Comparison of combined lumbar and sacral plexus block with sedation versus general anaesthesia on postoperative outcomes in elderly patients undergoing hip fracture surgery (CLSB-HIPELD): study protocol for a prospective, multicentre, randomised controlled trial

Junfeng Zhang, Xiaofeng Wang, Hui Zhang, Zhuolin Shu, Wei Jiang

ABSTRACT

Introduction Hip fracture in elderly people is a global public health problem, with substantial associated mortality and disability. Nearly all patients with hip fracture undergo surgical treatment, but optimal anaesthesia for hip fracture surgery in elderly patients is still inconclusive. Ultrasound-guided combined lumbar and sacral plexus block has been widely used in hip fracture surgery in recent years, especially for some high-risk patients. However, it is not clear whether it can improve the postoperative outcomes of elderly patients with hip fracture.

Method and analysis This research project is a two-arm, parallel, multicentre, prospective randomised controlled trial. A total of 1086 patients aged 75 and older scheduled for hip fracture surgery in five clinical trial centres of China will be randomised in a 1:1 ratio to receive either combined lumbar and sacral plexus block plus sedation or general anaesthesia. The primary outcome will be the postoperative 1-year all-cause mortality. The secondary outcomes will be the incidence of postoperative complications, high-sensitivity cardiac troponin T, early mobility after surgery, postoperative Visual Analogue Scale pain scores, Barthel Index and incidence of adverse events after discharge. Assessments will be conducted in four steps: preoperative, intraoperative, in-hospital data collection and post-discharge telephone follow-up.

Ethics and dissemination This study has been supported by Shanghai Municipal Commission of Health and Family Planning Foundation for Key Developing Disciplines (2015ZB0103) and approved by the Ethics Committee of Shanghai Sixth People’s Hospital (No: 2016–28–(2)). At the time of manuscript submission, the protocol version is V.1.6 (March 2nd, 2018) with one subsequent approved amendment. Results will be disseminated via an international peer-reviewed publication.

Trial registration number NCT03318133.

Strengths and limitations of this study

- This study will be the first prospective, multicentre, randomised controlled clinical trial to investigate the effect of the two anaesthesia techniques on long-term prognostic indicators in elderly patients with hip fracture.
- The results of this study will help elucidate whether combined lumbar-sacral plexus block plus sedation could be safely used in hip fracture surgery and reduce the incidence of perioperative complications and improve long-term outcome in elderly patients.
- Our study results will be limited to Chinese population, and further studies on other ethnic backgrounds will be required.

BACKGROUND

Hip fracture is a global public health problem with an incidence of more than 1.6 million worldwide each year. Owing to the global increase of the population aged 65 years and over, the total number of hip fracture is expected to surpass 6 million by 2050. While early surgery is the most effective treatment method, the postoperative mortality and disability rates are still high. The elderly patients with hip fracture frequently have multiple comorbidities, which put these patients at high risk of morbidity and mortality after anaesthesia. Seeking appropriate anaesthesia technique is in urgent need to ensure that these patients can safely and effectively get through the perioperative period. Most studies assessing the relationship between anaesthesia technique and outcomes mainly focus on the comparisons between
neuraxial anaesthesia (including spinal and epidural anaesthesia) and general anaesthesia (with an endotracheal tube or a laryngeal mask airway [LMA]). A recently updated systematic review and meta-analysis has found no difference between regional versus general anaesthesia, but they also supposed that the number of participants included in the review was insufficient to eliminate a difference between the two techniques in the majority of outcomes studied. Some other investigations have shown that neuraxial anaesthesia for hip fracture can reduce postoperative morbidity, but two recent large-sample size observational studies deemed that neuraxial anaesthesia could not significantly improve the prognosis of patients. However, all of the above are retrospective observational studies, in which anaesthesiologists might have selected the anaesthesia technique based on their practice style and a variety of patient-related factors. For example, patients with coagulation dysfunction would have contraindication to neuraxial anaesthesia and must receive general anaesthesia. Neuraxial anaesthesia is thought to be less postoperative complications, so elderly or critically ill patients might be more likely to receive neuraxial anaesthesia, rather than being randomly assigned to different anaesthesia groups. Therefore, there could be selection bias that affected the clinical significance of those results. In addition to general anaesthesia and neuraxial anaesthesia, ultrasound-guided lumbar and sacral plexus block has been widely used in hip fracture surgeries in recent years, especially for some high-risk patients with cardiopulmonary dysfunction. Compared with neuraxial anaesthesia, combined lumbar and sacral plexus block is associated with less sympathetic block and better cardiovascular function stability. In addition, combined lumbar and sacral plexus block plus sedation could avoid endotracheal intubation or LMA insertion and thereby might reduce the complications related to the general anaesthesia. A recent small sample size retrospective study compared the effect of general endotracheal anaesthesia, neuraxial anaesthesia and lumbar and sacral plexus block on the prognosis of patients with hip fracture, and the results showed that neuraxial anaesthesia and combined lumbar and sacral plexus block could reduce the total mortality, and there was no significant difference between neuraxial anaesthesia and combined lumbar and sacral plexus block. But the number of elderly and high-ASA (American Society of Anaesthesiologists)-grade patients in the combined lumbar and sacral plexus block group was significantly greater than that in the neuraxial anaesthesia group, suggesting that when comparing the effect of these two anaesthetic methods in similar conditions, combined lumbar and sacral plexus block might have more advantages. However, it is not clear whether ultrasound-guided combined lumbar and sacral plexus block plus sedation could improve outcomes of elderly patients with hip fracture.

This paper describes the design of a prospective, multicentre, parallel, randomised controlled clinical trial to assess the effect of ultrasound-guided combined lumbar and sacral plexus block plus sedation versus general anaesthesia on the postoperative outcomes in elderly patients with hip fracture.

METHODS AND ANALYSIS
Patient and public involvement
Patients and public were not involved in the design or conduct of the study. We do not have any specific plans to disseminate our results to patients.

Study design
This will be a two-arm, parallel, multicentre, prospective, randomised controlled trial and the design of this study protocol has referred to the Standard Protocol Items: Recommendations for Interventional Trials 2013 guideline.

Study location
The study will be conducted in five teaching hospitals including Shang Sixth People’s Hospital (Shanghai, China), Beijing Chaoyang Hospital (Beijing, China), Beijing Jishuitan Hospital (Beijing, China), First Affiliated Hospital of Wenzhou Medical University (Wenzhou, China) and Foshan Hospital of Traditional Chinese Medicine (Foshan, China).

Study population
Although elderly population was considered to be people older than 65 years in the present studies, introduction to ageing population is latening owing to increasing life expectancy. As shown in a recent study, age is the primary risk factor on first year mortality in patients older than 75 years old with hip fractures. In addition, China wants to increase its citizens’ average life expectancy to 77.30 by 2020 and 79.00 by 2030, up from 76.34 in 2015, according to ‘Plan of Health China 2030’ published in 2015. We thus used 75 years as an age cut-off for inclusion criteria in this study because optimal selection of anaesthesia technique in this age group might have more clinical significance.

Elderly patients above 75 years scheduled for hip fracture surgery will be recruited voluntarily according to the inclusion and exclusion criteria below. All included patients are suitable for either general endotracheal anaesthesia or combined lumbar and sacral plexus block plus sedation, which will not bring tendency to choose a specific type of anaesthesia.

Inclusion criteria
► Age ≥75 years old.
► First unilateral surgery for hip fracture including femoral neck, intertrochanteric or subtrochanteric fracture.
► Patient with planned hip fracture surgery within 24–72 hours.
► Patient without peripheral nerve block within 24 hours prior to surgery or patients with preoperative

peripheral nerve blockade but its effect had faded away at the beginning of the operation.

- The ability to receive written informed consent from the patient or patient’s legal representative.

**Exclusion criteria**

- Refuse to participate.
- Unable to perform nerve block.
- Multiple trauma, multiple fractures or other fractures outside the inclusion criteria, such as pathological fractures, pelvic fractures, femur fractures.
- Prosthetic fracture.
- Scheduled for bilateral hip fracture surgery.
- Usage of bone-cement fixation in the surgery.
- With recent cerebral stroke (<3 months).
- Concomitant active heart disease (unstable angina, acute myocardial infarction, recent myocardial infarction; decompensated heart failure; symptomatic arrhythmia; severe mitral or aortic stenosis heart disease).
- Patient with known severe lung and/or airway disease, acute respiratory failure, acute pulmonary infection and acute attack of bronchial asthma.
- Current enrolment in another clinical trial.
- Contraindication for general endotracheal anaesthesia (drug allergies to general anaesthesia, difficult airway).
- Contraindication for lumbar and sacral plexus block (infection at the site of needle insertion, coagulopathy, allergy to local anaesthetics).

**Interventions**

Eligible patients will be randomly assigned into either CLSB group receiving combined lumbar and sacral plexus block plus sedation or general anesthesia (GA) group receiving general anaesthesia with endotracheal intubation or LMA (figure 1). Standard anaesthetic and surgical methods will be applied to ensure the consistency of treatment in the participating centres. Experienced and qualified anaesthesiologists in every clinical centre...

*Figure 1* Consolidated Standards of Reporting Trials flowchart designed for subject enrolment. CSLB, combined lumbar-sacral plexus block; GA, general anesthesia; LMA, laryngeal mask airway.
will be specifically designated to perform CLSB plus sedative anaesthesia or GA in order to minimise the potential bias. To improve adherence to intervention protocols, study personnel are trained to follow the study protocol in accordance with the Good Clinical Practice principles.

In the CLSB group (CLSB with sedative anaesthesia), the procedures will be performed as followed:

- Peripheral venous access for fluid infusion will be established.

- In the lateral decubitus position with the operated side uppermost, ultrasound-guided lumbar plexus block (L2-3 or/and L3-4 vertebral space level, 0.375% ropivacaine 25 mL) will be performed, followed by sacral plexus block (0.375% ropivacaine 20 mL); We used the nerve stimulator to confirm the needle’s correct position by a quadratus femoris twitch for lumbar plexus block and hamstring, leg, or foot switches for sacral plexus block at a current within 0.4–0.6 mA, followed by relevant volume of 0.375% ropivacaine that was slowly injected in 5 mL increments to surround the target nerve under ultrasound monitoring.

- Radial arterial catheterisation under local lidocaine anaesthesia and arterial blood pressure monitoring will be performed. Blockade effectiveness will be evaluated 30 min after nerve block; The intervention will be discontinued for a given patient and convert to general anaesthesia with endotracheal intubation or LMA if the satisfactory blockade is not acquired. These patients are still followed up for further statistical analysis according to the formal protocol because they have been randomly allocated.

- After confirmation of satisfactory blockade, target-controlled infusion of propofol will be used to maintain Ramsay sedation score between 3–4 points. $P_{\text{ET}}CO_2$ will be monitored through nasopharyngeal airway. Small-dose sufentanil (1–2 µg each time) will be titrated to maintain spontaneous breathing.

In the GA group, the procedures will be performed as followed:

- Peripheral venous access for fluid infusion will be established.

- Radial arterial catheterisation under local lidocaine anaesthesia and arterial blood pressure monitoring will be conducted.

- Anaesthesia will be induced with propofol (1.5–3 mg/kg), rocuronium (0.3–0.9 mg/kg) and sufentanil (0.2–0.6 µg/kg) for tracheal intubation or LMA insertion. Mechanical ventilation will be performed to maintain normal $P_{\text{ET}}CO_2$.

- Sevoflurane, propofol and sufentanil will be used to maintain anaesthesia during surgery, while rocuronium will be added as needed.

During surgery, fluid infusion and blood transfusion will be used to maintain stable haemodynamics. Perioperative arterial pressure lower than 30% of the baseline will be defined as hypotension, on which ephedrine or phenylephrine will be administrated. The type and dosage of infusion depends on anaesthesiologist’s experience. Blood transfusion will be given according to blood loss and haemoglobin concentration (Hb) level (80–100 g/L). Following surgery, patients will be sent to the postanaesthesia care unit and then transferred to orthopaedic ward or intensive care unit (ICU) according to the local procedures of each clinical centre. Postoperative analgesia can be administrated with regard to the routine clinical practice of each trial site, aiming to maintain a Visual Analogue Scale (VAS) pain score ≤3.

Outcomes and measurements

Primary outcome

Postoperative 1-year all-cause mortality (follow-up time points are set as 1 month, 3 months, 6 months and 1 year after surgery).

Secondary outcomes

Occurrence of intraoperative complications, including:

- Intraoperative hypotension and vasopressor dosage.

- Intraoperative arrhythmia, myocardial ischaemia, myocardial infarction, massive haemorrhage, pulmonary embolism and hypoxaemia.

- Intraoperative blood loss and blood transfusion volume.

High-sensitivity cardiac troponin T (hs-cTnT), measured on the 1 and 3 days after surgery.

Early mobility after surgery.

Incidence of various complications and Comprehensive Complication Index (CCI) during hospitalisation after surgery.

Postoperative analgesic effectiveness within 3 days after the surgery.

Incidence of delirium on the 1, 2 and 3 days after surgery, diagnosed with confusion assessment method (CAM).

Sequential Organ Failure Assessment (SOFA), assessed on the 1 and 3 days after surgery.

Bauer Patient Satisfaction Questionnaire, assessed on the 3 days after surgery.

Length of stay in ICU and hospital.

Other observational variables

Economic parameters including total cost in hospital and expenditure for anaesthesia.

Functional recovery on the 30 days after surgery, evaluated by Barthel Activities of Daily Living Index (Barthel Index).

Post-discharge destination, and incidence of complications and adverse events after discharge.

Participant timeline

For a given participant, assessment will be performed 1 day prior to surgery and again on the day of surgery to confirm whether qualified for enrolment. Randomisation will perform on the day of surgery. And then intervention will be performed. The accrual period of this trial is expected to be about 1 year. The patients will be followed up on the 1, 2 and 3 days after surgery and on the day of discharge. The total follow-up period will be set as 1 year.
and the telephone follow-up will be conducted at the 1, 3, 6 and 12 months after surgery.

Power and sample size calculation
We estimate the sample size using the formula by Schoenfeld under the assumption of the validity of the proportional-hazards regression model.\(^\text{23 24}\) We take significance level 0.05 (one-sided) and power 0.80. Patients will be randomly assigned to one of the two anaesthesia groups in five different clinical centres. A retrospective study included patients over 65 years old showed that the 1-year mortality was 41.7\% for GA group and 28.3\% for combined peripheral nerve block group.\(^\text{14}\) In this study, only patients with age 75 years or older will be included, so we expect the actual mortality of the GA group will be higher than that in the previous study. Therefore, we assume the mortality to be 55\% for GA group and 46.75\% for CLSB group (15\% relative reduction compared with GA group). Then the sample size needed for this study is 868 (with 434 in each of the two groups). When the mortality of the GA group is only 45\%, the above calculated sample size can still detect a 20\% improvement in the CLSB group with the power of at least 0.80. In consideration of the possible lost to follow-up, we add an additional 20\% to the above calculated sample size. So, the total number of patients needed for this study is 1086.

Randomisation and blinding
On the receipt of informed consents, patients will be randomly assigned to the two groups in any one of the five centres. Sequentially numbered sealed opaque envelopes with group allocation inside altered anaesthetist to use CLSB or GA. The R programme will be used to generate randomisation block allocation for each of the five centres with randomly selected block sizes of four, six and eight. The envelopes will be placed in the patient’s chart before the start of each procedure by a doctor of the research team. The research staff who will interview patients postoperatively are blinded for the allocated treatment. The statistician will be blinded. A spreadsheet linking the patient number and name will be password protected and kept on a research computer. The recruitment will stop when the total number of patients reaches 1086. The subjects and intervention performers (anaesthesiologists) know the randomised allocation, but the follow-up personnel and statistician were blinded to the randomised allocation and intervention.

Data collection and management
Data will be collected in four steps: preoperative, intraoperative, in-hospital data collection and post-discharge telephone follow-up.

Preoperative data
Basic information including name, admission number, height, weight, gender, age, blood pressure, heart rate and ASA grade.

Preoperative information including diagnosis, type of surgery, type and dosage of anticoagulants, and days passed until surgery.

Preoperative complications and medication related to cardiovascular disease, stroke, respiratory disease, kidney disease, diabetes, Parkinson’s disease and deep venous thrombosis of lower extremity if any.

Preoperative examination results including blood gas analysis, ECG, echocardiography, blood routine testing, liver and kidney function testing, coagulation testing (D-dimer), Pro-BNP, hs-cTnT and lower extremity vascular ultrasonography.

Preoperative evaluation results including Mini-mental State Examination, SOFA and Barthel Index, all of which might be associated with the postoperative complications.

Intraoperative data
Duration of surgery, incidence of intraoperative hypotension or hypertension and vasoactive drug dosage.

Intraoperative blood loss, blood transfusion volume and intraoperative fluid infusion volume.

Intraoperative arrhythmia (sinus bradycardia, sinus tachycardia, ventricular arrhythmia, atrial arrhythmia, etc), myocardial ischaemia and myocardial infarction.

Intraoperative complications: massive haemorrhage, pulmonary embolism, allergic reaction, hypoxaemia, bronchospasm, gastric reflux and aspiration.

Intraoperative conversion of anaesthesia and the relevant causes.

In-hospital data
High-sensitivity cardiac troponin T (hs-cTnT), measured on the 1 and 3 days after surgery.

Earlier mobilisation and postoperative hip rehabilitation: the daily degree of maximal hip flexion and abduction will be recorded.\(^\text{25}\) The day after surgery, all two groups will start an identical physical therapy regimen. The patients will perform passive and active hip flexion and abduction exercises two times per day. Patients will be encouraged to get out of bed as soon as possible and try ambulation with a walker. The maximal degree of hip flexion and abduction tolerated by each patient will be recorded for 3 days. The day of first ambulation will be also recorded for each group.

Postoperative complications including incidence and severity of various complications and the CCI\(^\text{19}\) value at discharge. Complications were assessed and graded using the Clavien-Dindo classification. CCI will be derived from these features at discharge, using the CCI calculator available online (www.assessurgery.com). Complications include:

► Myocardial ischaemia, myocardial infarction, heart failure, arrhythmia.
► Pulmonary infection, respiratory failure, pulmonary embolism.
► Postoperative delirium.
► Cerebral ischaemia, cerebrovascular accident.
► Renal failure, urinary retention.
Regurgitation and pulmonary aspiration.
Postoperative nausea and vomiting.
Postoperative bleeding and 24 hours postoperative drainage volume.
Reoperation.

The intensity of postoperative pain at rest and on movement will be assessed with Visual Analogue Scale (VAS) (0 no pain and 10 worst possible pain) at the 24, 48 and 72 hours after surgery.
CAM will be evaluated on the 1, 2 and 3 days after surgery.
SOFA\(^\text{21}\) will be evaluated on the 1 and 3 days after surgery.
Bauer Patient Satisfaction Questionnaire will be assessed on the 3 days after surgery.
Length of ICU stay, length of hospital stays, total hospitalisation cost and expenditure for anaesthesia.

Post-discharge follow-up data
Telephone follow-up will be performed on the 1, 3, 6 and 12 months after surgery to collect the following information.
Discharge destinations. Disposition status after discharge will be classified as follows: dead, nursing home (eg, skilled nursing facility, intermediate care facility, extended care facility, nursing home), community dwelling (eg, home alone, home with others), or other.
Dead or not, specific cause and time.
Incidence of complications and adverse events: heart, lungs, brain, liver, kidney, four limbs and hospitalisation, etc.
Barthel Index for evaluation of functional recovery will be collected on the 30 days after surgery.

Data and safety monitoring
Preoperative, intraoperative and in-hospital data will be collected from the electronic medical record, monitor machines and relevant manual records by one of the research staff. Telephone follow-up will be conducted by the research team. Data will be securely managed by an independent contract research organisation (Shanghai Ruihui Biotech Co., Ltd, Shanghai). All serious adverse events, as well as all non-serious adverse events that are unexpected and judged to be related to the study treatment, will be recorded in the study database and reported as required to local IRBs (institutional review board) and to the Shanghai Jiao Tong University Affiliated Sixth People’s Hospital IRB. Data and safety monitoring will be the responsibility of the study director/principle investigator (PI), the study biostatistician, site clinical directors and an independent Data and Safety Monitoring Board (DSMB) selected by the study PI. The DSMB will be composed of 5–7 independent, multidisciplinary experts who are not have subordinate relationships with the PI or any member of the study team. The DSMB will review study implementation and the occurrence of adverse events.

Statistical analysis
The data will be analysed using intention-to-treat approach. Demographics information will be compared for patients of the two groups to ensure the data are balanced. Student t-test will be used for quantitative variables such as age, and heart rate, blood pressure. \(\chi^2\) test will be used for categorical variables such as sex, ASA classification grades. The VAS pain scores will be analysed using repeated measure ANOVA to test the effects of treatment, time and the interaction effect. The effects of different covariates on the mortality measured at 1 month, 3 months, 6 months and 12 months will be assessed using a logistic regression model. The primary analysis model will be Cox regression model with covariates. Either logistic regression or ordinary multiple regression method will also be used to assess the effects of the covariates on the secondary and other outcomes as well depending on the type of dependent variable. The proportional-hazards regression model will be used to compare the survival times of the patients in the two groups and to assess the effects of the covariates. The statistical analysis will be performed using statistical software SPSS V.24.0 (IBM Corporation, Armonk, New York, USA) with a significance level of 0.05.

Access to data
During the study, data will be stored in a password-protected system and can be accessed by the research staff who sign the confidential disclosure agreements. Data without patient identification will be publicly accessible after the study.

Confidentiality
Each participant will be given an identification number and referred by the identification number throughout the study and in all study-related information. This information will be securely stored in a password-protected access system provided by a local supplier. Relevant paper records will be stored in a locked cabinet in an access-controlled room. All records containing any patients’ personal identifiers will be separately stored similarly as above.

Trial status
At the time of manuscript submission, the study is in the preparation phase for recruitment.

DISCUSSION
Choice of anaesthesia for hip fracture surgery in elderly patients is still inconclusive. General anaesthesia with endotracheal intubation or LMA is a common procedure for hip fracture surgery, with advantages of wide indications and maintaining relatively stable haemodynamics. Compared with general anaesthesia, neuraxial anaesthesia avoids endotracheal intubation or LMA insertion. But vertebral degeneration and anatomical abnormalities in elderly patients often make neuraxial anaesthesia puncture difficult, and most of these patients are taking anti-coagulants, which are the contraindication of neuraxial anaesthesia. So, the neuraxial anaesthesia has limitations
in application for the elderly patient. The principle for anaesthesia selection is to reduce or avoid the effect of anaesthesia on systemic and vital organ functions as much as possible when meeting the needs of surgery. Previous lumbar and sacral plexus block depends on blind puncture technique and cannot ensure the clinical effectiveness. However, ultrasound visualisation technology has promoted the wide application of lumbar and sacral plexus block. Combined lumbar and sacral plexus block with sedative anaesthesia has gradually become an alternative approach for hip fracture surgery in elderly patients, and this anaesthetic technique has been massively applied in our department and achieved satisfactory clinical results in recent years, but there are few reliable clinical evidences on whether it can be safely used for hip fracture surgery in elderly patients and improve the short-term or long-term outcomes. Thus, we have designed this trial protocol to illustrate the clinical value of combined lumbar and sacral plexus block with sedative anaesthesia in elderly patients undergoing hip fracture surgery. In this study, we will observe the effect of the two anaesthetic methods (general endotracheal anaesthesia or combined lumbar and sacral plexus block plus sedation) on the early prognostic indicators in elderly patients with hip fracture, including postoperative complications, postoperative analgesic effect, postoperative early mobility, postoperative delirium, patient’s satisfaction to anaesthesia and length of stay in ICU and hospital. This study will be the first prospective, multicentre, randomised controlled clinical trial to investigate the effect of the two anaesthesia techniques on long-term prognostic indicators in elderly patients with hip fracture, including postoperative 1-year all-cause mortality and incidence of complications and adverse events. The results of this study will help elucidate whether ultrasound-guided combined lumbar and sacral plexus block with sedative anaesthesia can be safely used in hip fracture surgery in elderly patients and can reduce the incidence of perioperative complications and improve long-term prognosis, so as to solve the troubling clinical problem and provide a theoretical basis for elderly patients undergoing hip fracture surgery to choose the optimal anaesthetic method.

Contributors JZ and WJ designed the study and wrote the protocol. HZ, XW and ZS were involved in protocol conception and design and manuscript revision. WJ is the principal investigator of this clinical trial. All authors read and approved the final version of the manuscript.

Funding This study is supported by Shanghai Municipal Commission of Health and Family Planning Foundation for Key Developing Disciplines (2015ZB0103).

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

REFERENCES