

ORIGINAL RESEARCH



Prevalence and consequences of central venous catheter malposition in critically ill pediatric patients

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Abstract

Background: This study aimed to determine the prevalence of malpositioning of central venous catheters inserted into the internal jugular and subclavian veins and to identify the risk factors associated with such positioning in children. **Methods:** A retrospective cohort study in a pediatric intensive care unit (ICU) radiologically assessed central venous catheters (CVC) position in patients aged one month to 18 years from 2023 to 2024. Positioning was categorized based on proximity to the carina: “Good” (between the carina and two vertebral bodies below), “High” (above the carina), “Low” (below two vertebral bodies) and “Abnormal” (outside these regions). The associations between patient demographics, clinical data, and catheter tip positions were analyzed. **Results:** Out of 214 pediatric patients, 52.8% were males, with a median age of 35 months. Catheter tip positioning was classified as “good” (62.1%), “high” (17.7%), “low” (17.2%) and “other” (2.8%). Notably, High tip positions were associated with older and heavier patients, while Low tip positions were more common in younger and lighter patients. Patients weighing 20–40 kg had nearly three times higher odds of “High” catheter tip positions than those weighing 0–10 kg ($p = 0.032$). Temporary CVCs were five times more likely to result in “High” positions ($p = 0.035$). Right-sided placement reduced the risk of “High” positions by 71% ($p = 0.002$). In comparison, higher weight categories (10–20 kg and ≥ 40 kg) lowered the odds of “Low” positions by 79% and 74%, respectively ($p = 0.004$ and $p = 0.025$). **Conclusions:** In critically ill pediatric patients, the incidence of malposition in CVCs remains significantly high, influenced by factors type and location of catheter placement, direction of insertion and the patient’s age and weight.

Keywords

Central venous catheter malposition; Pediatric intensive care; Pediatric catheterization

1. Introduction

Central venous catheters (CVCs) and temporary hemodialysis/apheresis catheters are commonly used in critically ill pediatric patients for vital interventions such as fluid administration, drug therapies, total parenteral nutrition, blood sampling, central venous pressure monitoring, hemodialysis and therapeutic plasma exchange (TPE). Despite their essential role, placing these catheters can lead to severe bleeding and thrombotic complications—including arterial puncture, pneumothorax, hemothorax and air embolism—that can be fatal, especially in critically ill patients. Additionally, the presence of a catheter increases the risk of catheter-related bloodstream infections and thrombosis. The frequency of these complications depends on various factors, including the catheter’s location, duration of placement, patient-specific factors (such as body structure, comorbidities, coagulopathy and severity of illness) and the clinician’s experience [1–3].

The Food and Drug Administration (FDA) has advised that the catheter tip should not be placed within the heart or allowed to migrate there [4]. Studies have shown that positioning a central venous catheter (CVC) tip in the right atrium or other cardiac chambers can lead to serious complications—including arrhythmias, intracardiac thrombosis, perforation, tamponade and even death. Furthermore, placing the catheter tip too close to the superior vena cava (SVC) may cause thrombosis, extravasation and catheter dysfunction [5–7].

The optimal catheter tip position in pediatric patients remains a topic of ongoing debate. Studies in adults have suggested that the carina can be used as a radiographic marker for central venous catheter placement. Research investigating its applicability in children has confirmed that the carina is a superior and simpler anatomical-radiological landmark than the pericardial reflection point, even in neonates and young children [8].

In this study, we aimed to assess the prevalence of malpo-

sition in central venous catheters and temporary hemodialysis catheters inserted into the internal jugular and subclavian veins and to investigate the risk factors that contributed to this condition.

2. Materials and methods

In this study, we conducted a retrospective cohort study in a 15-bed, Level III Pediatric Intensive Care Unit (PICU) at Ümraniye Training and Research Hospital. Patients aged one month to 18 years who were admitted to the PICU and had central catheters inserted into the internal jugular or subclavian veins between 01 January 2023, and 31 July 2024, were included. Patients with catheters placed in the femoral vein or with insufficient data were excluded. Approval was obtained from the Ethics Committee of the University of Health Sciences, Ümraniye Training and Research Hospital.

The patients' age (months), gender, body weights, comorbidity status, length of stay in the PICU (days), prognosis, the purpose of CVC insertion (vascular access problems, therapeutic plasma exchange (TPE), continuous renal replacement therapy (CRRT)) and laboratory parameters (hemoglobin, international normalized Ratio (INR)) were recorded. In our clinic, the routinely employed X-ray method was used to assess catheter tip localization. During this process, CVCs were inserted using the standard Seldinger technique under ultrasound guidance. Four different proceduralists participated in the CVC placement (two intensive care specialists and two intensive care fellows). Catheter diameters were determined based on the weight-to-catheter diameter charts available in the unit, in accordance with the updated protocol (target ratio: catheter diameter/vein diameter <0.5) [9]. Following the procedure, all catheters were sutured to the skin using suture material and secured with a fixation dressing containing chlorhexidine gluconate gel pads. During patient follow-up, no changes in catheter localization were observed after the initial evaluation; catheters with abnormal localization were withdrawn and replaced with new ones.

To assess the characteristics and complications of central venous catheters (CVCs), we recorded details such as catheter types, insertion sites, directions, sizes, catheter tip positions and late complications—including central line-associated bloodstream infections (CLABSI), venous thromboembolism (VTE) and tissue plasminogen activator (tPA) administration. Using posteroanterior chest radiographs and classification criteria from a previous study, we evaluated the positions of the catheter tips [10]. We categorized these positions as “normal/good” when located between the carina and two vertebral bodies below it; “high” when above the carina; “low” when below the two vertebral bodies below the carina; and “abnormal” when outside these regions.

The statistical analysis was performed using SPSS® 12.0 (SPSS Inc., Chicago, IL, USA). The Kruskal-Wallis test was used to compare continuous variables such as age, weight, ICU days, catheter size diameter, INR and hemoglobin levels across different groups. The Chi-square (χ^2) test or Fisher's exact test was applied for categorical variables, including gender, type of central venous catheter (CVC), catheter site, side of catheter placement, presence of port or tunneled catheters, incidence

of central line-associated bloodstream infections (CLABSI), venous thromboembolism, and the use of tissue plasminogen activator (tPA). To evaluate how catheter positions (“Good”, “High”, “Low”, “Other”) influenced the probability of specific clinical outcomes—such as the utilization of tissue plasminogen activator, the development of venous thromboembolism, and the incidence of CLABSI—a simple logistic regression analysis was conducted. Additionally, to explore the relationships between various patient-specific factors (e.g., weight categories, gender and catheter type) and abnormalities in catheter position (“High”, “Low”, “Other”), multinomial regression analysis was employed with “Good Position” serving as the reference category. A p value of less than 0.05 was considered statistically significant.

3. Results

Over a two-year period, 290 patients underwent placement of central venous catheters (CVCs) and temporary hemodialysis catheters. After excluding 76 patients who underwent femoral vein catheter placement, the final cohort was composed of 214 patients. Of these, 52.8% were male, with a median age of 35 months and a median weight of 15 kg. The median length of stay in the pediatric intensive care unit (PICU) was 12 days. Additionally, 67.7% of the patients had comorbidities, and 21% (45 patients) died during the study.

Central venous catheters were significantly more prevalent than temporary hemodialysis catheters (76.2% vs. 23.8%, $p < 0.001$), with 28 catheters used for continuous renal replacement therapy (CRRT) and 24 for therapeutic plasma exchange (TPE) (Table 1). The internal jugular vein was the most common insertion site in 86% of cases ($p < 0.001$). Regarding catheter placement positions, 62.1% of CVC tips were in the “Good” position, 17.7% in “High Abnormal” position, 17.2% in “Low Abnormal” position and 2.8% in “Other” position (Table 1).

Continuous variables were compared using the Kruskal-Wallis test and are reported as median (interquartile range). Categorical variables were compared using the χ^2 or Fisher's exact test, as appropriate and are reported as n (%).

A comparison of the groups revealed that the patients in the “High Abnormal” group demonstrated the highest median age (77 months) and weight (21 kg) compared to those in the other groups ($p = 0.008$ for age and $p = 0.003$ for weight) (Table 1). Right-sided catheter placement was more frequently observed overall, with the “Good” (81.2%) and “Low Abnormal” (83.8%) groups having exhibited higher rates than the “High Abnormal” (55.3%) and “Other Abnormal” (66.7%) groups ($p = 0.006$). In terms of catheter placement site, the internal jugular vein was predominantly utilized in the “Good” (85%), “Low Abnormal” (89.2%) and “High Abnormal” (94.7%) groups, whereas the subclavian vein was more commonly employed in the “Other Abnormal” group (66.7%) ($p < 0.001$) (Table 1). Additionally, the “Good” (80.5%) and “High Abnormal” (94.7%) groups exhibited a higher prevalence of CVC-type catheters, while the “Low Abnormal” group had a greater proportion of temporary hemodialysis catheters (59.5%) ($p < 0.001$). No significant differences were observed between the patient groups concerning gender, duration of

TABLE 1. Comparison of clinical and laboratory parameters in patients by type of central venous catheter positions.

Parameter	Total (n = 214)	Good position (n = 133)	High abnormal (n = 38)	Low abnormal (n = 37)	Other abnormal (n = 6)	P
Age (mon)	35 (9.75–124.25)	36 (12–128)	77 (10.75–126.25)	9 (4–80)	14 (5.75–77.25)	0.008
Weight (kg)	15 (7–26.5)	15 (8–29)	21 (8.75–35)	7 (4–21)	8.5 (4–14.25)	0.003
ICU days	12 (5–30)	10 (5–29)	17.5 (4–42)	15 (6–20.5)	14.5 (6–27.5)	0.810
Gender						
Female	101 (47.2%)	64 (48.1%)	15 (39.5%)	19 (51.4%)	3 (50.0%)	0.750
Male	113 (52.8%)	69 (51.9%)	23 (60.5%)	18 (48.6%)	3 (50.0%)	
CVC type						
Temporary CVC	163 (76.2%)	107 (80.5%)	36 (94.7%)	15 (40.5%)	5 (83.3%)	<0.001
Hemodialysis CVC	51 (23.8%)	26 (19.5%)	2 (5.3%)	22 (59.5%)	1 (16.7%)	
Site						
Internal Jugular vein	184 (86.0%)	113 (85.0%)	36 (94.7%)	33 (89.2%)	2 (33.3%)	<0.001
Subclavian vein	30 (14.0%)	20 (15.0%)	2 (5.3%)	4 (10.8%)	4 (66.7%)	
Catheter side						
Right	164 (76.7%)	108 (81.2%)	21 (55.3%)	31 (83.8%)	4 (66.7%)	0.006
Left	50 (23.3%)	25 (18.8%)	17 (44.7%)	6 (16.2%)	2 (33.3%)	
Catheter size diameter (Fr)	5 (4–7)	5 (4–7)	5 (4.0–7.0)	7 (4.0–8.5)	4 (4.0–4.75)	0.070
Presence of port or tunneled	13 (6.1%)	10 (7.5%)	2 (5.3%)	1 (2.7%)	0 (0.0%)	0.650
Central line–associated blood stream infection	25 (11.7%)	17 (12.8%)	5 (13.2%)	2 (5.4%)	1 (16.7%)	0.620
Venous thromboembolism	11 (5.1%)	7 (5.3%)	4 (10.5%)	0 (0.0%)	0 (0.0%)	0.200
tPA application	9 (4.2%)	5 (3.8%)	4 (10.5%)	0 (0.0%)	0 (0.0%)	0.130
INR (s)	1.19 (0.97–1.37)	1.22 (1.02–1.35)	1.17 (0.95–1.36)	1.21 (0.53–1.52)	0.57 (0.11–1.38)	0.100
Hemoglobin (g/dL)	9.65 (8.9–11.5)	10.2 (8.85–11.5)	9.65 (8.85–11.8)	9.9 (8.75–11.2)	10.6 (9.1–12.4)	0.880

CVC: central venous catheter; tPA: tissue plasminogen activator; ICU: intensive care unit; INR: international normalized ratio.

PICU stay, catheter diameter or the presence of a port or a tunneled catheter (Table 1).

Multiple multinomial regression analysis for the association between patient and catheter characteristics and malposition type (with the reference being “Good” position) showed that patients weighing 20–40 kg had increased odds of having a “High Abnormal” tip position compared to the reference group (0–10 kg) (adjusted odds ratio (aOR): 2.920; 95% confidence interval (CI): 1.095–7.787; $p = 0.032$) and temporary CVCs compared with hemodialysis CVCs were also associated with higher odds of “High Abnormal” tip positions (aOR: 5.057; 95% CI: 1.118–22.881; $p = 0.035$) (Table 2). Conversely, right-sided catheters, as compared with left-sided catheters (aOR: 0.287; 95% CI: 0.129–0.638; $p = 0.002$), were associated with decreased odds of “High Abnormal” CVC tip positions (Table 2).

Similarly, temporary CVCs were associated with decreased odds of “Low Abnormal” tip positions compared with hemodialysis CVCs (aOR: 0.163; 95% CI: 0.072–0.370; $p < 0.001$) (Table 2). Additionally, weight categories of 10–20 kg (aOR: 0.212; 95% CI: 0.074–0.611; $p = 0.004$) and ≥ 40 kg

(aOR: 0.263; 95% CI: 0.082–0.845; $p = 0.025$) had decreased odds of having a “Low Abnormal” tip position compared with the reference group (0–10 kg) (Table 2). The internal jugular vein was associated with decreased odds of having an “Other Abnormal” tip position compared with the subclavian vein (aOR: 0.085; 95% CI: 0.013–0.552; $p = 0.01$) (Table 2).

CLABSI developed in 11.7% of the patients ($n = 25$); thromboembolism occurred in 5.1% ($n = 11$); and tissue plasminogen activator (tPA) was administered to nine patients (4.2%). There were no significant differences between the catheter position groups in the incidence of CLABSI, thromboembolism or tPA use (Table 1). A simple logistic regression analysis of the association between the CVC tip position and these health outcomes showed no significant associations in this cohort (Table 3).

4. Discussion

Our study found that 37.8% of patients who underwent internal jugular and subclavian central venous catheter placement in the pediatric intensive care unit had catheter tips positioned

TABLE 2. Association between types of malposition and patient and catheter characteristics.

Parameter	“High” Abnormal		“Low” Abnormal		“Other” Abnormal	
	aOR [95% CI]	<i>p</i>	aOR [95% CI]	<i>p</i>	aOR [95% CI]	<i>p</i>
Weight category						
0–10 kg	Reference		Reference		Reference	
10–20 kg	0.594 [0.211, 1.675]	0.320	0.212 [0.074, 0.611]	0.004	NA [0.000, ∞)	>0.999
20–40 kg	2.920 [1.095, 7.787]	0.032	0.674 [0.232, 1.953]	0.470	0.494 [0.054, 4.548]	0.530
>40 kg	0.922 [0.320, 2.658]	0.880	0.263 [0.082, 0.845]	0.025	NA [0.000, ∞)	>0.999
Male vs. Female	1.321 [0.610, 2.861]	0.480	1.065 [0.486, 2.332]	0.880	1.102 [0.100, 6.097]	0.910
Internal jugular vs. Subclavian	3.624 [0.783, 16.782]	>0.999	0.859 [0.253, 2.923]	0.810	0.085 [0.013, 0.552]	0.010
Right vs. Left	0.287 [0.129, 0.638]	0.002	1.296 [0.457, 3.674]	0.630	0.425 [0.066, 2.734]	0.370
Presence of port/tunneled cuffed-central venous catheter (No vs. Yes)	1.623 [0.325, 8.098]	0.560	2.341 [0.266, 20.585]	0.440	0.000 [0.000, ∞)	0.950
Temporary CVC vs. Hemodialysis CVC	5.057 [1.118, 22.881]	0.035	0.163 [0.072, 0.370]	<0.001	0.627 [0.057, 6.920]	0.700

Multinomial regression analysis was performed, using “Good Position” as the baseline. aOR: adjusted odds ratio; CVC: central venous catheter; NA: not applicable; CI: confidence interval.

TABLE 3. Association between catheter malpositions and various health outcomes.

Catheter position	Tissue plasminogen activator		Venous thromboembolism		CLABSI	
	Odds ratio [95% CI]	<i>p</i>	Odds ratio [95% CI]	<i>p</i>	Odds ratio [95% CI]	<i>p</i>
“Good”	Reference		Reference		Reference	
“High”	3.01 [0.76–11.83]	0.11	2.12 [0.59–7.66]	0.25	1.03 [0.35–3.01]	0.95
“Low”	NA		NA		0.39 [0.09–1.77]	0.22
“Other”	NA		NA		1.36 [0.15–12.40]	0.78

Simple logistic regression analysis was used to assess the impact of catheter position on the likelihood of tissue plasminogen activator usage, venous thromboembolism and central line-associated bloodstream infection (CLABSI). NA: not applicable; CI: confidence interval.

outside the recommended areas. We observed correlations between catheter malposition and factors such as body weight, insertion site, directional approach and catheter type (CVC or temporary hemodialysis). However, no statistically significant associations were found between catheter malposition and variables such as gender, catheter diameter, presence of port/tunneled catheters, thromboembolic events (TVE), central line-associated bloodstream infections (CLABSI) or the administration of tissue plasminogen activator (tPA).

The ideal location of the catheter tip is at the junction of the SVC and right atrium. However, catheter tips can sometimes migrate from this ideal position. The determination of the optimal catheter tip position in pediatric patients remains a subject of ongoing debate. Studies in adults have suggested that the carina be used as a radiographic landmark for SVC placement. A specific study on the usability of this landmark in children found that the carina offers a superior and simpler anatomical-radiological reference point for SVC placement in neonates and young children compared with the pericardial reflection point [8]. Chest radiography is the standard method for confirming that the catheter tip is correctly positioned and for ruling out procedure-related complications.

The radiation dose associated with chest radiography is 0.1–0.2 mSv. Furthermore, advances in ultrasonography have yielded promising results in verifying central venous catheter (CVC) tip positioning. Several studies have demonstrated that the ultrasonographic visualization of bubbles—appearing as opacification in the right atrium following the injection of normal saline through the CVC—effectively confirms proper catheter placement. Given its excellent performance, absent radiation exposure, lower cost, time efficiency, and higher accuracy, we believe that ultrasonography will eventually replace the conventional practice of X-ray verification.

Research indicates that the rate of catheter malposition varies significantly, ranging from 3.6% to 14% [9]. A study involving pediatric patients evaluated 100 computed tomography (CT) scans and identified the optimal CVC tip position as the region from the carina to two vertebral bodies below it [10]. In many intensive care units, however, the blind-landmark technique, which relies solely on anatomical landmarks and lacks imaging guidance, is still commonly used for superior vena cava (SVC) placement [11]. Research indicates that using point-of-care ultrasound (POCUS) for central venous catheter placement significantly improves

success rates compared to the traditional landmark technique [12]. However, no study in the literature has directly compared the two techniques with regard to malposition.

In a meta-analysis evaluating catheter malposition rates, it was found that malposition occurred in 5.3% of internal jugular vein catheterizations and 9.3% of subclavian vein catheterization [13]. Schummer *et al.* [14] found malpositions in 6.7% of 1794 adult patients, with a significantly higher incidence of malposition in catheterizations performed on the left side than on the right. Consistent with prior studies, our analysis showed that malpositions were higher on the left side than on the right side. Specifically, left-sided placement increases the risk of “High Abnormal” tip positions by approximately 3.5 times compared to right-sided placement.

In a pediatric study dated 2022, 61.6% of central venous catheter tips were positioned as recommended, with 20.1% positioned higher and 16.8% lower than intended, whereas 1.5% were abnormally placed. The researchers reported that for patients weighing over 40 kg and those with left-sided catheters, the SVC tip was positioned higher, while in patients weighing 20–40 kg and female patients, it was positioned lower [15]. In our study, we found that patients weighing between 10–20 kg and those over 40 kg had a lower risk of “Low Abnormal” position compared to other patients ($p = 0.004$ and $p = 0.025$, respectively), while those weighing 20–40 kg had a higher risk of “High Abnormal” position ($p = 0.032$). Additionally, gender did not have a significant effect on catheter tip positions in our study.

Point-of-care ultrasound (POCUS) and/or intracavitary electrocardiogram (IC-ECG) can be utilized as methods to prevent catheter malpositioning. POCUS is employed for vein localization, needle guidance, and confirmation of guidewire placement in the internal jugular vein (IJV) or subclavian vein (SCV) [16–18]. Intracavitary ECG has shown a 95.8% accuracy rate in pediatric patients in assessing catheter tip positions [19]. Nevertheless, despite its significant benefits, this approach has several disadvantages, including the need for specialized equipment and trained staff, potentially longer procedure times, and additional costs for radiological imaging. Since these practices are not currently employed in our unit, we did not use these methods for verification during the study.

Guidelines recommend positioning the tip of dialysis catheters in the right atrium in adult patients to optimize flow dynamics; however, there is a lack of data supporting the suitability of this practice in children [20]. Previous studies have shown that the presence of the CVC tip in the right atrium or other cardiac cavities can lead to arrhythmia, intracardiac thrombosis, perforation, tamponade and even death. Conversely, placement in the proximal SVC has been associated with thrombosis, extravasation and catheter dysfunction [21–23].

The increased risk of malposition in left-side central venous access can be attributed to the anatomical challenges posed by the longer left brachiocephalic vein, its more oblique trajectory towards the heart, and the presence of small vascular branches in this area. Proper bevel orientation during needle insertion is critical for guiding the guidewire in the intended direction, thereby ensuring accurate catheter placement [24].

The preferred location for CVC placement is chosen due to

the high blood flow, which is thought to prevent thrombosis, and because it lies outside the atrium, thereby preventing arrhythmias [25]. A prospective 3-year study on adults in France revealed a higher risk of complications with misplaced ports when compared to a CVC with its tip at the correct location (46% vs. 5.7%, $p < 0.001$) [26]. In pediatric patients, the overall incidence of VTE, including Catheter-Related Thrombosis (CRT), is much lower than in adults, with rates varying from 2% to 82% [27]. However, the rate of pediatric VTE has significantly increased by 30–70% among hospitalized children over the last two decades [28]. The presence of a CVC is the single most common risk factor for pediatric VTE. Infections related to CVCs are a common complication in pediatric patients, with a mean incidence of 0.9–3.5 infections per 1000 catheter days, and represent the most frequent type of healthcare-associated infection in pediatric care [29, 30].

In our study, 11.7% of patients developed CLABSI; 5.1% developed thromboembolism; and 4.2% (9 patients) were administered tPA. We found no significant differences between catheter groups regarding CLABSI, thromboembolism, and tPA administration. Similarly, Weber *et al.* [15] reported a 0.8% incidence of CLABSI and 1.9% of VTE in critically ill patients. They also observed no correlation between catheter tip position and tPA administration frequency or dosage. Similarly, no prognostic differences were observed between the patient groups.

5. Conclusions

Our study found a high rate of malposition in central venous catheters commonly used in the treatment of critically ill children. We identified several important factors—such as the child’s body weight, the catheter’s insertion site and direction, and the type of catheter—that influenced the risk of placement errors. Recognizing and addressing these factors may improve placement accuracy and reduce complications. It is important to note that our study was retrospective and conducted at a single center, which may limit the generalizability of our findings. Moreover, our study did not compare catheters placed under ultrasound guidance with those inserted using the blind technique, and ultrasound was not used to evaluate the catheter tip position and we were unable to assess other known complications of malpositioned CVC, including dysrhythmias. No comments or conclusions can be made about other types of central venous access, including femoral CVCs or peripherally inserted central catheters, as these lines were not investigated in this study.

AVAILABILITY OF DATA AND MATERIALS

The raw data underlying this study contain sensitive clinical information from paediatric participants and, in accordance with local regulations and patient-privacy laws—and the restrictions set by the approving ethics committee—are not publicly available. De-identified data may be made available from the corresponding author upon reasonable request and with prior ethics approval.

AUTHOR CONTRIBUTIONS

SE, İP, HCT, CB and GA—conceptualized the study. SE, İP, MEP, HCT, CB and GA—performed data curation; wrote the original draft; reviewed and edited the manuscript. MEP, SE and İP—conducted formal analysis; validated the data; managed visualization. SE—acquired funding; supervised the project. SE, İP and HCT—carried out the investigation; provided resources. SE, MEP, İP, CB and GA—developed the methodology. SE and İP—administered the project. MEP—handled the software. All authors contributed to editorial changes in the manuscript, and all authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of the University of Health Sciences, Ümraniye Training and Research Hospital (Reference Number: 07/11/2024-08). Informed consent was obtained from all individual participants or their legal guardians after they were fully informed about the nature of the study and voluntarily agreed to participate.

ACKNOWLEDGMENT

We would like to express our sincere gratitude to the entire team at the Ümraniye Training and Research Hospital Department of Pediatrics, and in particular, the Pediatric Intensive Care Unit staff, for their invaluable support and assistance throughout this study. Their dedication, professionalism, and collaboration were integral to the successful completion of our research.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflicts of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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How to cite this article: Seher Erdogan, İlknur Pence, Mahmud Esad Pence, Hazal Ceren Tugrul, Ceren Bilgun, Gurkan Atay. Assessing the prevalence and impact of central venous catheter malposition on prognosis in critically ill pediatric patients. *Signa Vitae*. 2025; 21(9): 43–49. doi: 10.22514/sv.2025.127.