, patients will not be involved in the recruitment of participants or in decisions regarding the research profiles.

**ETHICS AND DISSEMINATION**

The trial will be conducted in compliance with this study protocol. All procedures performed in the study involving human participants will be in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The Data Safety Monitoring Committee will monitor the adverse events at the indicated checkpoints of the study period. This study will be reported in accordance with the CONSORT statement for non-pharmacological trials.

**Current trial status**

Recruitment of participants began in December 2018, and the last participant is expected to reach the primary endpoint (5-year follow-up) in December 2025. Primary data analysis will begin in December 2023. The naturalistic follow-up phase of the trial will continue until December 2025.

**CONCLUSION**

In this phase III multicentre randomised controlled study, study centres and individual surgeons will be...
integrated as important influencing factors in survival outcomes in patients with early-stage cervical cancer receiving different surgical approaches (MIS vs ARH). Other important surgery-associated profiles, such as the role of nerve-sparing procedures, QoL and cost-effectiveness, will also be assessed.

Contributors LL and MW conceived of the original idea for the study, carried out the statistical analysis, edited the paper and were overall guarantors. XC obtained ethical approval, contributed to the preparation of the data set and contributed to drafts of the paper. SM, XT, SZ, JL, AC and WL contributed to the study design, interpretation of results and commented on drafts of the paper.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study has been approved by the Institutional Review Board of Peking Union Medical College Hospital (registration no. JS-1712) and filed on record by all other centres.

Provenance and peer review Not commissioned; externally peer reviewed.

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