Construction of a rabbit model with vinorelbine administration via peripherally inserted central catheter and dynamic monitoring of changes in phlebitis and thrombosis

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Abstract. Peripherally inserted central catheters (PICCs) are used for the administration of chemotherapy drugs, including vinorelbine. The present study aimed to construct a rabbit model with vinorelbine administration via PICC, and to dynamically monitor the formation of phlebitis and thrombosis. PICC was inserted into 48 rabbits following specific clinical procedures. The rabbits were randomly divided (n=6 per group) into the following eight groups: i) Control (PICC in place for 1 day); ii) 2nd day of PICC placement (received the first cycle of vinorelbine administration); iii) 3rd day of PICC placement; iv) 7th day of PICC placement; v) 14th day of PICC placement; vi) 21st day of PICC placement; vii) 23rd day of PICC placement (received the second cycle of vinorelbine administration); and viii) 24th day of PICC placement. Hematoxylin and eosin staining was performed on catheter, ear vein and anterior vena specimens. Prothrombin time was measured using an automatic coagulation analyzer, followed by routine blood tests. Serum levels of inflammation- and thrombosis-related factors, including C-reactive protein, D-dimer, interleukin-2, interleukin-6, P-selectin and E-selectin, were measured using ELISAs. X-ray examination confirmed that the rabbit model with vinorelbine administration via PICC was successfully constructed. On the 1st and 23rd day of PICC placement, thrombosis was observed in the catheter. Furthermore, on the 1st day of PICC placement, thrombosis was clearly observed in the ear vein and anterior vena samples. After vinorelbine administration, phlebitis occurred in the ear vein and anterior vena cava samples. With increasing time after vinorelbine administration via PICC, thrombosis and phlebitis were notably ameliorated. Moreover, on the day of vinorelbine administration, prothrombin time was significantly decreased and the serum levels of inflammation- and thrombosis-related factors were significantly increased compared with previous days. Collectively, the present study observed the formation and specific evolution of phlebitis and venous thrombosis after vinorelbine administration, providing a reference for the early prediction, timely prevention and treatment of PICC-related chemotherapy complications.

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Abbreviations: PICC, peripherally inserted central catheter; CRP, C-reactive protein; D2D, D-dimer; IL-2, interleukin-2; IL-6, interleukin-6; ELISA, enzyme-linked immunosorbent assay; H&E, hematoxylin and eosin

Key words: PICC, vinorelbine, catheter-related thrombosis, inflammation, prothrombin time

Introduction

Peripherally inserted central catheters (PICCs) have been widely applied for the administration of chemotherapy drugs (1-3). PICCs have the advantages of convenient operation, high safety, long indwelling time and low maintenance difficulty (4), and can provide patients with intravenous treatment for 7 days to 1 year, which is beneficial to reduce damage to blood vessels and avoid patient suffering associated with repeated punctures (5). Furthermore, PICC provides good venous access for nutrition and chemotherapy in patients with cancer (6). However, previous studies have indicated that PICC application has a significant association with the risk of adverse reactions, such as infection, phlebitis and deep venous thrombosis, for patients with solid malignancies receiving chemotherapy drugs (7-9). Nevertheless, the application of PICC for chemotherapy drugs is still relatively safe and effective (6). To ensure patient safety and increase the detection rate of venous complications, clinical observation alone is not sufficient. Therefore, conducting in-depth research on the microscopic level of blood vessels is important.

Vinorelbine, a semi-synthetic vinca alkaloid, may bind to tubulin and suppress mitotic microtubule polymerization (10). It is a potent chemotherapeutic drug for treating breast and

non-small cell lung cancer (11-13). Although oral administration was approved for the clinical application of vinorelbine in 2006 due to convenience and the low risk of venous thrombosis, intravenous infusion exhibits higher efficacy (14). For example, the results of a phase II study demonstrated that patients with non-small cell lung cancer treated with oral vinorelbine exhibited good tolerance, but displayed limited overall survival time compared with those treated with intravenous vinorelbine (15). Although PICCs exhibit various advantages, the catheter is left in the vein for a long time, thus phlebitis often occurs due to the stimulation of the blood vessel wall by the catheter, the chemical stimulation of blood vessels via the drug infusion and the low obstruction in patients with cancer (1-3). Therefore, it is important to strengthen clinical observation and actively prevent, reduce or eliminate the occurrence of complications as much as possible. Certain patients with an invisible thrombus do not exhibit clinical symptoms, but present with abnormal pathological and laboratory indicators, despite thrombus formation. Therefore, to ensure patient safety and increase the detection rate of venous complications, clinical observation alone is not adequate. Thus, it is important to conduct in-depth research at the microscopic level of blood vessels. However, there is a lack of models with vinorelbine administration via PICC and a lack of evidence regarding pathological changes of PICC vein complications at different stages. The present study aimed to construct a rabbit model with vinorelbine administration via PICC to dynamically monitor phlebitis and thrombosis changes, which may provide a reference for early prediction, timely prevention and treatment of PICC-related chemotherapy complications.

Materials and methods

Animals. The present study was approved by the Ethics Committee of the School of Medicine, Jinhua Polytechnic (Jinhua, China; approval no. 2019017). In total, 48 healthy New Zealand rabbits (weight, 2.5-3.0 kg; age, 3-month-old) were provided by Jinhua Center of Laboratory Animals, Jinhua Food and Drug Inspection and Testing Institute (Jinhua, China), including 24 non-pregnant female rabbits and 24 male rabbits. The rabbits were adaptively fed for 1 week in the animal experimental center in single cages and randomly numbered. The housing conditions were as follows: 18˚C; humidity, 65%; light/dark cycles, 12/12 h; and with sufficient food and clean water. The animal experiments were performed in accordance with the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health (ncbi.nlm.nih.gov/books/NBK54050/).

Construction of the PICC rabbit model. The 1.9 Fr x50 cm single-lumen PICCs (Fr, unit of the circumference of the catheter) were purchased from Unijet. The lumen and outer wall of the catheter were rinsed with 15 ml normal saline. Before use, the catheter was further rinsed with 5 ml normal saline to remove bubbles. The rabbits were anesthetized via an intraperitoneal injection of 30 mg/kg sodium pentobarbital (3%; Sigma-Aldrich; Merck KGaA). After successful anesthesia, the length of the PICC insertion was measured for each rabbit. To perform the measurement procedures, the rabbit was placed in a supine position, and keeping the rabbit's ears upright and parallel to the body at 180˚, the length of the PICC insertion was determined (21-26 cm) by measuring the length from the puncture point (posterior auricular vein) to the most evident stop of the cardiac apex (Fig. 1A). Following skin preparation (Fig. 1B), disinfection (Fig. 1B) and puncture (Fig. 1C), the PICC tube was inserted into posterior auricular vein to the predetermined length (Fig. 1D). After checking patency and initial fixation, 0.5 ml Lipiodol® (Jiangsu Hengrui Pharmaceutical Co., Ltd.) was intrathecally injected. Subsequently, whether the PICC tube reached the anterior vena cava was observed under X-ray fluoroscopy. Blood samples (1.8 ml) were collected from the ear vein. After flushing the PICC tube with 10 ml saline, the catheter was closed and fixed with a 3M applicator. To prevent accidental extubation from the rabbit ear, a recovery collar was placed on each animal so as not to affect the blood circulation or food intake.

Evaluation of PICC models. The criteria for evaluating the successful establishment of PICC models were as follows: i) The established animal model of PICC was successful with one puncture; ii) there was no local damage or bleeding in the puncture; iii) the end of the catheter was not twisted or folded under X-ray fluoroscopy; and iv) the PICC tube was placed in the anterior vena cava. As presented in Fig. 2, the transparent dot corresponded to the end of the catheter.

Animal grouping and modeling. The PICC model rabbits were randomly divided into the following eight groups (n=6 per group): i) Control group (PICC in place for 1 day); ii) 2nd day of PICC placement (received the first cycle of vinorelbine administration); iii) 3rd day of PICC placement; iv) 7th day of PICC placement; v) 14th day of PICC placement; vi) 21st day of PICC placement; vii) 23rd day of PICC placement (received the second cycle of vinorelbine administration); and viii) 24th day of PICC placement. Vinorelbine (10 mg/ml) was purchased from Jiangsu Haosoh Pharmaceutical Group Co., Ltd. After being dissolved in 10 ml normal saline, vinorelbine was slowly injected into the rabbit using an infusion pump for 15 min. The drug was administered once on the 2nd day and once on the 23rd day after intubation. After each administration, the tube was sealed with heparin saline according to the pulse positive pressure method (16). Based on the Meeh-Rubner formula (17), the body surface area of each rabbit was calculated, and 25 mg/m^2 was used as the optimal dose of vinorelbine. During the intermittent period of chemotherapeutics, PICC intubation maintenance was completed according to regular operations: The dressing was changed once a week; and when the dressing was wet or curled, it was disinfected and replaced. After the experiment, considering humane endpoints and animal welfare (when the rabbit experienced severe pain, suffering or dying or when the experiment was complete), all rabbits were euthanized via an intravenous injection of 100 mg/kg sodium pentobarbital to minimize suffering and distress. Death was verified by the complete cessation of the heartbeat and breathing and disappearance of reflexes.

General indicator observations. The local skin temperature, redness and extent of swelling at the puncture point were observed for the rabbits in each group. The criteria for evaluating the degree of phlebitis according to the phlebitis

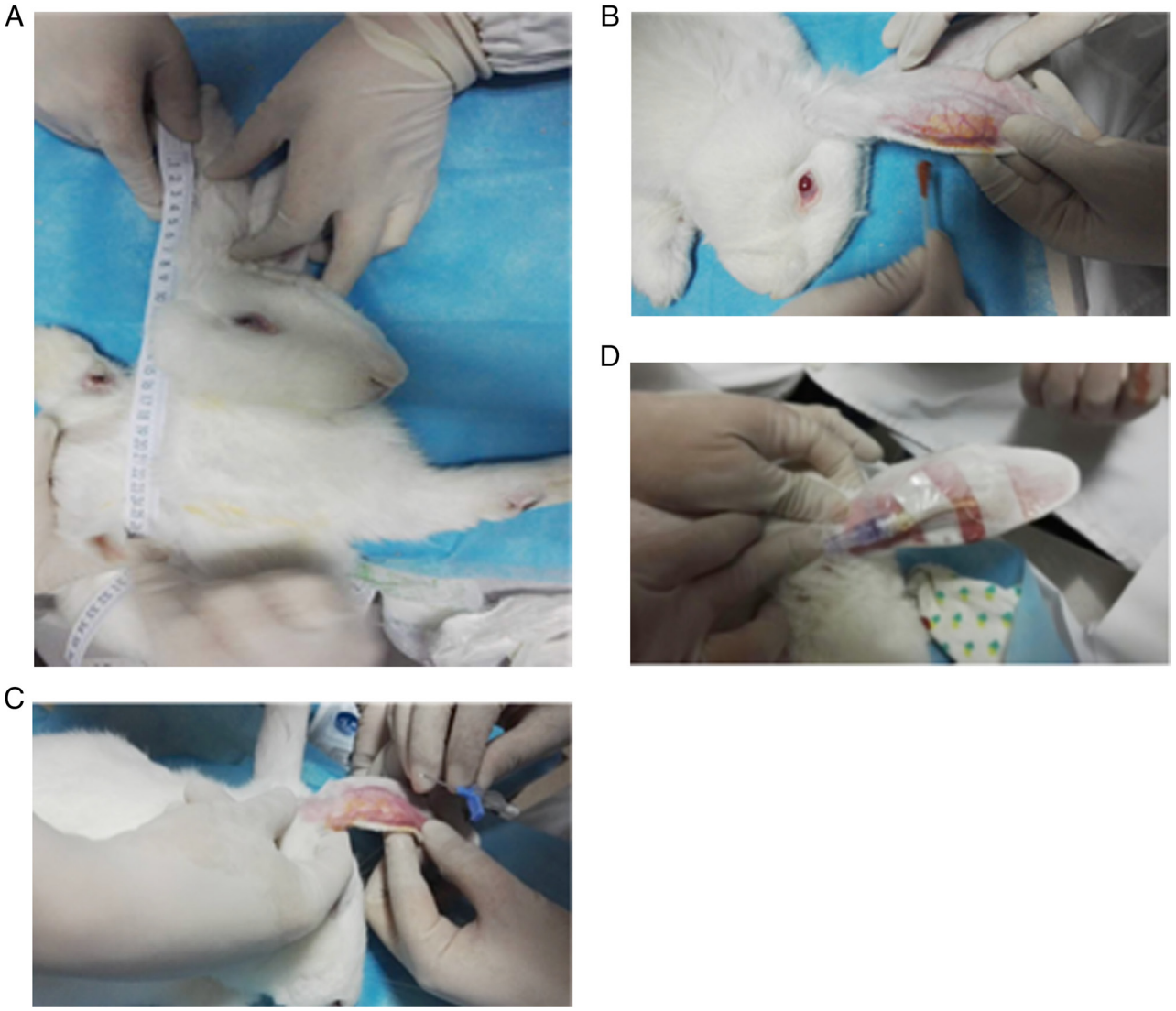

Figure 1. Construction of PICC chemotherapy rabbit model. (A) Measurement of the length of the PICC insertion. (B) Skin preparation and disinfection, (C) puncture and (D) PICC insertion. PICC, peripherally inserted central catheter.

grading standard of the American Society of Intravenous Nursing (18) were as follows: i) Grade 0, no clinical symptoms and signs; ii) grade I, local pain, redness or edema, no cord-like changes in the vein and no induration on touch; iii) grade II, local pain, redness, swelling or edema, string-like changes in veins, no induration, mild swelling, burning sensation and moderate pain; and iv) grade III, local pain, redness or edema, string-like changes in veins and palpable induration. Furthermore, venous thrombosis was evaluated based on the following indicators: i) Whether the puncture blood vessel infusion was unobstructed or not; ii) whether the local skin was swollen and displayed edema or not; and iii) the thrombus shape, color and composition according to pathological analysis.

Hematoxylin and eosin (H&E) staining. Following removal of the PICC tube, two sections (5 cm) were removed at the front and back of the catheter; furthermore, the ear vein and the anterior vena cava (3 cm) were removed. Ear vein, anterior vena cava and catheter samples were fixed with 10% formalin for 24 h at 4˚C. Following dehydration using an ethanol series, the samples were cleared using xylene I/II. Paraffin-embedded samples were sliced into 20, 50, 100 or 200 μm-thick sections. Subsequently, H&E staining was performed. Following dewaxing and rehydrating, the sections were stained with hematoxylin dye solution for 20 min at room temperature, followed by eosin staining for 1 min at room temperature. The sections were then dehydrated and cleared. After sealing with a neutral balsam, stained sections were visualized using a light microscope (Olympus Corporation; magnification, x15 or x20).

Prothrombin time. A total of 2 ml ear vein blood samples were collected for measuring prothrombin time. Prothrombin time was determined using ACL-TOP700 automatic coagulation analyzer [ACL-TOP700; Wofen Medical Equipment Trading (Beijing) Co., Ltd.].

ELISA. Blood samples obtained from the ear vein were used for ELISA. Samples were maintained at room temperature for 2 h. Subsequently, the samples were centrifuged at 1,000 x g for 20 min at 4˚C and then stored at -20˚C. The serum levels of

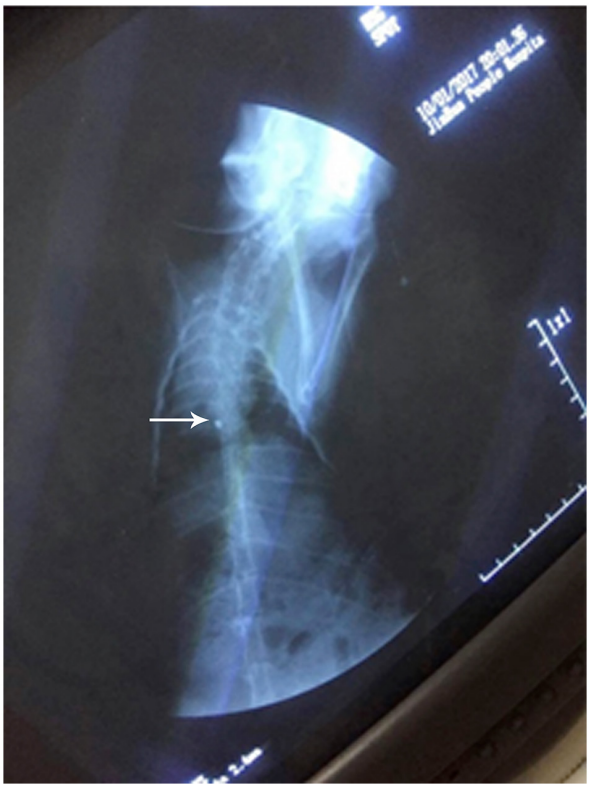

Figure 2. X-ray fluoroscopy of the PICC tube. X-ray demonstrated that the end of the PICC tube reached the anterior vena cava of the rabbit. Arrow indicates the transparent dot that highlights the end of the catheter. PICC, peripherally inserted central catheter.

E-selectin (cat. no. SEA029Rb; Cloud-Clone Corp.), P-selectin (cat. no. SEA569Ra), interleukin (IL)-2 (cat. no. SEA073Rb), IL-6 (cat. no. SEA079Rb), C-reactive protein (CRP; cat. no. SEA821Rb) and D-dimer (D2D; cat. no. CEA506Rb; all Cloud-Clone Corp.) were detected using the corresponding ELISA detection kits according to manufacturer's instructions. Optical density values were determined using a microplate reader (Bio-Rad Laboratories, Inc.).

Statistical analysis. Statistical analyses were performed using GraphPad Prism software (version 7.0; GraphPad Software, Inc.). Data are presented as the mean ± standard deviation. Each experiment was repeated three times independently. Comparisons among multiple groups were performed using one-way ANOVA followed by Tukey's post hoc test. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Construction of a PICC chemotherapy rabbit model. In the present study, a PICC chemotherapy model was successfully established in 48 rabbits. To observe the pathological changes of the puncture point during PICC catheterization, the rabbits were randomly separated into eight experimental groups. A course of chemotherapy includes 2-3 cycles (19); the present study was based on two cycles. X-rays were captured to confirm that the end of the catheter was not twisted or folded, and was placed in the anterior vena cava (Fig. 3). In each group, the local puncture site displayed no injury or bleeding. Thus, it was determined that the PICC models were successfully constructed.

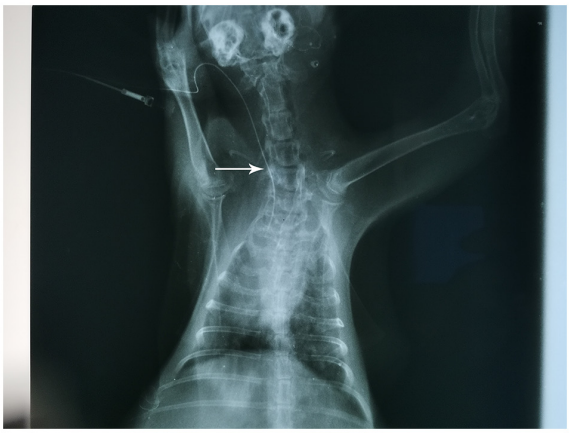

Figure 3. X-ray imaging determination of successful peripherally inserted central catheter model construction. The end of the catheter was not twisted or folded, and it was placed in the anterior vena cava. Arrow indicates the catheter.

Dynamic monitoring of catheter-related thrombosis in rabbits with administration of vinorelbine via PICC. At different time periods, the PICC tube was removed and the two segments at the front and back of the catheter were surgically dissected. H&E staining of the middle of the catheter was performed to observe catheter-related thrombosis. On the 1st day of PICC implantation, the H&E staining results revealed that a thrombus filled the catheter (Fig. 4). On the 2nd day of PICC implantation, no thrombus was observed in the catheter after administration of vinorelbine. The catheter-related thrombus was continuously monitored on the 3rd, 7th, 14th and 21st days of PICC implantation. As indicated by the H&E staining results, there was no thrombus in the catheter. On the 23rd day of PICC implantation, a small thrombus was observed in the catheter. However, the thrombus was no longer visible on the 24th day. Collectively, the results indicated that catheter-related thrombosis primarily occurred on the 1st day of PICC implantation and the 23rd day of chemotherapy administration.

Dynamic monitoring of ear vein thrombosis after administration of vinorelbine via PICC. H&E staining was performed to examine the pathological changes in ear vein tissues at numerous time points (Fig. 5). On the 1st day of PICC implantation, the intima of the ear veins was irregularly ruptured, and the lumen was characterized by thrombosis. On the 2nd day of catheterization, there was slight ear vein thrombosis, the intima was irregularly ruptured, and inflammatory cell infiltration was observed following vinorelbine administration. On the 3rd, 7th and 14th days of PICC implantation, ear vein thrombosis and inflammatory cell infiltration were notably improved, the intima was hyperplastic, and scars were formed in the lumen of the ear veins. Furthermore, the media and adventitia had no obvious lesions, and the lumen was not completely occluded. On the 21st and 23rd (after vinorelbine administration) days of PICC implantation, the results revealed that there were evident scars and inflammatory cell infiltration in the lumen. On the 24th day, the blood vessels of the

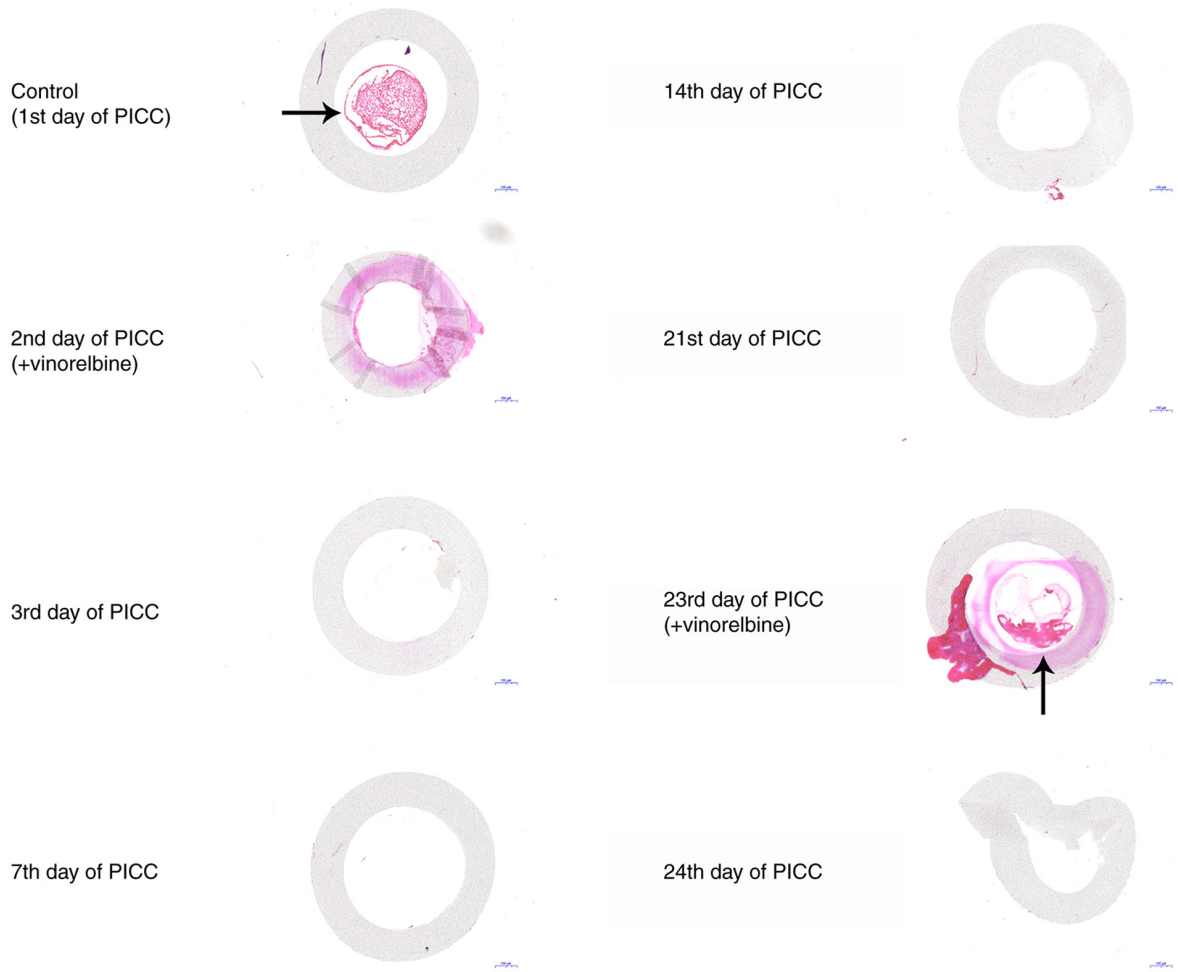

Figure 4. Dynamic monitoring of catheter-related thrombosis in rabbits with PICC administration of vinorelbine. Hematoxylin and eosin staining was performed to assess catheter-related thrombosis in rabbits with PICC placement at eight different time points. Arrows indicate the thrombus. Magnification, x15. Scale bar, 100 μm. PICC, peripherally inserted central catheter.

ear veins were not damaged, there was no obvious scar in the lumen and thrombosis had disappeared. Therefore, the results indicated that ear vein thrombosis was primarily caused by PICC puncture, and administration of vinorelbine may induce inflammatory cell infiltration.

Dynamic monitoring of pathological injury in the anterior vena cava after administration of vinorelbine via PICC. The end of the anterior vena cava was obtained at different time periods to investigate pathological injury via H&E staining. On the 1st day of PICC implantation, the vascular intima of the anterior vena cava was irregularly ruptured (Fig. 6). Furthermore, the vessel wall was thickened, which was accompanied by immune cell infiltration. On the 2nd (after vinorelbine administration), 3rd and 7th days of PICC implantation, the vascular intima of the anterior vena cava was relatively intact, with a slightly thickened wall. Moreover, inflammatory cell infiltration was distinctly ameliorated. On the 14th and 21st days, the vascular intima of the anterior vena cava was intact and the wall was normal. However, low level immune cell infiltration was observed. On the 23rd day of PICC implantation after administration of vinorelbine, there was distinct inflammatory cell infiltration in the anterior vena cava. On the 24th day, the vascular intima of the anterior vena cava was relatively intact, the wall was normal and there was almost no infiltration of inflammatory cells. These results indicated that vinorelbine administered via PICC could induce phlebitis, and over time phlebitis was gradually ameliorated within the first cycle of vinorelbine and phlebitis was significantly alleviated within 1 day of the second cycle of vinorelbine

Evaluation of prothrombin time after administration of vinorelbine via PICC. To assess the function of the extrinsic coagulation system, the prothrombin time of ear vein blood samples that were collected at different time points was assessed. The results demonstrated that the prothrombin time was significantly shortened after administration of vinorelbine on the 2nd day of PICC implantation compared with that on the 1st day (Fig. 7). Compared with that on the 2nd day of PICC implantation with vinorelbine administration, the prothrombin time was significantly prolonged on the 7th, 14th and 21st days. On the 23rd day, after administration of vinorelbine, the prothrombin time was significantly reduced compared with that on the 21st day. By contrast, the prothrombin time was significantly increased on the 24th day compared with that on the 23rd day. Therefore, the results indicated that administration of vinorelbine via PICC reduced prothrombin time on the day of administration.

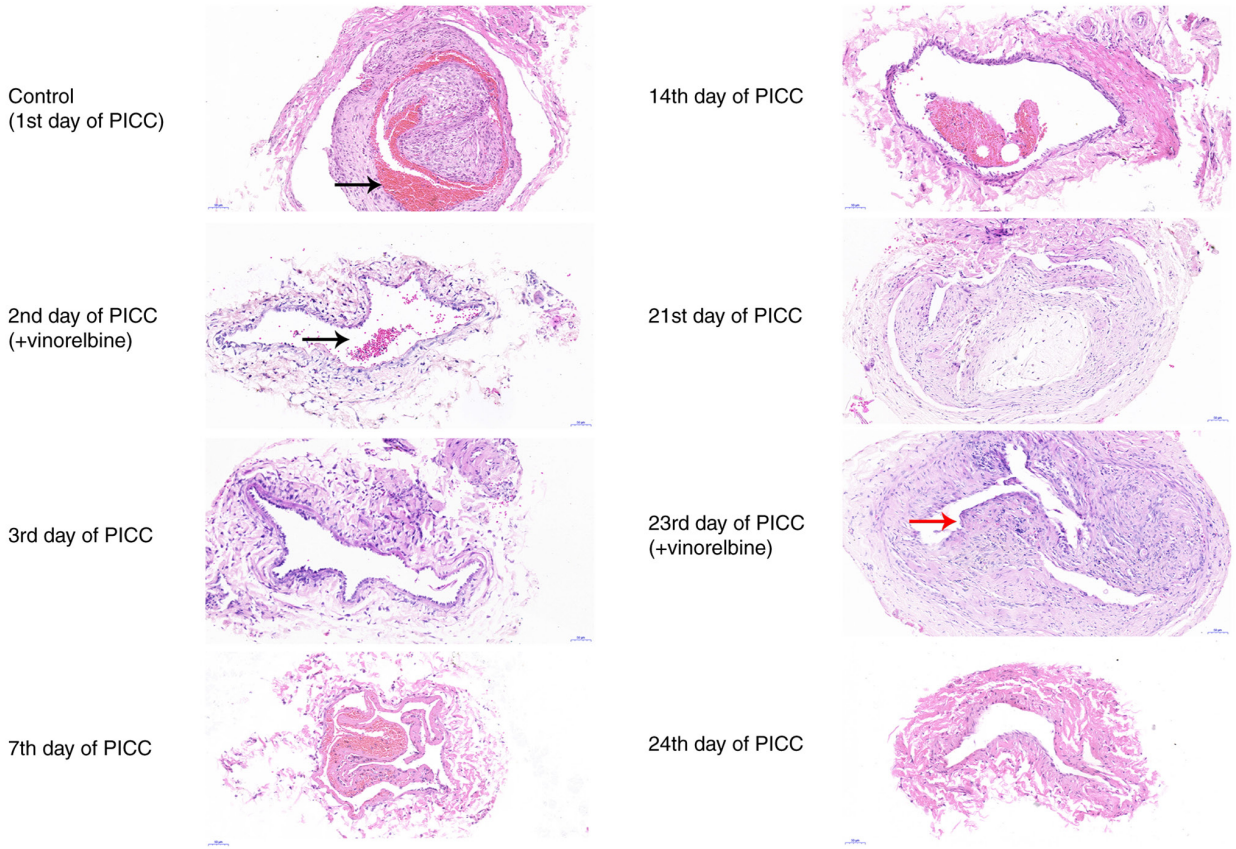

Figure 5. Dynamic monitoring of ear vein thrombosis in rabbits with PICC administration of vinorelbine. Hematoxylin and eosin staining was performed to assess the ear vein thrombosis in rabbits with PICC placement at eight different time points. Black arrows indicate ear vein thrombosis. Red arrow indicates inflammatory cell infiltration. Magnification, x20. Scale bar, 50 μm. PICC, peripherally inserted central catheter.

Dynamic monitoring of inflammation- and thrombosis-related factors in rabbits administered with vinorelbine via PICC. Inflammation- and thrombosis-related indexes were examined in blood samples obtained from ear veins via ELISA at different time points. The levels of CRP after administration of vinorelbine on the 2nd day of PICC implantation were significantly increased compared with those on the 1st day of catheterization (Fig. 8A). However, on the 7th, 14th and 21st days of PICC implantation, CRP levels were significantly lowered compared with those on the 2nd day. On the 23rd day of PICC implantation after vinorelbine administration, CRP levels were significantly elevated compared with those on the 21st day, but this effect was significantly reversed on the 24th day. The levels of P-selectin, E-selectin and IL-6 were also determined in ear vein blood samples. P-selectin, E-selectin and IL-6 levels were significantly higher on the 2nd day of PICC after vinorelbine administration compared with those on the 1st day of catheterization (Fig. 8B-D). Nevertheless, the levels of these markers were significantly decreased on the 7th, 14th and 21st days of PICC implantation compared with those on the 2nd day. Following administration of vinorelbine on the 23rd day of catheterization, P-selectin, E-selectin, and IL-6 levels were significantly elevated compared with those on the 21st day, but this effect was reversed on the 24th day. As demonstrated in Fig. 8E, IL-2 levels were significantly reduced after vinorelbine administration on the 2nd day of PICC catheterization compared with those on the 1st day of catheterization. On the 7th, 14th and 21st days, IL-2 levels were significantly increased in a time-dependent manner compared with those on the 2nd day. After administration of vinorelbine on the 23rd day of catheterization, IL-2 levels were significantly reduced compared with those on the 21st day, but then significantly increased on the 24th day. D2D levels were significantly higher on the 2nd day of PICC implantation after vinorelbine administration compared with those on the 1st day of PICC (Fig. 8F). On the 7th, 14th and 21st days, D2D levels were significantly decreased compared with those on the 2nd day. However, significantly increased D2D levels were detected following administration of vinorelbine on the 23rd day compared with those on the 21st day. The levels of D2D displayed a significant decline on the 24th day compared with those on the 23rd day. These results revealed that vinorelbine administration via PICC could induce an inflammatory response and thrombosis formation.

Discussion

In the present study, a rabbit model with vinorelbine administration via PICC was successfully established. During each time point of PICC intubation, the puncture points, vascular pathological changes and serum observation indexes were assessed. Eight time points of PICC intubation were used to observe phlebitis and venous thrombosis. Administration of vinorelbine via PICC distinctly induced catheter-related thrombosis, ear vein thrombosis and pathological damage in the anterior vena cava. Furthermore, prothrombin time was

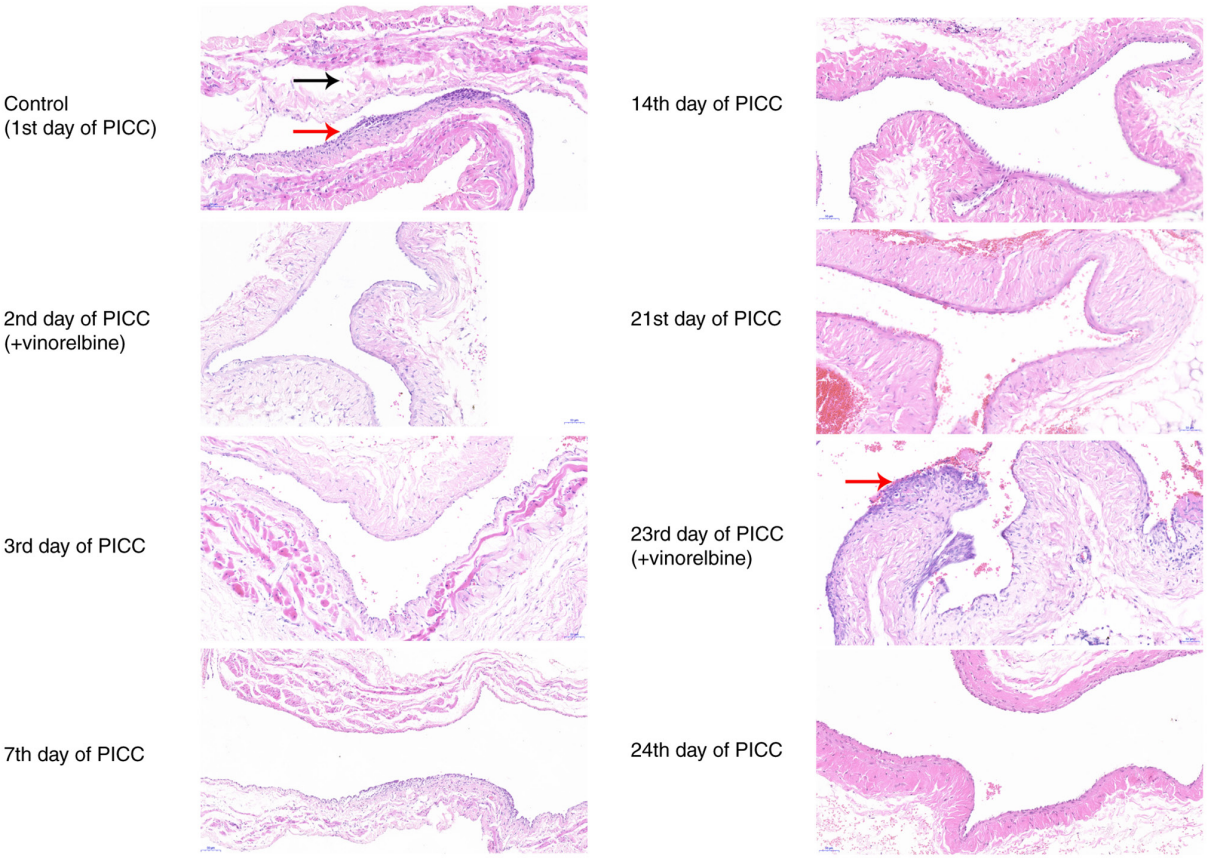

Figure 6. Dynamic monitoring of pathological injury in the anterior vena cava in rabbits with PICC administration of vinorelbine. Hematoxylin and eosin staining was performed to assess the pathological changes in the anterior vena cava tissues in rabbits with PICC placement at eight different time points. Black arrow indicates irregularly ruptured vascular intima. Red arrows indicate immune cell infiltration. Magnification, x20. Scale bar, 50 μm. PICC, peripherally inserted central catheter.

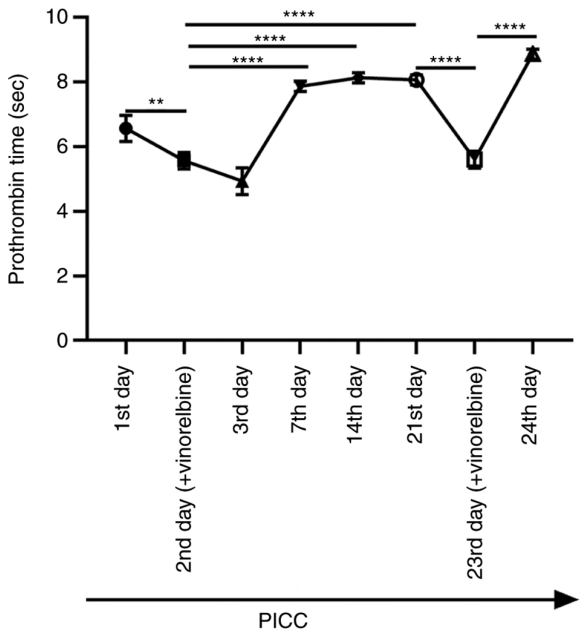

Figure 7. Prothrombin time of ear vein blood samples in rabbits with PICC placement. Prothrombin time was assessed at eight different time points. **P<0.01; ****P<0.0001. PICC, peripherally inserted central catheter.

significantly decreased, and the inflammatory response was significantly enhanced after vinorelbine administration via PICC. With increasing time after PICC administration of vinorelbine, the aforementioned pathological changes were notably improved.

X-rays confirmed that the PICC rabbit model was successfully constructed in the present study. For patients with cancer receiving chemotherapy or nutrition, PICC has become the main method of venous access (20-22). However, PICC-related venous thrombosis is the most common complication (23). For example, it has been reported that PICC is associated with a high risk of catheter-related deep venous thrombosis in a randomized multicenter trial (3). Consistently, the results of the present study revealed that the catheter was filled with a thrombus on the 1st day of PICC implantation. However, after administration of 25 mg/m^2 vinorelbine on the 2nd and 23rd day of PICC, the vein thrombus was observed. Furthermore, pathological damage in the anterior vena cava was relatively minimal on the day of vinorelbine administration. However, with increasing time the pathological damage was gradually ameliorated. In a recent monocentric and randomized trial, PICC displayed higher safety and effectiveness compared with a centrally inserted central catheter. Moreover, the use of PICC could effectively reduce the risk of infection and thrombosis (24). However, whether vinorelbine injection via PICC is effective and safe requires long-term investigation in a larger cohort.

Prothrombin time refers to the time required to add excessive tissue thromboplastin and calcium ions to plasma lacking

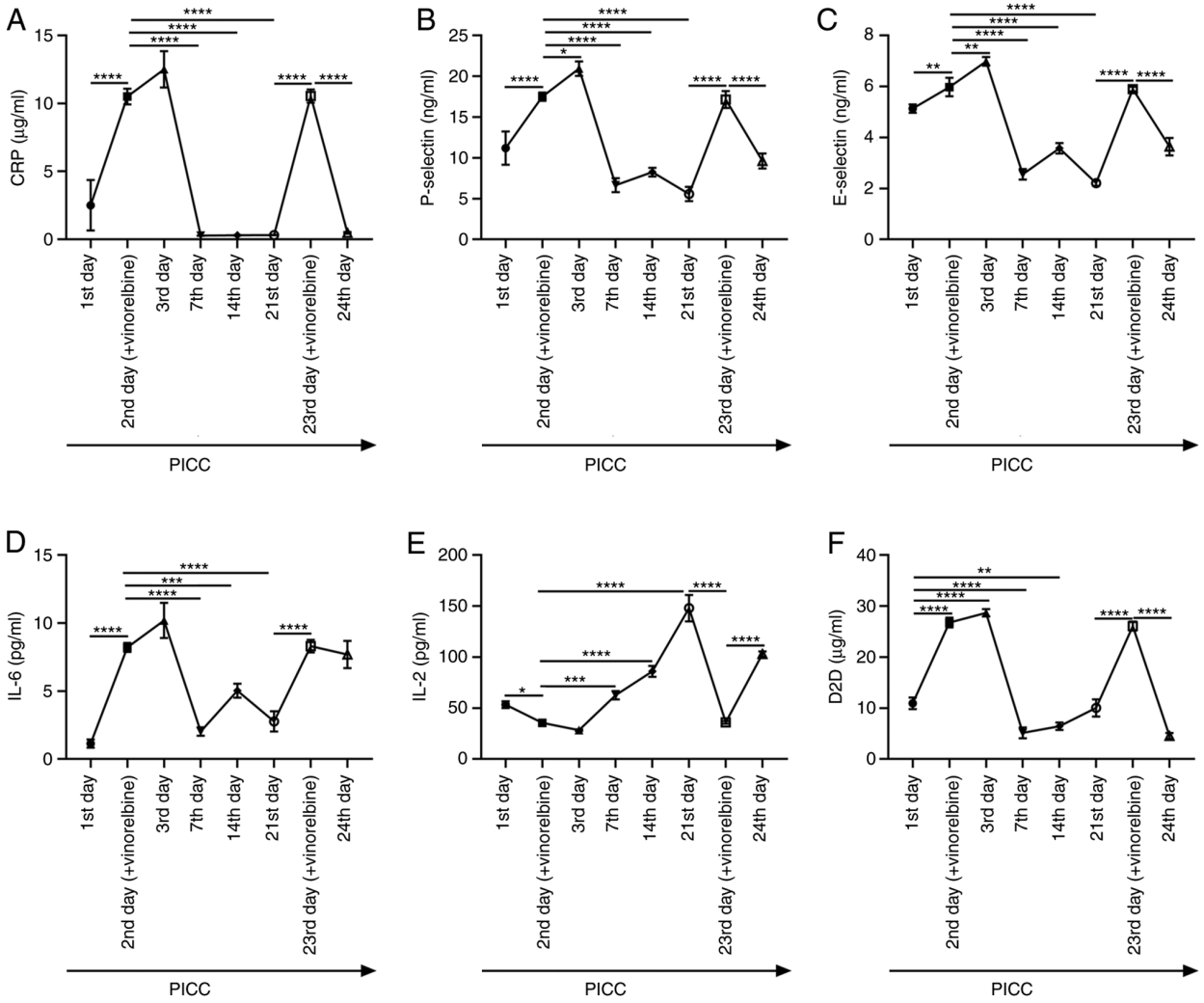

Figure 8. Inflammation- and thrombosis-related factors in rabbits with PICC administration of vinorelbine. Levels of (A) CRP, (B) P-selectin, (C) E-selectin, (D) IL-6, (E) IL-2 and (F) D2D were determined in ear vein blood samples from rabbits with PICC placement at eight different time points by performing ELISA. *P<0.05, **P<0.01, ***P<0.001 and ****P<0.0001. PICC, peripherally inserted central catheter; CRP, C-reactive protein; IL, interleukin; D2D, D-dimer.

platelets to convert prothrombin to thrombin, resulting in plasma coagulation (25-27). Prothrombin time is an indicator reflecting the activity of coagulation factors I, II, V, VII and X in the plasma (28). The prothrombin time measurement is a barrier-free screening test to check the function of the extrinsic coagulation system, and it is also an important monitoring index for clinical anticoagulation therapy (29). In the present study, compared with that on the 1st day of PICC, the prothrombin time was significantly shortened following vinorelbine administration, but significantly increased over time. In a previous study, a positive correlation between serum vinorelbine levels and the number of platelets was reported (30).

Serum inflammation- and thrombosis-related factors were examined by performing ELISA. The results demonstrated that CRP, P-selectin, E-selectin, IL-6 and D2D levels were distinctly elevated following vinorelbine administration. CRP, which is a non-specific diagnostic inflammatory biomarker, is involved in mediating innate immune responses (31). The levels of CRP in the plasma rise sharply when the body is infected or tissues are damaged (32). In the early stage of acute inflammation, P-selectin participates in the process of recruiting leukocytes to the injured site (33). Moreover, P-selectin is closely related to deep vein thrombosis (34). D2D is a fibrin degradation product, and its elevated levels indicate a hypercoagulable state and secondary fibrinolysis in the body (35). It has become a diagnostic marker for deep vein thrombosis (36). In the present study, administration of vinorelbine via PICC significantly elevated serum CRP, P-selectin, E-selectin, IL-6 and D2D levels but decreased serum IL-2 levels, indicating that inflammation and thrombosis could be induced by vinorelbine administration via PICC. A previous study demonstrated that vinorelbine reduces serum IL-2 levels in a Lewis lung cancer mouse model (37).

However, the present study had certain limitations. Firstly, to dynamically observe phlebitis and venous thrombosis, additional time points should be assessed. Moreover, the potential underlying mechanisms should be explored in future studies.

The present study successfully constructed a rabbit model with vinorelbine administration via PICC, and dynamically observed phlebitis and venous thrombosis. On the day of vinorelbine administration via PICC, there was a high risk of phlebitis and thrombosis, which suggested that anticoagulation therapy and patient care should be provided in that time period. Therefore, the present study provided a reference for early

prediction, timely prevention and treatment of PICC-related chemotherapy venous complications, and also provided a theoretical basis for timely vascular protection, anticoagulation therapy and effective patient care.

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Availability of data and materials

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

Authors' contributions

LH conceived and designed the study. GC and QH performed the majority of experiments and data analysis, and wrote the manuscript. BH, LZ and LF performed a small number of experiments and data analysis, and wrote and revised the manuscript. LH and GC confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of the School of Medicine, Jinhua Polytechnic (Jinhua, China; approval no. 2019017).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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