

# Comparison of bedside ultrasonography and bedside chest radiography in neonatal peripherally inserted central catheters—a before and after self-control study

Liping Wu (✉ [lipingwu@cqmu.edu.cn](mailto:lipingwu@cqmu.edu.cn))

Children's Hospital of Chongqing Medical University

Xuexiu Liu

Children's Hospital of Chongqing Medical University

Xiaojun Tao

Children's Hospital of Chongqing Medical University

Ye Xu

Children's Hospital of Chongqing Medical University

Xianhong Zhang

Children's Hospital of Chongqing Medical University

Yanhan Chen

Chongqing Medical University

---

## Research Article

### Keywords:

**Posted Date:** March 7th, 2022

**DOI:** <https://doi.org/10.21203/rs.3.rs-1346562/v1>

**License:**  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

---

# Abstract

The study is a prospective before and after self-control clinical trial. To compare the applications of bedside ultrasonography (US) and bedside chest radiography (CR) in positioning peripherally inserted central venous catheter (PICC) at Neonatal Intensive Care Units (NICUs). A consecutive series of 181 neonate patients were finally enrolled for PICC placement. CR, followed by US, was used to evaluate and readjust the sites of catheter tips. The imaging capability for PICC key structures, fluctuation of the measured data, measurement of tip-to-atrium distance, operation time, infants' body temperature changes and direct expenses of the two imaging modalities were obtained and compared. The following results are obtained: 1. Comparison in viewing PICC key structures: the display rate of catheter tip, SVC-and-right-atrium junction, IVC-and-right-atrium junction and tip-to-atrium distance is 99.47%, 100%, 100% and 99.47% for US and 100%, 98.42%, 97.37% and 95.79% for CR, respectively. 2. Fluctuation of the measured data by US and CR: the tip-to-atrium distance measured by US is 0.631 (0.435-0.820) cm; and that measured by CR is 0.593 (0.210-0.825) cm. US showed narrower range of datum variance. 3. Consistency and correlation between US and CR: for consistency analysis, Kappa coefficient ( $\kappa$ ) was 0.843 ( $P < 0.05$ ), showing their favorable consistency; for correlation analysis, Pearson correlation coefficient ( $r$ ) was 0.739 ( $P < 0.05$ ), suggesting a close correlation. 4. Comparison of operation time and infants' body temperature drop: for a CR exam, the time period taken was significantly longer than that of US ( $59.7 \pm 26.33$  min vs  $79.6 \pm 28.06$  min,  $P < 0.001$ ); and CR operations caused a significant babies' body temperature drop compared to US ( $0.14 \pm 0.11^\circ\text{C}$  vs  $0.34 \pm 0.19^\circ\text{C}$ ,  $P < 0.001$ ). 5. Comparison of the direct expenses: the total cost for CR positioning was significantly higher than that for US (¥153.99 yuan vs. ¥143 yuan,  $P = 0.026$ ). It can be inferred that US positioning of PICC tip exhibited superior traits to CR. We suggest that US can be used routinely for the neonates' PICC placement at NICU.

## Background

Peripherally inserted central catheter (PICC) is a technique by inserting a catheter through peripheral veins so that the catheter tip is placed in the superior vena cava (SVC) or inferior vena cava (IVC) to establish a safe and stable infusion pathway. Currently, PICC has been widely used in Neonatal Intensive Care Units (NICU) for intravenous nutritional support and long-term drug infusion. Ensuring the catheter tip within vena cava is critical because malposition may induce adverse outcomes such as infectious endocarditis, atrial fibrillation and pleural effusion, etc<sup>1,2</sup>. Clinically, chest radiography (CR) has been applied as the "gold standard" to confirm the sites of catheter tips<sup>3,4</sup>. However, accumulating evidence showed the drawbacks of CR positioning including complex operation requirements, nondynamic and retrospective imaging, ionizing radiation and longer time consumption, etc<sup>3</sup>. Compared to CR, ultrasonography (US) is easier to operate at bedside and able to view catheter tips and cardiovascular structures in real time without ionizing radiation.

Ultrasound (US) devices are becoming increasingly available in many neonatal intensive care units as a tool the teams can use in routine clinical care<sup>5</sup>. Largely because of the many advantages, it has recently

been used, with success, for the evaluation of PICC location in adult patients<sup>6</sup>. US for catheter placement is not current standard of practice, however, because of limitations of cost of equipment and the perceived high degree of training required to perform US routinely for catheter placement. And, due to the light weight and small blood vessels of newborns, it is difficult to accurately find the position of catheter tip, which greatly increases the difficulty and accuracy of neonatal PICC positioning. At present, PICCs are inserted and advanced blindly to a predetermined length based on an external anatomical<sup>0</sup> measurement of the estimated catheter pathway. In order to check the adequacy of catheter placement, CR was placed after catheter placement. Frequently these catheters are not placed at optimal position the first time necessitating repositioning the catheters followed by further CR. This involves movement of often critically ill infants, extending time away from optimal nursing care, as well as radiation exposure<sup>7</sup>. During repositioning before permanently fixing the catheter, the catheter may shift, which is also a significant risk<sup>7</sup>. Therefore, we hope to find a more suitable PICC localization method for newborns. Whether US localization of PICC can overcome the problem of CR localization in newborns and whether it will be more suitable for newborns needs further research. To our best knowledge only a few studies were reported about its application in NICU.

Hence in this study, we enrolled a consecutive series of 181 neonates, aiming to understand more about the values of bedside US in neonatal PICC locating, by comparison with bedside CR.

## Methods

### Estimation of sample size

A software PASS 15.0 was used for estimating the sample size. We postulated Kappa coefficient between CR and US is about 0.843 with a standard deviation of 0.12. If class I error of the relevant parameters are set as 0.05 ( $\alpha = 0.05$ ) with an allowable error of 0.05 ( $\delta = 0.05$ ), the calculated sample size is 89 children. With the addition of 10% sample loss, at least 98 patients are required.

### Participants

A consecutive series of 190 neonates who needed PICC in NICU of Children's Hospital of Chongqing Medical University were enrolled into the study. The period of recruitment was from April 2021 to August 2021. Inclusion criteria are newborns: (1) asking for PICC; (2) able to tolerate US and CR exams; (3) having the informed consent. Exclusion criteria are newborns: (1) with cardiovascular diseases; (2) with spinal deformity; (3) experiencing failed PICC attempts; (4) having contraindications of PICC including infection, skin allergy, skin injury and phlebitis, immune deficiency disease, abnormal bleeding and coagulation time and severe collapse of peripheral blood vessels, etc. The institutional review board has approved the study (Institutional Review Board of Children's Hospital of Chongqing Medical University, Approval No., 2021-159; clinical trial registration No., ChiCTR2100045948).

# Placement of PICC line

PICC placement was performed by two nurses with PICC operation qualification. Briefly, the child was placed in an incubator. Catheterization was performed with a puncturing kit containing 26 GA (1.9 F) single-lumen PICC catheter according to the neonatal PICC catheterization operation specifications<sup>8</sup>. After inserting the line, CR was taken to locate the catheter tip, then followed with US for relocating and guided adjustment.

According to the specifications, it should be avoided placing the catheter tip in the heart of neonates and infants<sup>9</sup>. The optimal tip position complied with the recommendation of the 2016 guidelines by the American Infusion Nurses Society (INS), i.e., the safest PICC tip be located within the lower third of SVC or just below the IVC-and-right-atrial junction<sup>10-12</sup>.

## Locating catheter tips by CR

CR was conducted under a 0.7/1.3U163C-36 system (Shimadzu, Japan). An experienced radiologist and a PICC specialist nurse read the images together. According to the INS guidelines, a catheter tip at the level of 4<sup>th</sup>-6<sup>th</sup> thoracic vertebrae is regarded as the optimal placement for upper limb PICC and at the level of 8<sup>th</sup>-10<sup>th</sup> thoracic vertebrae for lower limb PICC<sup>13</sup>. Besides, our hospital also took the tracheal carina and the right cardiophrenic angle as the imaging marks of SVC-and-right-atrium junction and IVC-and-right-atrium junction, respectively.

## Locating catheter tips by US

US is conducted under a LOGIQ e color Doppler ultrasonic diagnostic system (6S and 8C probes, GE company, USA) by two research members who have at least 3 years of experience in ultrasonic PICC positioning. The ultrasonic probe was set at the midline of the subxiphoid region or at the parasternal line of the right subclavicle region. A hyperechoic "equal sign" like or sandwich-like structure would be detected within the vena cava, which represents the inserted line. In detail, for clearly viewing the "equal sign" like echoes of the catheter tip in SVC, the probe was placed longitudinally at the 2<sup>nd</sup>-3<sup>rd</sup> intercostal spaces on the right of the sternum to delineate the long axis of aortic arch and the short axis of SVC, and then rotated clockwise for about 15° and tilted slightly to the right to show the long axis of SVC and the right atrial entrances of SVC and IVC (Fig. 1A)<sup>14</sup>. Under US guidance a small dose of 0.9% sodium chloride solution was injected into the catheter to confirm the position of the tip. Subsequently, distance between the tip and the right atrial inlet (thereafter referred to as "tip-to-atrium distance") was measured and improper tip position was US-guided readjusted. For clearly viewing the "equal sign" like echoes of the catheter tip in IVC, the probe should be placed longitudinally at the midsagittal position of the subxiphoid region and scan along the inferior rib to delineate the IVC and right atrial inlet (Fig. 1B). The tip-to-atrium distance was measured and improper tip position was readjusted.

## **Observation and analysis**

### ***Comparing US with CR in visualizing the key structures at PICC***

Catheter tip, right-atrium inlets of SVC and IVC and tip-to-atrium distance that can be viewed on US and CR was recorded for each patient. US-visible right-atrium inlets of SVC or IVC is defined when it visually depicts the superior or inferior inlet of the right atrium. CR-visible right-atrium inlets of SVC or IVC is defined when it clearly images the tracheal carina or the right cardiophrenic angle. Measurement of tip-to-atrium distance is considered feasible when both of the tip and the right-atrium inlet are shown on a single image of US or CR.

### ***Fluctuation of the measured data by US and CR***

Tip-to-atrium distance of each patient was measured separately by US and CR. The quartile is calculated to represent fluctuation of the measured data; and fluctuation between the two data sets was compared. Narrower data fluctuation indicates the measurements made by the imaging tool more stable and reliable.

### ***Consistency and correlation between US and CR***

For further clarifying the validness of US, tip-to-atrium distances measured by US and CR were compared to investigate their consistency and correlation.

### ***Comparison of operation time and babies' body temperature drop between US and CR***

Time period for each imaging checkup was recorded in minutes using a stopwatch. The time period recorded was defined as from the start of the imaging procedure to the time point the operators had confirmed the tip position. Data of the time periods were compared between US and CR. In addition, babies' body temperature drop brought by US exam and CR exam was compared as well. For a bedside CR exam, babies must be taken out of incubators and sent to a dedicated room in NICU. The process may lead to babies' body temperature drop.

### ***Comparison of the direct expenses between US and CR***

The direct cost of US and CR in locating the tips were recorded and compared.

# Statistics

A software SPSS 24.0 was used to statistically process the data. Data with normal distribution were expressed in mean  $\pm$  standard deviation ( $x \pm s$ ); the count data were expressed in number of cases and percentage (%); and fluctuation of data was expressed in quartile. Intra-group correlation coefficient (ICC), Kappa coefficient analysis and Pearson correlation coefficient were used to investigate consistency and correlation between US and CR. Paired T-test was used to test the inter-group difference of operation time, body temperature change and direct cost.  $P < 0.05$  means the difference is statistically significant.

## Results

### Patients

One hundred and ninety babies were initially enrolled in this study. Except nine cases were excluded for failed PICC attempts, the remaining 181 babies, 90 males and 91 females, were finally in the cohort, including 64 of upper limb placement and 117 of lower limb placement. Their average gestational age and average birth weight were ( $31.74 \pm 2.58$ ) weeks and ( $1630.51 \pm 529.36$ )g, respectively.

## Comparing US with CR in visualizing the key structures at PICC

Comparison between US and CR in viewing the catheter tips and key anatomical structures was summarized in Table 1. US failed to show the position of PICC tip in only one case, whereas CR failed to show the position of SVC-and-right-atrium junction in three babies and the position of IVC-and-right-atrium junction in five.

Table 1

Comparison of the imaging capability for the key structures between US and CR at PICC

	PICC tip	SVC-and-right-atrium junction	IVC-and-right-atrium junction	Tip-to-atrium distance
Cases viewed by US (%)	189 (99.47)	190 (100)	190 (100)	189 (99.47)
Cases viewed by CR (%)	190 (100)	187(98.42)	185 (97.37)	182 (95.79)

## Fluctuation of the measured data by US and CR

The tip-to-atrium distance measured by US is 0.631 (0.435-0.820) cm; and that measured by CR is 0.593 (0.210-0.825) cm. The dispersion degree of the measured tip-to-atrium distances represents their fluctuation. Compared to CR, US showed narrower range of datum variance, indicating its favorable stability and reliability in measurement.

## Consistency and correlation between US and CR

The tip-to-atrium-distance measurements of CR presented with a skewed distribution, which we think largely due to the inappropriate patients' positions at image acquirement. For the sake of calculation convenience, both of the data sets of US and CR were transformed into three scores, i.e., a distance less than 0 cm was scored as 1; 0-1 cm was scored as 2; greater than 1 cm scored as 3. Score 1, 2 and 3 separately represented PICC failure, satisfaction and fairness; and score 2 and 3 are viewed as "PICC success". The scores were compared between US and CR. Resultantly, for consistency analysis, Kappa coefficient ( $\kappa$ ) was 0.843 ( $P < 0.05$ ), showing their favorable consistency; for correlation analysis, Pearson correlation coefficient ( $r$ ) was 0.739 ( $P < 0.05$ ), suggesting a close correlation. Notably, in two patients satisfactory PICC tip position was shown on CR, but a followed US demonstrated the tips go wrongly into cardiac cavities. The tips were subsequently withdrawn into SVC under US guidance.

## Comparing operation time and babies' body temperature drop between US and CR

For a CR exam, the time period taken was significantly longer than that of US  $59.7 \pm 26.33$ min vs  $79.6 \pm 28.06$ min,  $P < 0.001$ , Fig. 2). Moreover, to have a CR exam, infants must be taken out of their incubators and sent to a special room. Such CR operations caused a significant babies' body temperature drop compared to US ( $0.14 \pm 0.11^\circ\text{C}$  vs  $0.34 \pm 0.19^\circ\text{C}$ ,  $P < 0.001$ , Fig. 3).

## Comparing the direct expenses between US and CR

Positioning of PICC by US and CR would separately paid ¥153.99 yuan and ¥143 yuan on average. The total cost for CR positioning was significantly higher than that for US ( $P = 0.026$ , Fig.4).

## Discussion

Traditionally, CR was regarded as the "gold standard" for PICC positioning. However, the position of PICC tip on a CR picture is readily affected by improper patient's position, blurred bronchial carina and thoracic malformation. By contrast, US is able to directly visualize heart, blood vessels and the inlying PICC tip, thus avoid the downsides above-mentioned. At US imaging, the catheter in the blood vessel presents a special image structure of "high and low", just like the equal sign "=". SVC, IVC and their right-atrium inlets can also be depicted clearly by US. These merits provide grounds for US-guided PICC placement<sup>15</sup>. In

fact, US has been used in adult patients to guide and adjust PICC placement, and has been demonstrated largely reducing the placement-and-positioning related complications<sup>16,17</sup>. In this study we focused its applications in newborns at NICU.

Different to the previous studies, this study adopted a prospective before and after self-control method in the hope of obtaining more comparable measurements between US and CR. The results showed that US and CR have significant consistency and correlation in locating the tip position, as was also confirmed by other studies<sup>18,19</sup>. We then compared the stability of data measured by US and by CR. Resultantly, the data of US presented definitely narrower fluctuation than those of CR, suggesting its nice reliability. Notably, we do not think the wide fluctuation of CR data results only from unsatisfied placement, but tend to think it from inaccurate measurements caused by the effects aforementioned. So herein we did not think it is appropriate to take CR as the “gold standard” method at PICC positioning. This is why we did not test the specificity and sensitivity of US positioning. As for the operation time, US exhibited less time consumption than that of CR ( $P < 0.05$ ). Less operation time means reduced risk of complications<sup>20</sup>. Measurement of the infants’ body temperature change revealed that positioning by CR incurred significant body temperature drop than by US. Complex preparation, more time of exam and operating out of incubators means that the infants would expose to the indoor air for a longer time. Long time out of incubator would induce hyperthermia of the infants<sup>21-24</sup>. Different from CR, US exam can be conducted totally within incubators. Besides, we recorded both of the cost for US and CR and found that a direct expense for US positioning was ¥143 yuan on average, significantly smaller than ¥153.99 yuan for CR positioning.

## Limitations

This study has at least two limitations. First, due to the wide fluctuation of CR measurements, this study did not calculate the specificity and sensitivity of US positioning. Second, we did not execute a longitudinal study to in depth understand the pros and cons of US in PICC placement.

## Conclusions

In general, this study showed that US positioning of PICC tip exhibited superior traits to CR, including visual evaluation of catheter tip and the cardiovascular system, real-time and dynamic imaging, no X-ray exposure, relatively less operation time and low cost. These advantages mean high success rate and safety at neonates’ PICC placement. So we come to the conclusion that US, although currently not the standard of practice, can be used routinely for the neonates’ PICC placement at NICU.

## Declarations

## Funding:

This work was supported by the Chongqing Science and Technology Commission (2020MSXM028)

## **Conflicts of interest/Competing interests:**

The authors declare no conflicts of interest

## **Availability of data and material:**

The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

## **Code availability:**

Not applicable

## **Authors' Contributions:**

All six authors made substantial contributions to the study and manuscript and met the criteria for authorship defined in the author instructions:

Xuexiu LIU contributed to acquisition, analysis and interpretation of the data and acquisition, analysis and interpretation of the data and the drafting and final approval of the manuscript.

Xiaojun TAO, Ye XU, Xianhong ZHANG and Yanhan Chen provided technical support and conceptual advice.

Liping WU designed the study.

All authors read and approved the final manuscript.

## **Ethics approval:**

The institutional review board has approved the study :Approval No. 2021-159

## **Consent to participate:**

Written informed consent was obtained from individual or guardian participants.

## **Consent for publication:**

## References

1. Kolaček S, Puntis JWL, Hojsak I. ESPGHAN/ESPEN/ESPR/CSPEN Guidelines On Pediatric Parenteral Nutrition: Venous Access. *Clinical nutrition (Edinburgh, Scotland)*. **37**, 2379-2391 (2018).
2. Weil BR, Ladd AP, Yoder K. Pericardial Effusion and Cardiac Tamponade Associated with Central Venous Catheters in Children: An Uncommon but Serious and Treatable Condition. *J. Pediatr. Surg.* **45**, 1687-1692 (2010).
3. Han Z, Liu G, Zhang H. [Advances in the Application of Peripheral Central Venous Catheter Tip Positioning Technology]. *Zhongguo yi liao qi xie za zhi = Chinese journal of medical instrumentation*. **44**, 56-59 (2020).
4. Sneath N. Are Supine Chest and Abdominal Radiographs the Best Way to Confirm PICC Placement in Neonates? *Neonatal network : NN*. **29**, 23-35 (2010).
5. Jain A, McNamara PJ, Ng E, El-Khuffash A. The Use of Targeted Neonatal Echocardiography to Confirm Placement of Peripherally Inserted Central Catheters in Neonates. *Am J Perinatol*. **29**, 101-106 (2012).
6. Subramanian S, Moe DC, Vo JN. Ultrasound-Guided Tunneled Lower Extremity Peripherally Inserted Central Catheter Placement in Infants. *J. Vasc. Interv. Radiol*. **24**, 1910-1913 (2013).
7. Sharma D, Farahbakhsh N, Tabatabaie SA. Role of Ultrasound for Central Catheter Tip Localization in Neonates: A Review of the Current Evidence. *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians*. **32**, 2429-2437 (2019).
8. [Operation and Management Guidelines for Peripherally Inserted Central Catheter in Neonates (2021)]. *Zhongguo dang dai er ke za zhi = Chinese journal of contemporary pediatrics*. **23**, 201-212 (2021).
9. Blackwood BP, Farrow KN, Kim S, Hunter CJ. Peripherally Inserted Central Catheters Complicated by Vascular Erosion in Neonates. *JPEN. Journal of parenteral and enteral nutrition*. **40**, 890-895 (2016).
10. Ren XL, Li HL, Liu J, Chen YJ, Wang M, Qiu RX. Ultrasound to Localize the Peripherally Inserted Central Catheter Tip Position in Newborn Infants. *Am. J. Perinat*. **38**, 122-125 (2021).
11. Isemann B, Sorrels R, Akinbi H. Effect of Heparin and Other Factors Associated with Complications of Peripherally Inserted Central Venous Catheters in Neonates. *Journal of perinatology : official journal of the California Perinatal Association*. **32**, 856-860 (2012).
12. Connolly, B. et al. Influence of Arm Movement On Central Tip Location of Peripherally Inserted Central Catheters (PICCs). *Pediatr. Radiol*. **36**, 845-850 (2006).
13. The 2016 Infusion Therapy Standards of Practice. *Home healthcare now*. **35**, E1-E2 (2017).

14. Motz P, Von Saint Andre Von Arnim A, Iyer RS, Chabra S, Likes M, Dighe M. Point-Of-Care Ultrasound for Peripherally Inserted Central Catheter Monitoring: A Pilot Study. *J. Perinat. Med.* **47**, 991-996 (2019).
15. Ren XL, Li HL, Liu J, Chen YJ, Wang M, Qiu RX. et al. Ultrasound to Localize the Peripherally Inserted Central Catheter Tip Position in Newborn Infants. *Am. J. Perinat.* **38**, 122-125 (2021).
16. Barton A. Confirming PICC Tip Position During Insertion with Real-Time Information. *British journal of nursing (Mark Allen Publishing)*. S17-S21 (2016).
17. Tawil KA, Eldemerdash A, Hathlol KA, Laimoun BA. Peripherally Inserted Central Venous Catheters in Newborn Infants: Malpositioning and Spontaneous Correction of Catheter Tips. *Am. J. Perinat.* **23**, 37-40 (2006).
18. Tauzin L, Sigur N, Joubert C, Parra J, Hassid S, Moulies ME. Echocardiography Allows More Accurate Placement of Peripherally Inserted Central Catheters in Low Birthweight Infants. *Acta paediatrica (Oslo, Norway : 1992)*. **102**, 703-706 (2013).
19. Katheria AC, Fleming SE, Kim JH. Randomized Controlled Trial of Ultrasound-Guided Peripherally Inserted Central Catheters Compared with Standard Radiograph in Neonates. *Journal of perinatology : official journal of the California Perinatal Association*. **33**, 791-794 (2013).
20. Telang N, Sharma D, Pratap OT, Kandraj H, Murki S. Use of Real-Time Ultrasound for Locating Tip Position in Neonates Undergoing Peripherally Inserted Central Catheter Insertion: A Pilot Study. *The Indian journal of medical research*. **145**, 373-376 (2017).
21. Mance MJ. Keeping Infants Warm: Challenges of Hypothermia. *Advances in neonatal care : official journal of the National Association of Neonatal Nurses*. **8**, 6-12 (2008).
22. Tander B, Baris S, Karakaya D, Ariturk E, Rizalar R, Bernay F. Risk Factors Influencing Inadvertent Hypothermia in Infants and Neonates During Anesthesia. *Paediatric anaesthesia*. **15**, 574-579 (2005).
23. Mank A, van Zanten HA, Meyer MP, Pauws S, Lopriore E, Te Pas AB. Hypothermia in Preterm Infants in the First Hours after Birth: Occurrence, Course and Risk Factors. *PLoS One*. **11**, e164817 (2016).
24. O'Brien EA, Colaizy TT, Brumbaugh JE, Cress GA, Johnson KJ, Klein JM, Bell EF. Body Temperatures of Very Low Birth Weight Infants On Admission to a Neonatal Intensive Care Unit. *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians*. **32**, 2763-2766 (2019).

## Figures

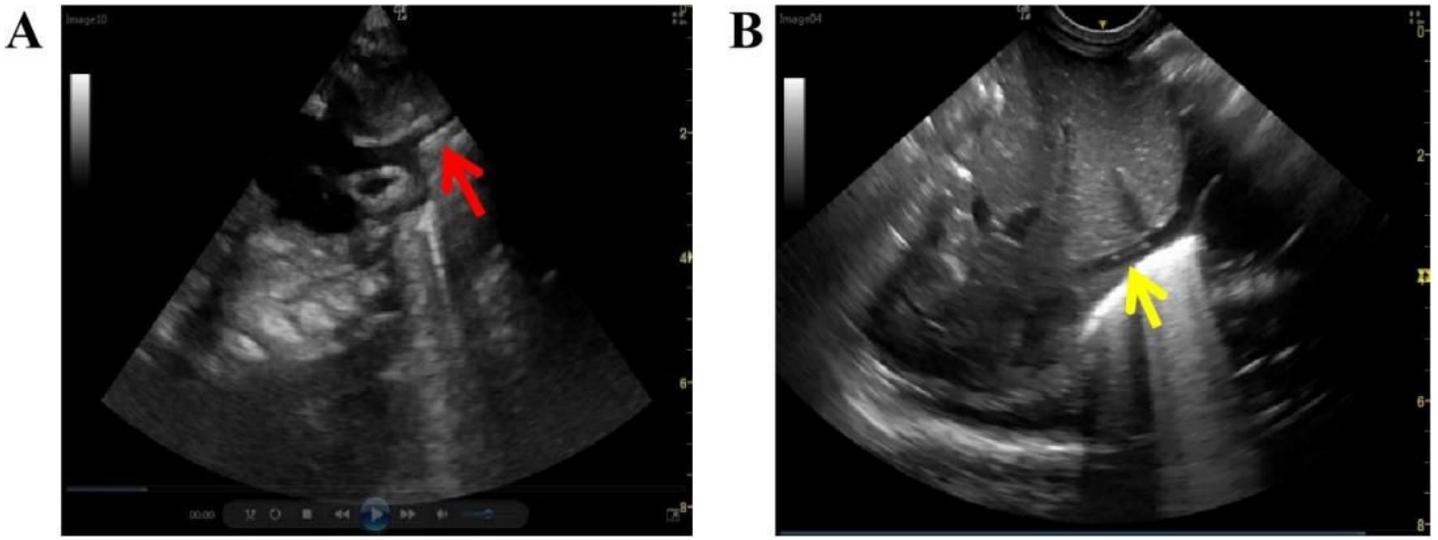


Figure 1

PICC ultrasonic imaging of vena cava.A superior vena cava (red arrow),B inferior vena cava(yellow arrow)

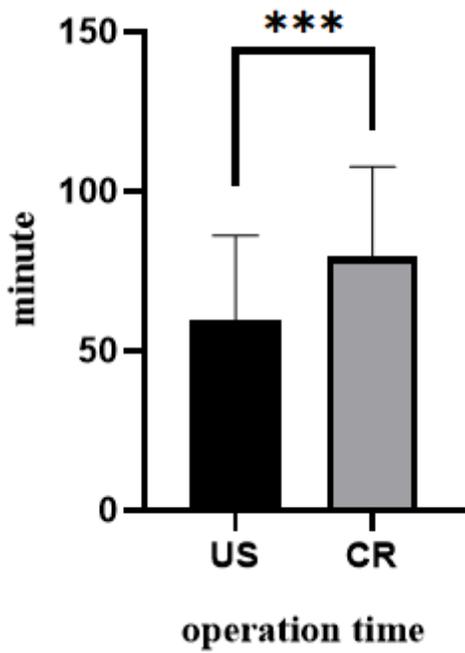


Figure 2

Comparison of operation time between US and CR.(\*\*\*P < 0.001)

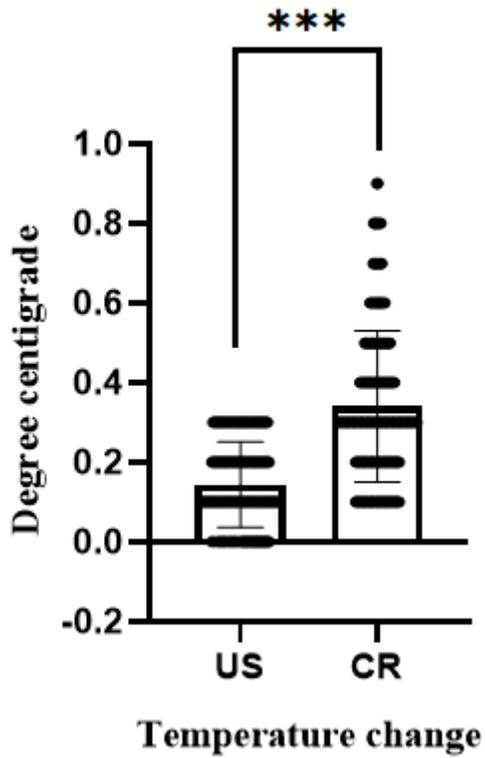


Figure 3

Comparison of temperature change between US and CR. (\*\*P < 0.001)

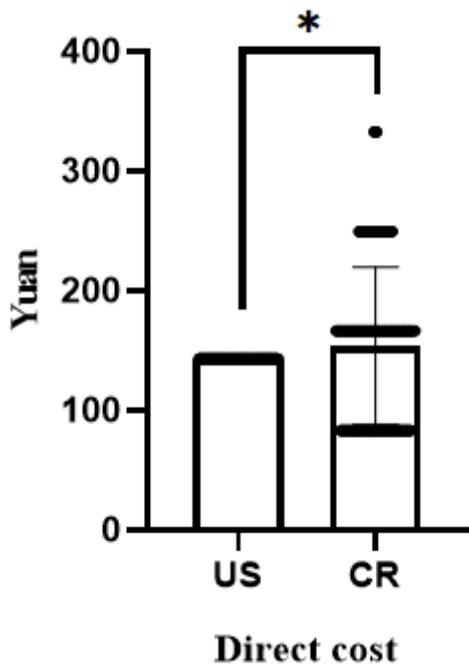


Figure 4

Comparison of direct cost between US and CR. (\*P = 0.026)