Received: 20 August 2022 | Revised: 2 May 2023 | Accepted: 3 May 2023

DOI: 10.1111/nicc.12933

RESEARCH ARTICLE

Nursing in Critical Care WILEY

Change in prefilter pressure as a key determinant in the decision to return blood in continuous renal replacement therapy: An observational study

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Abstract

Background: During continuous renal replacement therapy (CRRT), circuit coagulation is an important event that can result in suboptimal outcomes. Nurses must remain alert throughout the treatment and observe machine pressures. Transmembrane pressure (TMP) is commonly used for monitoring but it is sometimes too late to return blood to the patient.

Aim: To compare the capacity of prefilter pressure (FP) versus TMP to predict the risk of circuit coagulation in adult patients with acute renal failure on CRRT.

Study Design: An observational, longitudinal, prospective study. This study was carried out in a tertiary referral hospital over 2 years. Data collected included the following variables: TMP, filter or FP, effluent pressure, venous and arterial pressure, filtration fraction, and ultrafiltration constant of each circuit. Means and their trends over time were collected, for both diffusive and convective therapy and for two membrane types.

Results: A total of 151 circuits (24 polysulfone and 127 acrylonitrile) were analysed, from 71 patients ($n = 22$ [34%] women; mean age, 66.5 [36–84] years). Of the total treatments, 80 were diffusive, and the rest were convective or mixed. In the diffusive circuits, a progressive rise in FP was observed without an increase in TMP and with an increasing trend in effluent pressure. Circuit lifespan was between 2 and 90 h. In 11% ($n = 17$) of the cases, the blood could not be returned to the patient.

Conclusion: These findings allowed the creation of graphs that indicate the appropriate point to return blood to the patient. FP was a major determinant in this decision; in most cases, TMP was not a reliable parameter. Our findings are applicable to convective, diffusive, and mixed treatments as well as both types of membranes used in this acute setting.

Relevance to Clinical Practice: This study provides two clear reference graphs showing risk scales for the assessment of circuit pressures in CRRT. The graphs proposed here can be used to evaluate any machine on the market and the two types of membranes used in this acute setting. Both convective and diffusive circuits can be assessed, allowing safer evaluation in patients who change treatment.

KEYWORDS
acute renal failure (ARF), circuit coagulation, circuit lifespan, continuous renal replacement therapy (CRRT), prefilter/filter pressure (FP)

1 | INTRODUCTION

Acute renal failure (ARF) is an independent risk factor for morbidity and mortality. Its incidence in the intensive care unit (ICU) can reach 50% depending on the patient's underlying pathology. Of those with ARF, some will need renal replacement therapy (RRT).[1–3] Current guidelines prioritize continuous (CRRT) over intermittent therapy in patients with hemodynamic instability.[3–6]

To prolong circuit lifespan, pharmacologic and non-pharmacologic strategies should be used. The pharmacologic measures usually relate to systemic anticoagulation with heparin or regional anticoagulation with citrate. Although citrate is the best evidence-based option, its use is discouraged in some patients with severe septic shock, multiple organ failure or severe hepatic dysfunction. In these cases it could cause poisoning as a result of its hepatic metabolism.[7–9] Non-pharmacologic measures include ensuring the correct position and function of the catheter and the use of diffusive treatments. If convective treatment is used, there are two options to ensure the filtration fraction is not too high: increasing the flow in the blood pump and using prefilter replacement fluid. Prolonging the circuit lifespan is a critical aim in clinical management.[8,10–13]

The main non-pharmacological measure is analysis of pressures.[14] Prefilter pressure, also known as filter pressure (FP), is measured before the filter and depends on the flow of blood and the status of the filter. FP can increase with increased filter resistance to the passage of blood as a result of coagulation or saturation. Effluent pressure indicates the difficulty to extract the prescribed ultrafiltrate volume. Transmembrane pressure (TMP) indicates the permeability of the membrane and gradient pressure on both sides of the membrane and is calculated based on prefilter, effluent and return (venous) pressures. Pressure drop indicates the resistance of the filter to blood and measures the difference before and after the filter.[15,16] When these variable increases, it means that the filter is clotting or that blood flow is too high for the filter size.[17]

The existing literature shows that the most-used techniques in CRRT are convective (when a pressure gradient is applied), diffusive (when a concentration gradient is applied) or convective plus diffusive.[11,16,18–21] However, in recent years, the use of diffusive treatments has increased. Analysis of pressures to predict filter coagulation may differ between these two types of therapy (e.g., TMP may not be useful in diffusive treatments).

What is known about the topic

- In CRRT Nurses currently evaluate circuit coagulation by observing only TMP. However, in diffusive therapy, this evaluation cannot be made by observing only TMP. Patients lose blood from the circuit as a result of clogging or clotting.

What this paper adds

- FP is more important than TMP in the evaluation of circuit pressure.
- The most determining factor is the trend rather than a fixed value.
- Nurses should consider returning the blood to the patient by assessing the FP evolution.

Failure to detect early coagulation of a CRRT circuit entails a high cost of treatment in terms of filter replacement and transfusion of blood products, with the associated risks. Moreover, workload increases considerably each time a circuit must be changed.[22,23] Clearance of solutes and the effectiveness of the technique are additional problems, as the circuit is usually stopped for a period of time until it is replaced.[4,19,21,24]

In usual practice, TMP is used to indicate filter clogging, and FP and/or pressure drop is used to indicate filter clotting; however, cutoff values for when blood should be returned to the patient have not been elucidated.[16,18,25] This study aims to provide a helpful interpretation of pressures in the clinical management of diffusive and convective treatments to determine when to return blood to the patient and avoid blood loss caused by coagulation of the extracorporeal system.

2 | AIM AND HYPOTHESIS

Aim: To compare the capacity of FP versus TMP to predict the risk of circuit coagulation in adult patients with ARF on continuous RRT.

Hypothesis: FP predicts filter coagulation better than TMP in continuous renal replacement circuits for any type of treatment.

3 | DESIGN AND METHODS

This was an observational, longitudinal, prospective study conducted in a multipurpose ICU at Hospital X. This hospital is a tertiary referral centre for 400 000 inhabitants and has 600 hospital beds. The ICU has 34 beds organized in three well-defined spaces with a horseshoe structure and a central monitor area, allowing immediate access to the alarms. The number of patients who require CRRT treatments per year is around 150. The hardware used for CRRT treatments was Prismaflex (Baxter, Software version 8.2) and Multifiltrate (Fresenius Medical Care, Software version 5.1). The filters used were acrylonitrile (AN69) with a surface area of 1.5 m^2 in the Baxter system and polysulfone with a surface area of 1.4 m^2 in the Fresenius system. The nurses who managed these machines were ICU staff, who care for critically ill patients with a nurse-to-patient ratio of 1:2. Each nurse holds a master's degree in critical care nursing, which includes training on the interpretation of the curves generated by the pressure sensors and how to act accordingly, the functioning of the two types of circuits studied here, and anticoagulation with heparin and citrate. In convective treatments, the nurses calculated the filtration fraction (FF) and the ultrafiltration coefficient (K_{UF}). Every 4 h, they recorded the pressures displayed on the machine, on the follow-up sheet for each therapy. They were responsible for the decision to return the blood to the patient when there were signs of coagulation in the circuit. When TMP increased to twice its starting value, they observed the filter more carefully, knowing that the risk of clotting was increased. When K_{UF} decreased to less than 50% of its starting value, they discussed the treatment goal with the doctor. In some cases, therapy could be stopped because the treatment goal had been achieved; if it was necessary to continue, especially in septic procoagulant patients, the filter was changed to be more effective. In diffusive treatments, FP was the most relevant value assessed. If FP increased suddenly, they would first check the catheter and venous chamber were functioning; after that, they would check the filter permeability. All these factors influenced their decision; there was not a fixed value at which to act, but rather, the pressure trends helped the nurses decide what to do.

3.1 | Calculations

TMP was calculated as (FP + venP)/2 − efIP, where FP is the prefilter/filter pressure, venP is the postfilter/venous pressure and efIP is the effluent pressure. So, filter (or prefilter) pressure is measured by a sensor, and TMP is calculated based on three determinants.

The ultrafiltration coefficient (K_{UF}) was calculated as (PreR + PostR + Bal)/TMP where PreR is prefilter replacement, PostR is postfilter replacement, Bal is negative balance and TMP is transmembrane pressure.

Blood flow resistance (Br) was calculated as (FP − venP)/Qb, where FP is filter pressure, venP is postfilter pressure (venous pressure) and Qb is blood flow.

FF was calculated as (PreR + PostR + Bal)/(Qpl + PreR). Where Qpl is the plasmatic flux: Qpl = Qb (1 − haematocrit)/100.

3.2 | Setting

The sample was composed of patients with ARF admitted to the ICU who required CRRT. Data were collected from January 2019 to December 2020. The sample was selected using the following criteria:

Inclusion criteria: adult patients with any admission diagnosis who required temporary CRRT.

Exclusion criteria: patients who required CRRT and received treatment with fondaparinux or citrate for anticoagulation or those with membrane filters of 0.9 m^2.

3.3 | Data collection tools and methods

The data collected for each filter were: TMP, efIP, FP, venP, artP, FF, K_{UF}, and Br.

These data and their trends were recorded for all convective and diffusive treatments and both membrane types. Data were recorded every 4 hours from the start of the replacement therapy, and the recording ended when the replacement therapy ended. A sequential collection with photographs was performed to compare the evolution of the coagulation of the capillaries and the chamber, especially after the return of blood to the patient. After that, we related the trends of the pressures with the visual evidence of the different coagulation points of the whole circuit.

Data were collected on demographics, blood test results (coagulation status: platelets, international normalized ratio [INR], partial thromboplastin time ratio [PTTR]) and the anticoagulant drugs used. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines were followed regarding ultrasound-guided catheter insertion and insertion site preferences. Type, size, and site of insertion of the temporary catheter were also recorded. A flow test was performed in each vascular access lumen after placing the catheter and before connecting the circuit. Likewise, the FF was calculated in convective treatments: in all of them, it stayed below 22%. In those circuits that did not have anticoagulation, the saline-flushing technique was not used because it has not been shown to prevent circuit clotting.[26–29] Circuit lifespan was defined as the total time between starting the technique and the return of blood for any reason or coagulation of the circuit.

3.4 | Data analysis

Variables with normal distribution were expressed as mean and standard deviation, and those without, as median and interquartile range (IQR). Circuit lifespan was described using Kaplan–Meier curves. The prediction model for circuit coagulation was carried out with Cox regression equations, using all the possible Cox regression equations built with the variables considered.[30]

The prediction equation includes the variables PTM and FP. The procedure for choosing the variables of the predictive

TABLE 1 Descriptive pressure data for convective and diffusive treatments and with and without heparin.

				TMP	efIP	FP	venP	artP	FF	KUF	Br
DIFFUSIVE	NO HEPARIN	PERCENTILES	1%	10	1	50	40	−190	0	0	0
			25%	10	100	100	60	−60	0	0	0.22
			50%	10	100	130	80	−50	0.66	2.6	0.26
			75%	20	100	150	90	−40	1.25	5.7	0.33
			99%	60	130	290	116	−30	3.8	21	1.05
		MEAN		16.7	91.7	131.2	78.8	−57	0.81	4.2	0.29
		SD		10.7	23.2	37.6	18.3	34	0.94	5.2	0.16
	HEPARIN	PERCENTILES	1%	10	10	56	20	−120	0	0	0.2
			25%	18	36	100	50	−53	0.75	1.1	0.28
			50%	24	55	122	67	−43	1.46	2.5	0.32
			75%	30	90	155	85	−31	2.41	4.9	0.45
			99%	80	210	450	280	−20	4.0	14	2.3
		MEAN		29.5	63	144.3	75.8	−45	1.56	3.4	0.46
		SD		24	42	73.8	50.5	23	1.1	3.3	0.44
CONVECTIVE OR MIXED	NO HEPARIN	PERCENTILES	1%	10	−60	50	37	−105	3.5	2.3	0
			25%	40	−4	100	50	−60	11.7	10.6	0.27
			50%	52	25	123	78	−43	16.9	14.4	0.31
			75%	78	74	160	97	−37	20.1	18.4	0.38
			99%	220	110	320	200	−20	25	50	1.4
		MEAN		67.9	32.2	135.9	80.7	−50	16.8	17.7	0.33
		SD		51.9	45.2	53.4	41.3	23.8	6.3	15.5	0.22
	HEPARIN	PERCENTILES	1%	10	−112	70	26	−170	2.2	1.6	0
			25%	47	2	110	58	−63	11.9	10.6	0.27
			50%	62	25	132	76	−50	17.6	13.3	0.32
			75%	84	51	174	100	−40	21	18.5	0.4
			99%	250	150	350	200	−10	25	32	1.4
		MEAN		72.4	31.3	147.4	83	−55	17.3	15.9	0.37
		SD		44	52	57	40.8	28.8	6.4	9.9	0.22

model was made from all possible equations constructed with the following candidate variables: TMP, efIP, FP, venP, Qb, Qd, PreR, PostR.

The choice of variables included in the chosen predictive equation was made using the adjustment indicators AIC (Aikaike Information Criterion),[31] BIC (Bayesian Information Criterion)[32]; Harrell's C index[33]; the clinical criteria of the researchers and the parsimony of the selected model.

The sample was divided into two parts: two-thirds of the sample to obtain the predictive model, and the remaining third for model validation.[34,35] Preference was given to parsimonious models and to models with fewer variables in the equation.

Once the equation with the variables that best-predicted filter coagulation was obtained, a baseline risk was established. The risk of filter coagulation, in relation to the baseline risk, is expressed by means of colour-coded graphs.

Statistical analysis was performed using Stata 17 (StataCorp 4905 Lakeway Dr College Station, TX 77845).

3.5 | Ethical and institutional approvals

Ethical approval of this project was granted by the Hospital Ethics Committee. The protocol number was IIBSP-CIT-2019-34. Patients received an information sheet about the study and which data would be collected. As normal clinical practice was unchanged, request for consent was waived. Data collection followed current data protection laws.

4 | RESULTS

A total of 151 circuits (24 polysulfone and 127 acrylonitrile) were analysed, from 71 patients ($n = 22$ [34%] women, mean age 66.5 [36–84] years). The admission diagnoses were coronary disease ($n = 13$), postoperative cardiac surgery ($n = 21$), and a mix of pneumonia, polytrauma, major surgery, and so forth. ($n = 37$). The catheter insertion sites were: 10 in the right internal jugular vein, 3 in the left internal

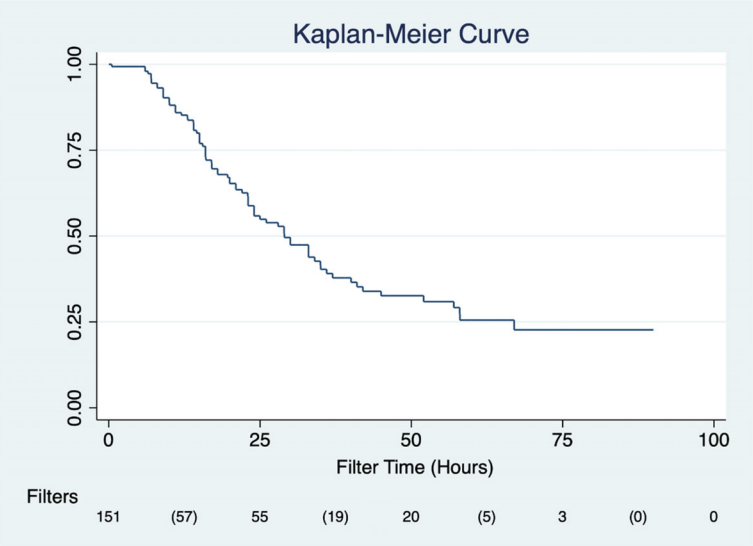

FIGURE 1 Kaplan–Meier survival curve of the circuit lifespan of all 151 circuits.

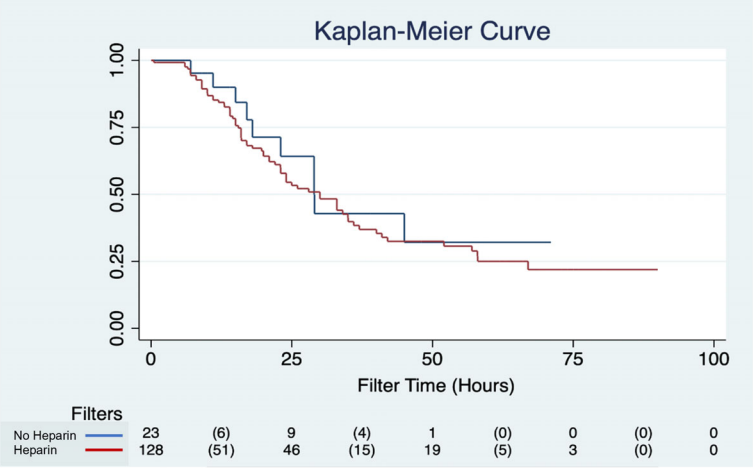

FIGURE 2 Kaplan–Meier curve of circuit lifespan of all 151 circuits depending on whether or not heparin was used. There were no differences in terms of circuit lifespan between circuits that did or did not receive heparin.

jugular vein, 44 in the right femoral vein and 14 in the left femoral vein.

Of the total treatments, 80 were diffusive only, and the rest were convective or mixed. In the diffusive circuits, a progressive rise in FP was observed without an increase in TMP and with an increasing trend in effluent pressure. As shown in Table 1, the lower percentiles (1%) show very low values and the higher percentiles show the differences. In convective treatments, it is possible to see negative values in effluent pressures and very high TMP, corresponding to a clotting situation. In these cases, FP is also high. There are clear differences between convection and diffusion, but there are no differences between heparinized and unheparinized treatments.

Circuit lifespan was between 2 and 90 h. In 11% ($n = 17$) of the cases, the blood could not be returned to the patient. Of 127 acrylonitrile circuits, 96 received sodium heparin as anticoagulation in the circuit and 31 did not receive anticoagulation: 20 as a result of low platelet count and 11 because they were receiving systemic anticoagulation. Of 24 polysulfone circuits, 16 received sodium heparin in the circuit, 5 did not receive anticoagulation as a result of low platelets and 3 because they were receiving systemic anticoagulation.

Descriptive values of the pressures can be seen in Table 1. FP was the only variable that was significantly associated with the circuit coagulation.

Total circuit lifespan ranged from 2 to 90 h, with a median of 20 h, 25th percentile of 13 h, and 75th percentile of 33 h (Figure 1). Figure 2 shows the circuit lifespan according to whether or not heparin was used as anticoagulation. In 11% ($n = 17$) of the sample, the blood could not be returned to the patient. In 11 cases, a sharp rise in pressures was detected, caused by the impact of clots at the filter access port; in 3 cases, there was a problem with the machine that blocked the system; and in 3 cases the catheter prevented blood return.

4.1 | Comparison of TMP and FP results

4.1.1 | Comparative scales of TMP and prefilter pressure

Two scales with different colour bands were created using the pressure data gathered from the 151 circuits. The initial mean

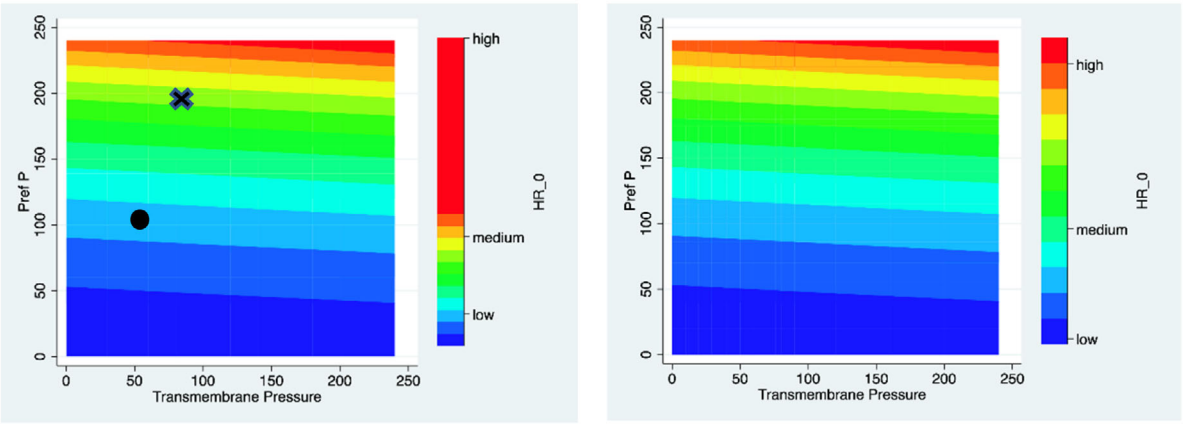

FIGURE 3 Graph to guide the decision to return blood to the patient in diffusive treatment. The black dot indicates the starting point, and the cross indicates the latest point at which (we suggest) blood should be returned to the patient. On the right, with heparin; on the left, without heparin in the circuit (very similar data). *Source*: Own elaboration.

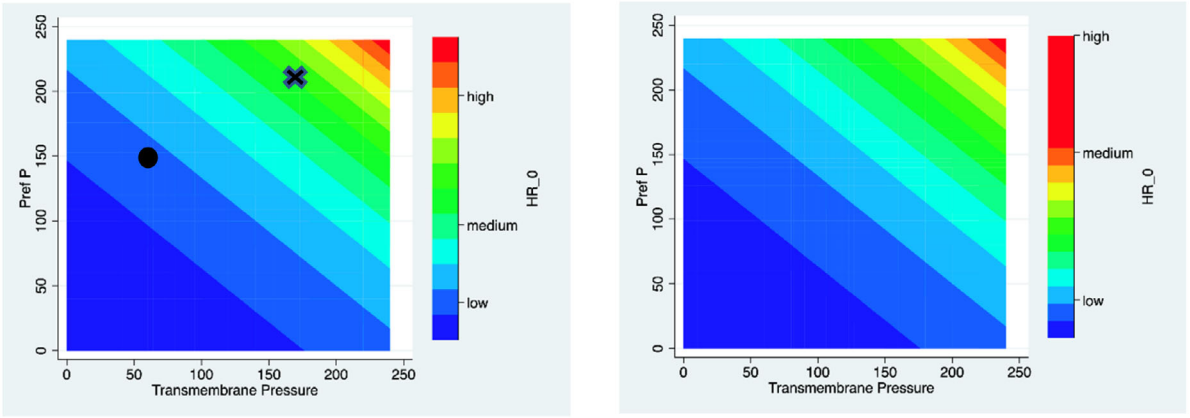

FIGURE 4 Graph to guide the decision to return blood to the patient in convective treatment. The black dot indicates the starting point, and the cross indicates the latest point at which (we suggest) blood should be returned to the patient. On the right, with heparin; on the left, without heparin in the circuit (very similar data). *Source*: Own elaboration.

TMP for the total 151 circuits was 38.3 mmHg and the FP was 123.4 mmHg. These initial values were used to create the risk scale.

Based on these values, the risk lines were established according to what was found in the treatment data. The sample was divided into two parts: two-thirds of the sample was used to obtain the predictive model and the other third for model validation. It is important to note that the two graphs are for different treatments: convective and diffusive (Figures 3 and 4).

The two scales show the level of risk for diffusive (Figure 3) and convective (Figure 4) treatments, with colour ranging from blue, indicative of low risk, to red, indicative of high risk. Both scales should be interpreted by identifying a starting point on the graph using the initial TMP and FP recorded at the start of CRRT, and in our opinion, no more than 3 colour bands should be exceeded before blood is returned to the patient. For example, the nurse starts the diffusive treatment and evaluates the pressures according to the initial parameters: TMP is 20 and FP is 120. After 10, 20 or 30 h of continuous assessment by the nurse, the pressures do not increase much, except in the last hour where FP increases to 200. TMP has not increased or is very low. According to our study, this is the time to consider returning the blood to the patient (Figure 3). It is possible to continue, of course, but the risk of clogging is very high.

When the treatment was convective, TMP increased over time, as did the FP.

5 | DISCUSSION

This study sought to provide practical information on the appropriate time to return blood from the circuit to reduce potential blood loss. Our findings suggest that filter pressure is the best predictor of circuit coagulation in both convective and diffusive treatments. As can be seen in the colour graphs, the behaviour is very different depending on the type of treatment. It is safest to consider FP in all cases. Rather than use an absolute numerical cut-off value, we advise using the

proposed risk scales, identifying the starting point based on each circuit's TMP and FP and observing the trend in each case. Our results suggest returning blood when three colour bands have been crossed. This decision may be changed by the staff involved but it is important to consider the potential risk.

In diffusive treatments, a progressive increase in FP was observed without a TMP increase as effluent pressures tended to rise gradually. This can be seen in Table 1: the 1st and 99th percentiles are very different in FP and eflP values, but not in TMP values. If only TMP is used as a reference, clogging is sure to occur. The values in the table were evaluated and when the blood was returned to the patient, the presence of filter capillary coagulation was detected. The literature describes TMP as a reliable indicator of circuit coagulation in continuous techniques. However, most existing research has focused on convective or mixed treatments rather than diffusive, as they are more commonly used.[20,36,37]

In convective treatments, trends of both pressures, TMP and FP, are important when deciding to return blood to the patient. Nevertheless, it should be considered that TMP is a parameter that is calculated using FP; we could therefore conclude that in both diffusive and convective treatments, observing only FP would allow us to make a decision.

ICU nurses managing CRRT need to be well educated around these aspects. Fluid mechanics are complicated, and it gets more complicated when the fluid is blood because important factors such as haematocrit, temperature and filter membrane can change the circuit situation very quickly. We analysed different parameters proposed by engineers but only FP proved to be the best predicter of clotting. Each of the sample circuits had at least three photos of the points of greatest coagulation when the blood was returned to the patient. So, the pressure trends were not a simple value but a demonstrated one with several images.

In some hospitals, nurses change filters every day to avoid blood loss. We sought to try to prolong circuits, helping nurses to decide when to change them.

We also observed that there were no major differences between circuits that were anticoagulated with heparin and those that were not. Therefore, the trends in the pressure curves can be interpreted independently of the drugs used in the extracorporeal circuit.

Of the variables studied, change in K_{UF} seems not to be useful in diffusive treatments and difficult to interpret in convective treatments. Although we had thought it may be a robust variable to help decide when to return blood, our data suggest that it is not useful. The same can be said for resistance, for which values over 1.5 are reported by one manufacturer as indicative of imminent coagulation of the filter (Table 1). Therefore, TMP, K_{UF}, and Br were ruled out as reliable parameters on their own for the prediction of circuit coagulation and cannot be generalized for all treatments. This was not the case for FP: it seems to encompass all coagulation situations regardless of where they occur in the circuit and of treatment type (convective, diffusive, or mixed). Some studies have suggested a threshold for FP of 270 mmHg for the return of blood to the patient.[38] In our experience, we have seen some circuits reach this level with high blood flows or systems connected to ECMO (in the arterial section) without showing signs of coagulation, although no such patients were included in this study.

Additionally, a rapid response to alarms associated with blood flow stoppages is an important factor to reduce blood loss.[39]

6 | LIMITATIONS

There are several limitations in our study. First, it was performed in only one centre and must be validated. Second, the number of days on CRRT was different between patients; we tried to minimize this effect statistically. Third, although the number of determinations was high, the patient sample size was relatively small. Fourth, in this study, only the circuit pressures were assessed to decide when to return the blood to the patient. Clearance capacity, as a measure of filter function, has previously been analysed in this situation.[25] However, sometimes, the clotting process does not affect filter function, and in clinical practice, we cannot always delay such decisions while awaiting blood test results. Finally, although the nurses had guidance on when to return the blood to the patient, variability in interpretation between individual nurses could exist. Highly experienced nurses may be more risk-tolerant, and therefore more willing to delay the return of blood to the patient; with this, however, the risk of clotting is higher. On the other end of the spectrum, some nurses may return blood unnecessarily early, in the name of patient safety, but also increasing workload and economic costs. Although this could represent a limitation, it is also central to the goal of this study, to help nurses decide on the optimal course of action. In our centre, nurses do not return blood to the patient until the FP is high enough, as the graphs show. We believe the results of this study are useful and help nurses' decision-making and may reduce costs.

7 | RECOMMENDATIONS AND FURTHER RESEARCH

This study recommends following the proposed graphs to decide the return of blood to the patient.

The graphs proposed here can be used to evaluate any machine on the market and the two types of membranes used in this acute setting.

Both convective and diffusive circuits can be assessed, allowing safer evaluation in patients who change treatment.

Some more studies may help in the effectiveness of these graphs.

8 | CONCLUSIONS

The main conclusion of our observational study is that TMP is not suitable as a parameter to guide the return of blood in diffusive treatments.

The change in FP value over time seems to be the best predictor of when to return blood and thus prevent blood loss. This should be incorporated into nurse education around CRRT.

Trends in the pressure curves can be interpreted independently depending on the drugs used in the extracorporeal circuit.

AUTHOR CONTRIBUTIONS

Almudena Mateos-Dávila: Conceptualization, Data Curation, Writing-Original draft, Visualization.

Antonio Jorge Betbesé Roig: Conceptualization, Supervision, Writing-Review.

José Alberto Santos Rodríguez: Data Curation, Formal Analysis, Software.

Eva Maria Guix-Comellas: Methodology, Project Administration, Supervision, Writing-Reviewing and Editing.

ACKNOWLEDGEMENTS

We are grateful for the collaboration of Iris Viñolas Soria, José Martínez Pérez and Mateu Castellà Vàzquez, and thank them for their professionalism in the data collection of this project.

FUNDING INFORMATION

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST STATEMENT

The researchers declare that they have no conflict of interest with any trademark that provides the machines.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ETHICS STATEMENT

Ethical approval of this project was granted by the Hospital Ethics Committee. The protocol number was IIBSP-CIT-2019-34. Patients received an information sheet about the study and which data would be collected. As normal clinical practice was unchanged, request for consent was waived. Data collection followed current data protection laws.

Permission to reproduce material from other sources: It was not necessary in this study.

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How to cite this article: Mateos-Dávila A, Betbesé Roig AJ, Santos Rodríguez JA, Guix-Comellas EM. Change in prefilter pressure as a key determinant in the decision to return blood in continuous renal replacement therapy: An observational study. *Nurs Crit Care*. 2023;1-9. doi:10.1111/nicc.12933