A study protocol for investigating the sonographic characteristics of neonates with critical illness: an observational cohort study

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ABSTRACT

Background  Haemodynamic instability and hypoxaemia are common and serious threats to the survival of neonates. A growing body of literature indicates that critical care ultrasound has become the optimal evaluation tool for sick neonates. However, few studies have described sonographic characteristics of haemodynamics systematically in the neonates with critical illness. This protocol describes a prospective observational cohort study aimed at (1) characterising the sonographic characteristics of the neonates with critical diseases; and (2) assessing the mortality, significant morbidity, utility of vasoactive medications, fluid resuscitation, duration of ventilation, etc.

Methods and analysis  This is a single-centre, prospective and observational study conducted in Chengdu Women’s and Children’s Central Hospital from 1 December 2022 to 31 December 2027. Neonates admitted to the neonatal intensive care unit will be recruited. After inclusion, the neonates will undergo the neonatal critical care ultrasound. The data collected via case report forms include clinical variables and sonographic measures. The primary outcome is to identify the sonographic characteristics of sick neonates with different diseases, and the secondary outcome is to describe the mortality, significant morbidity, utility of vasoactive medications, fluid resuscitation and duration of ventilation.

Discussion  Our study provided an organised neonatal critical care ultrasound workflow, which can be applied in practice. Accordingly, this study will first set up large data on the sonographic description of the neonates with critical illness, which can help to understand the pathophysiology of the critical illness, potentially titrating the treatment.


BACKGROUND

Haemodynamic instability and hypoxaemia are common and serious threats to the survival of neonates, which are associated with mortality, bronchopulmonary dysplasia (BPD), intraventricular haemorrhage (IVH) and long-term neurological development delay. However, the management of haemodynamic instability and hypoxaemia is challenging due to the complexity of the physiology and pathophysiology in the neonatal period.

The physiological characteristics of neonatal haemodynamics are significantly different from those of children and adults. For example, every neonate experiences a transition from fetal circulation to postnatal circulation with rapid changes in environmental conditions. Physiological pulmonary hypertension is presented in the first few months of life. The neonatal myocardium is particularly vulnerable to hypoxia.
and hyperoxia due to the imbalance between oxidant and antioxidant levels.\textsuperscript{11, 12} Therefore, the ability to respond to additional stress may be limited. Regarding the developing brain, the neonatal cerebral autoregulation seems intact in term infants\textsuperscript{13, 14} but lacking in the preterm brain.\textsuperscript{15-18} In addition to the above challenges, several events can easily disrupt the perinatal transition and contribute to the pathophysiology of haemodynamic instability.\textsuperscript{1} For example, asphyxia at birth, respiratory distress syndrome (RDS), pneumothorax, sepsis, haemodynamically significant patent ductus arteriosus (hsPDA),\textsuperscript{17} hypothermia and hyperosmolarity. Importantly, end-organ perfusion is easily impacted, resulting in the increased occurrence of IVH, periventricular leucomalacia, retinopathy of prematurity and necrotising enterocolitis (NEC).\textsuperscript{18-21} Therefore, an understanding of the physiology and pathophysiology of the critical illness will improve the quality of care in sick neonates.

Currently, some assessment techniques are used in the neonatal intensive care unit (NICU) settings to monitor and assess haemodynamic conditions and oxygenation,\textsuperscript{22} for example, blood pressure (invasive or non-invasive), heart rate, non-invasive cardiac output measurement, near-infrared spectroscopy, echocardiography, lactate, central venous pressure, etc. However, some of the techniques are invasive, or the sensitivity and specificity of some indicators are relatively low, or the clinical significance of some indicators is limited.\textsuperscript{23} For example, systemic blood pressure probably does not provide precise cerebral blood flow information. A growing body of literature indicates that critical care ultrasound (CCUS) (also known as point-of-care ultrasound) has become the optimal tool for evaluation, diagnosis, monitoring and guidance for invasive procedures in sick neonates,\textsuperscript{24-27} which can help clinicians treat patients based on physiology and pathophysiology.\textsuperscript{9} It is characterised as a real-time bedside assessment tool used by frontline clinicians.\textsuperscript{28} The modality of CCUS consists of the brain, heart, pulmonary and vascular system, abdomen and kidneys.\textsuperscript{24} Unlike ultrasound studies performed in the radiology department, which evaluate all organs in an anatomical region, CCUS is often performed to evaluate a particular pathophysiology. Its key purpose is to apply goal-directed examinations to immediately diagnose and manage life-threatening conditions, such as respiratory failure and undifferentiated shock.\textsuperscript{29} The studies in adults have demonstrated that CCUS, in addition to clinical assessment, can improve diagnostic accuracy, identify life-threatening signs rapidly, guide the management of haemodynamic instability and further improve outcomes.\textsuperscript{28, 30-35}

For the sick neonates, the pulmonary system, cardiovascular system and brain are usually involved together. Therefore, a thoughtful and structured sono- graphic workflow in sick neonates is required. Few studies have proposed a sonographic workflow in sick neonates,\textsuperscript{19, 24, 36} but mainly focused on echocardiography (Targeted neonatal Echocardiography, TnECHO) or lung ultrasound rather than comprehensive sonographic assessment.\textsuperscript{37-42} The comprehensive sonographic characteristics in critically ill neonates remain uncertain.\textsuperscript{9, 24, 43-44}

**OBJECTIVES**

The aims of this study are to (1) characterise the sonographic characteristics of the sick neonates with different diseases, such as sepsis, persistent pulmonary hypertension of the newborn (PPHN), etc; and (2) assess the mortality, major morbidity, utility of vasoactive medications, etc.

**Methods and analysis**

**Study design and setting**

This is a single-centre, prospective and observational study conducted in Chengdu Women’s and Children’s Central Hospital from 1 December 2022 to 31 December 2027 (see the design schematic in figures 1 and 2). Chengdu Women’s and Children’s Central Hospital is a level IV NICU and the neonatal critical care referral centre in Sichuan province. CCUS has been performed in our centre since 2018. Six trained neonatologists are in charge of the CCUS reporting. All had attended the uniform training programme and were certified by the Chinese Critical Ultrasound Study Group. The medical information questionnaires (case report form, CRF) include clinical variables and sonographic measures. Two researchers independently check and record the data to ensure accuracy. Each CRF is assigned a unique identifier number and the initials of the patient’s first name and family name to maintain confidentiality.

**Study population**

Study participants will enter the cohort after they meet the inclusion/exclusion criteria.

**Criteria for patient inclusion:**

1. Age from day 0 to 28.
2. Need for respiratory or circulatory support. The respiratory support includes invasive or non-invasive ventilation support, such as continuous positive airway pressure, high-flow nasal cannula oxygen therapy and non-invasive positive pressure ventilation. The circulatory support includes volume expansion, and vasoactive or positive inotropic drugs.
3. Requiring hypothermia, blood exchange transfusion, extracorporeal membrane oxygenation, continuous renal replacement treatment, any surgery and anti-convulsant therapy, and having severe intraventricular haemorrhage (sIVH) (grade 3 or 4).\textsuperscript{45}
4. Consent to participate in the study.

**Criteria for patient exclusion:** discharged within 24 hours after admission.

**SAMPLE SIZE**

This study first aims to characterise the sonographic characteristics of the sick neonates with different diseases.
Therefore, we will include all the participants who met the inclusion/exclusion criteria in Chengdu Women’s and Children’s Central Hospital from 1 December 2022 to 31 December 2027. Because there are approximately 1000 sick neonates admitted to our NICU per year, a minimum of 5000 individuals will be recruited.

The definition and scope of the Neonatal Intensive Critical Ultrasound Examination

The Neonatal Intensive Critical Ultrasound Examination (NICUltra) workflow is constructed based on the principle of adult CCUS, which is based on neonatal physiology, disease spectrum and treatment strategy. This workflow included the heart, pulmonary system, brain, other end-organ perfusion assessments, volume assessment and peripheral vascular resistance. In practice, the sick neonates are in the emergency condition when they are admitted to the NICU, and we need to get key information to stabilise the neonates. The diagnoses could be uncertain. Therefore, we designed three stages according to the neonates’ condition including the unstable stage, stable stage and recovered stage. Further, we developed three major protocols including the NICU protocol, the NICU-pre protocol and the NICU-plus protocol based on the above three stages (see online supplemental figures 1–3 and online supplemental table 2).

Equipment in the NICU

The ultrasound instrument (Wisonic Clivia or Carnation, Shenzhen, China) has a high-frequency convex probe (L15-4-H) used for lung, kidney and gastric image collection and a phased array probe (P8-3-H) that was used for echocardiography and brain image collection. To obtain better sonographic images, we optimised the ultrasound image frequency in the neonate model. Saving 3–6 s for each ultrasound video, ultrasound examination findings were collected in a standardised recorded form. Appropriate manufacturer warranties and technical support should be included in the purchase because of heavy use and the high likelihood of maintenance.

Quality and infection control of ultrasound in the NICU

Quality assurance is critical; therefore, six senior neonatologists are certified by the Chinese Critical Ultrasound Study Group in the quality group. Two of them interpreted each ultrasound image every day. We followed the quality assessment referring to the revised reporting scale (online supplemental table 1). Meanwhile, to prevent pathogen transmission during ultrasound use, we will follow the cleaning and disinfection protocol in our NICU referred to in previous studies. Also, this is a part of our training programme. The protocol proposed that all high-use areas (touch screen, keyboard, handles,

Figure 1  The design schematic and follow-up of the sick neonates. *See the details of the Neonatal Intensive Critical Ultrasound Examination (NICUltra) workflow in online supplemental figures 1–3.
probes and cords) were wiped thoroughly by using a fresh disinfecting wipe before and after the clinicians used the machine. The NICULtra reports are made by two senior neonatologists certified by the Chinese Critical Ultrasound Study Group. If they do not agree with each other, the third senior neonatologist certified by the Chinese Critical Ultrasound Study Group will judge the report.

Study measures
Primary outcomes are the sonographic characteristics (see online supplemental table 2) of the sick neonates with different diseases, such as sepsis, asphyxia, RDS, hsPDA, PPHN, severe anaemia, etc, and the number of neonates who completed the NICULtra workflow.

Secondary outcomes are listed below:
1. The types of vasoactive or positive inotropic drugs that include dopamine, dobutamine, norepinephrine, epinephrine, milrinone and vasopressin.
2. The time of the use of vasoactive or positive inotropic drugs (the cumulative time of different kinds of those drugs in hours).
3. The rate of vasoactive or positive inotropic drugs given (defined as the number of participants using any kind of vasoactive or positive inotropic drugs divided by the total number of participants).
4. The types and duration time of systemic steroids given (in hours).

Figure 2  The application of the Neonatal Intensive Critical Ultrasound Examination (NICULtra) workflow. (1) Special therapies include hypothermia, blood exchange transfusion, extracorporeal membrane oxygenation, continuous renal replacement treatment and any surgeries; (2) neonatal intensive critical ultrasonic examination protocol (NICU protocol) and neonatal intensive critical ultrasonic examination of preterm infant protocol (NICU-pre protocol); (3) plus neonatal intensive critical ultrasonic examination protocol (NICU-plus protocol). The NICULtra workflow included three protocols. The NICU protocol is performed when the neonates are unstable (stage 1). We only measure the key sonographic variables providing the critical information to help clinicians to make the decisions. The NICU-pre protocol is for very preterm infants. The very preterm infants are fragile and at a high risk of intraventricular haemorrhage and hypothermia. Accordingly, we developed NICU-pre protocol. We require less views and take less time to perform this protocol but receive the critical sonographic information. The NICU-plus protocol is performed when the neonates are stable and recovered. The NICU-plus protocol is a systematic sonographic assessment. NICU, neonatal intensive care unit; NIRS, near-infrared spectroscopy.
5. The number of fluid resuscitations given. Fluid resuscitation (normal saline) was defined as 10–20 mL/kg within 30 min.
6. The duration of ventilator use during hospitalisation (defined as the cumulative time of the utility of invasive or non-invasive ventilation).
7. Mortality and discharge against medical advice of neonates at the time of discharge.
8. The incidence of sIVH.
9. The incidence of BPD.
10. The incidence of NEC.
11. Neurological assessment at a corrected age of 6 months using Gesell Developmental Schedules (GDS). The GDS comprises comprehensive checklists for assessing infants’ and toddlers’ neuromotor wholeness, functional maturity and mental development from the perspectives of adaptability, extensive exercise, fine motor skills, language and personal social networking. The GDS score objectively assesses neurological and mental development in this age group. The neonates born at more than 35 weeks+0 days are evaluated at 6 months after birth, and those born at less than 35 weeks+0 days are evaluated at a corrected age of 6 months.
12. The length of hospitalisation with complete medical care.
13. Total hospitalisation expenses with complete medical care.

The study explores clinical variables and the NICUltra data. The clinical variables included demographic characteristics, maternal history, resuscitation information, time and clinical manifestations, clinical diagnoses, time and laboratory examinations, time and therapeutic data, and time and line placement. The NICUltra data included numbers of parameters that can be automatically exported (see the NICUltra workflow in online supplemental figures 1–3 and online supplemental table 2).

Consent to participate
Informed consent forms and participants’ information sheets were reviewed and approved by the research ethics committees. The written informed consent was obtained from each legal guardian before the enrolment. The researchers followed ethical principles of beneficence, respect for human dignity and justice. All the personal information was used anonymously to preserve respondents’ privacy. All the participants had the right to withdraw from the study at any time.

Statistical analysis plan
Descriptive statistics will be used to summarise the neonates’ characteristics. Continuous variables will be expressed as the mean with SD, and median values with the IQR. The categorical variables will be expressed as numbers and percentages. The Student’s t-test for independent groups will be used for data with a normal distribution. The comparisons of categorical variables will be performed by the X² test or Fisher’s exact test. The differences in abnormally distributed quantitative variables will be analysed by the Mann-Whitney U test. The ORs and 95% CIs were estimated in the multiple logistic regression. Longitudinal data with repeated measures will be analysed using the generalised estimating equations.

The missing data will be displayed in our dataset. We only impute the sonographic data because this is our primary outcome. If these measures are more than 20% of missing values, we will fill the missing values via multiple imputation. Otherwise, we will not fill the values.

Stata V.16.0 software (Stata Corp, Texas, USA) or SAS V.9.4 software (copyright 2016 by SAS Institute) is used for statistical analysis. All statistical tests were two-tailed tests. We set α=0.05, and p<0.05 was considered statistically significant.

Study status
The study began recruitment on 1 December 2022. Thus far, 420 critically ill neonates have been recruited. Among these, 355 neonates were performed the NICUltra workflow.

Patient and public involvement
Patients or the public are not involved in the design, or conduct, or reporting, or dissemination plans of our research.

DISCUSSION
The neonatal critical care ultrasound has been performed in assessing the neonates with haemodynamic instability and hypoxaemia, but the neonatologists performed mainly TnECHO or pulmonary ultrasound rather than comprehensive sonographic assessment. According to the current studies and our experience, we developed a NICUltra workflow, helping to structure the performance of CCUS in the NICU setting. In this study, we aim to obtain sonographic data from a large cohort of sick neonates with different diseases, such as sepsis, asphyxia, RDS, hSPDA, PPHN, severe anaemia, etc. We will provide a time-series sonographic description of these sick neonates in three stages, and further characterise the sonography in the neonates with critical illness. Importantly, the study findings will help to further understand the pathophysiology of the sick neonates with different diseases and to potentially titrate the treatment. The future plan is to evaluate the impact of NICUltra workflow on the management of the sick neonates with different diseases in a large multicentre study.

It is difficult to make final diagnoses before we receive more clinical information. Initially, we will perform NICUltra workflow guided by clinical issues. However, the management should be based on the pathophysiology. For example, neonates with PPHN can present with hypoxic respiratory failure (HRF). Current evidence has proved that the use of inhaled nitric oxide (iNO) should be based on the physiology of pulmonary hypertension.
Although the neonates have similar clinical issues (HRF), the underlying pathophysiology has to be revealed by CCUS. If the neonates have HRF and severe left ventricular systolic or diastolic dysfunction confirmed by CCUS, iNO may worsen HRF. Therefore, the whole clinical picture from sonographic findings in addition to clinical history, clinical symptoms and other routine laboratory examinations would guide the clinician to make an optimal decision.

Currently, limited high-level evidence has been provided about the fact that the CCUS can improve newborns’ outcomes. One study investigated the association of in-hospital outcomes and early haemodynamic management via CCUS, which indicated that the neonatologist-performed echocardiography used in preterm infants with hypotension was not associated with in-hospital outcomes and had little influence on the nature of and reasons for antihypotensive treatments. However, this is a retrospective study, and it was unknown how the ultrasound was performed and the quality control of the interpretation of CCUS.

The primary limitation of this study is that the data are from our single centre; thus, the generalisability may be limited. The second limitation is loss to follow-up for these sick neonates. Efforts to minimise loss to follow-up will include formal tracking procedures that require multiple contacts for arranging follow-up and regular telephone follow-up.

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Competing interests None declared.

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Patient consent for publication Parental/guardian consent obtained.

Ethics approval This study involves human participants. Approval of the study by Chengdu Women’s and Children’s Central Hospital Ethics Committee (reference number 2022/104) was obtained. The study will only be initiated after the consent forms are approved by the institutional review board. This work will be disseminated by publishing peer-reviewed manuscripts and presentations in abstract form at scientific meetings.

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