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REVIEW ARTICLE

# Needle Direction and Distance of Arteriovenous Fistula Cannulation in Hemodialysis Adequacy; a Systematic Review and Meta-Analysis

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**Abstract:** **Introduction:** This systematic review and meta-analysis aimed to summarize the evidence regarding the impact of needle direction and distance of arteriovenous fistula (AVF) cannulation on KT/V (where k is the dialyzer urea clearance, t, the duration of dialysis, and V, the volume of distribution of urea) and access recirculation (AR) as hemodialysis (HD) adequacy criteria. **Methods:** A comprehensive systematic search was performed on international and domestic electronic databases from the earliest to June 4, 2022 using keywords. Analysis was performed in STATA software v.14. **Results:** Three randomized control trials (RCTs) and four non-RCT articles were included in the final review. Six studies reported the effects of direction, while four mentioned the effects of distances of AVF cannulation on outcomes of HD adequacy based on KT/V or AR. Results of three non-RCT studies showed that retrograde direction decreased KT/V more than antegrade direction (ES: 0.44, 95% CI: -0.38 to 1.27). Two non-RCT studies showed that antegrade decreased AR compared to the retrograde direction (ES: -0.64, 95%CI: -1.94 to 0.67). However, the results of two RCTs indicated uncertainty about this issue. Two of the four studies suggested that a distance of 5 cm or more in arterial and venous needles had greater adequacy than a distance of less than 5 cm. However, other studies did not confirm this finding. **Conclusion:** Overall comparison of the results qualitatively and quantitatively indicated uncertainty about the effects of direction and distance of AVF cannulation on HD adequacy outcomes. More studies with high-quality designs, such as RCTs, are required to better understand and adjudicate the effects of needle direction and distance of AVF cannulation on HD adequacy outcomes.

**Keywords:** Vascular Access Devices; Arteriovenous Fistula; Catheterization; Renal Dialysis

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## 1. Introduction

As chronic renal failure progresses to end-stage renal disease (ESRD), maintaining the quality of life and survival depend on the effectiveness of kidney replacement therapies (KRT), including hemodialysis (HD), peritoneal dialysis, and kidney transplantation (1). It was estimated that 4.9-9.7 million people required KRT in 2010 (2). The main objective of

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these treatments (HD or kidney transplantation) is to reduce life-threatening consequences and ultimately reduce deaths from uremia (3). Transplantation is superior to HD in improving quality of life, ensuring more prolonged survival, and lowering costs. However, HD is widely used in cases where transplantation is impossible and as a maintenance KRT (1, 4).

HD accounts for 89% of treatments for ESRD patients worldwide (5). Adequate HD requires reliable vascular access (VA). If proper VA is not possible, the consequence will be prolonged hospitalisation and increased costs (6). There are three types of VA for HD: arteriovenous fistulas (AVFs), arteriovenous grafts, and central venous catheters (7). AVF is the optimal method for VA due to its fewer complications, reduced mortality rate, and increased durability compared to other VA types (8). For each HD, two needles are used to cannulate the fistula (9). The arterial needle is responsible for drawing blood from the patient, while the venous needle is used to return the purified blood (10). In the usual approach, the arterial needle is placed at least 3 cm from the anastomosis site with the flow towards the end of the limb (retrograde) or heart (antegrade) and should be at least 5 cm away from the venous needle (11). Proper distance and direction of needles inserted into the AVF can reduce recirculation and thus, increase HD quality (8, 11).

Proper needle placement, prevents increased frequency or duration of HD, which puts patients at a lower risk of infections and incurs increased costs (12). HD access recirculation (AR), in any case, reduces the quality of HD (13). Therefore, AR measurement can be considered an acceptable method for evaluating the quality of HD (14). AR is detected in HD when dialyzed blood returns to the dialysate through an arterial needle instead of entering the systemic circulation after returning by the venous needle (15). Various factors can cause AR, including improper needle insertion, fistula stenosis, and mechanical stenosis at the end of the vein (16).

There are conflicting findings on the effect of the direction and distance of needles on the quality of HD. A study by Lim et al. showed no significant difference between the antegrade and retrograde cannulation methods and their needle distance regarding the amount of AR (17). On the other hand, the results of another study by Vahedi et al. showed that AR in antegrade cannulation and a 3 cm needle distance was significantly higher than in a retrograde manner with a 6 cm needle distance (13). Therefore, given the importance of the subject and the contradictory findings in this regard, this systematic review and meta-analysis aimed to summarize the evidence regarding the impact of needle direction and distance of AVF cannulation on HD adequacy.

## 2. Methods

### 2.1. Study registration and reporting

The present systematic review and meta-analysis was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist (18). However, this review study has not been registered in the international prospective register of systematic reviews (PROSPERO) database.

### 2.2. Patient/population, intervention, comparison, and outcomes (PICO) framework

The PICO framework was used to clarify the purpose of the study. Accordingly, population (articles in which patients with AVF cannulation were examined), intervention (studies that compared needle direction and distance of AVF cannulation), and comparison (studies that had control or placebo groups to compare with the intervention groups), and finally, outcome (studies that measured the adequacy of HD based on KT/V and AR in relation to the insertion of the catheter in the AVF), were considered when including studies in the systematic review and meta-analysis.

### 2.3. Search strategy

A comprehensive systematic search was performed on international electronic databases such as Scopus, PubMed, Web of Science, and Iranian electronic databases such as Iranmedex, and Scientific Information Database (SID) with keywords extracted from Medical Subject Headings such as "Vascular access", "Arteriovenous fistula", "Graft", "Catheterizations", "Puncture", “Cannulation”, “Hemodialysis”, “Dialysis adequacy”, and “Recirculation” from the earliest to June 4, 2022. For example, the search strategy in PubMed/MEDLINE database included such search terms as ((“Vascular access”) OR (“Arteriovenous fistula”) OR (“Graft”) OR (“Catheterizations”) OR (“Puncture”) OR (“Cannulation”) OR (“Needle distance”) OR (“Needle direction”)) AND ((“Hemodialysis”) OR (“Renal dialysis”) OR (“HD”)) AND ((“Renal circulation”) OR (“dialysis adequacy”) OR (“recirculation”)). Keywords were combined with Boolean operators "AND" and "OR". Similar to the method mentioned in the keyword search, Persian equivalents of the words were searched in Iranian electronic databases. The search was performed by two researchers, independently. Items such as expert opinions, conference presentations, dissertations, research and committee reports, and ongoing research, known as the gray literature, were not included in this systematic review. Gray literature includes articles produced in print and electronic formats but not peer-reviewed or evaluated by a commercial publisher (19).

### 2.4. Inclusion and exclusion criteria

RCTs and non-RCT studies in English and Persian, focusing on the effect of direction of AVF cannulation or needle distance on HD adequacies such as kt/v, Urea Reduction Ratio (URR), and recirculation in the HD patients were included in this study. Letters to the editor, case reports, qualitative studies, and reviews were excluded.

### 2.5. Study selection

Data management was performed using EndNote 8X software. Two researchers independently evaluated the eligibility of studies for inclusion based on pre-determined inclusion and exclusion criteria. Studies included in this review were selected after eliminating duplicates, evaluating titles and abstracts, and reviewing the full texts of the selected articles. A third researcher resolved any differences and contradictions between the other two researchers. Finally, the resource list was evaluated manually to prevent data loss.

### 2.6. Data extraction and quality assessment

The Joanna Briggs Institute (JBI) critical appraisal checklist was used to assess the quality of randomized control trials (RCTs) and non-RCTs studies (20). This tool assesses the internal validity, the similarity of participants of compared groups, the reliability of outcomes measured, and the appropriateness of statistical analysis of RCT and non-RCT studies in 13 and 9 items, respectively. In this systematic review and meta-analysis, researchers extracted information including first author name, year of publication, location, design, sample size, type of intervention, duration of the study, duration of intervention and follow-up, male/female ratio, age, type of control group, tool characteristics, specific statistical tests, and key results of studies. The quality of the studies in this systematic review and meta-analysis was evaluated by two researchers, separately, using a three-point reading range that included "yes" (score 1), "no" (score 2), and "not applicable / not clear" (score 0) (20). The quality assessment levels of the studies in the JBI checklists were good (≥8), fair (6-7), and poor (≤5) (21).

### 2.7. HD adequacy assessment techniques

#### 2.7.1. KT/V

KT/V, where K is the dialyzer urea clearance (expressed in liters per hour), T is the duration of dialysis (expressed in hours), and V is the volume of distribution of urea, is a dimensionless ratio that represents fractional urea clearance (expressed in liters) (22). A level less than 0.8 indicates insufficient HD (23).

#### 2.7.2. AR

Blood is typically pumped from the dialysis access at 300 to 500 cc/min during HD. A failing AV access can significantly reduce flow to less than the HD machine's blood pump rate. This situation can result in some dialyzed blood exiting the dialyzer through the venous needle and then reentering the dialyzer through the arterial side to support the extracorporeal blood flow rate set by the blood pump. This condition is known as AR (24, 25).

#### 2.7.3. URR

Another method of measuring HD adequacy is URR. This method is calculated using the formula (pre-urea – post-urea/pre-urea) in HD (26). The acceptable level of URR is 65% and above (23). A URR of less than 65% is linked to higher patient morbidity and mortality. The mortality rate was observed to drop by up to 11% for every 5% rise in URR (27).

#### 2.7.4. Ultrasound-based technique

The ultrasound dilution (USD) method measures access flow (Qa) during HD. The advantages of the USD technique include being easy to use and providing an immediate response. Qa is measured through USD using the formula (Qa=Qb(1-r/r)), where Qb is the dialyzer blood flow rate and r is the fraction of recirculated blood entering the dialyzer (28).

### 2.8. Statistical analysis

Analysis was performed using STATA software v.14. Heterogeneity was measured using I2 statistic. 0% to 40% was considered unimportant; 30% to 60%: may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100% considerable heterogeneity. Due to the considerable heterogeneity between studies, the random effect model and inverse-variance method were used to estimate the mean difference. Since RCTs and non-RCT studies have different weights in the evidence hierarchy pyramid, each should be analysed separately. A confidence interval of 95% was considered a significant level. Pooled effect size related to the effects of needle direction on the KT/V and AR was reported on a forest plot.

### 2.9. Publication bias

Although the number of effect sizes related to the effect of needle direction on the KT/V and AR was less than 10, a publication bias test was performed. The funnel plot and result of the Egger's test were used to assess publication bias.

### 2.10. Sensitivity analysis

Sensitivity analysis was performed to determine the pooled effect sizes related to the effect of needle direction on the KT/V and AR.

### 2.11. Certainty of evidence

The certainty of the evidence was assessed through the Grade of Recommendation, Assessment, Development, and Evaluation (GRADE) approach.

**Table 1:** Basic characteristics of the studies included in this systematic review

| First Author/year | Location | Study characteristics* | Male/ Female ratio (%) | Age (year) mean(SD) | Control group | Tool characteristics | Specific statistical tests | Key results | JBI Score |
|---|---|---|---|---|---|---|---|---|---|
| Dias et al., 2008 (29) | Brazil | 1. Quasi-experimental<br>2. 174<br>3. Antegrade vs. retrograde cannulation with distance between needles more than 5 cm vs. less than 5 cm<br>4. N/A<br>5. 4 hours<br>6. 0 | 59.77/ 40.23 | 51.90 (15.57) | N/A | • Kt/V<br>• AR | • ANOVA<br>• Pearson linear correlation | • Kt/V in the group of retrograde cannulations with 5 cm or more distance between needles was higher than in other groups (except temporary double lumen catheter group) (P<0.05).<br>• AR in the group of retrograde cannulations with 5 cm or more distance between needles was lower than in other groups (P<0.05). | Fair |
| Ozmen et al., 2008 (30) | Turkey | 1. Quasi-experimental<br>2. 22<br>3. Antegrade vs. retrograde cannulation<br>4. 8 weeks<br>5. N/A<br>6. 0 | N/A | N/A | N/A | Kt/V | T-test | There was no significant difference between antegrade and retrograde cannulation in the amount of Kt / V (P=0.123). | Fair |
| Rothera et al., 2011 (10) | UK | 1. RCT (Crossover)<br>2. 12<br>3. Cannulation with distance between needles 5 cm vs. 2.5 cm<br>4. N/A<br>5. N/A<br>6. 0 | N/A | N/A | The distance between the two needles in five consecutive HD sessions was 5 cm in half of the participants and 2.5 cm in the same number of HD patients. | • AR<br>• Blood access flow rate<br>• EID | • Kolmogorov–Smirnov normality test<br>• Shapiro–Wilk normality test<br>• Paired t-test | • The blood access flow rate was significantly higher when the distance between the two needles was 2.5 cm than when the distance between the two needles was 5 cm (P=0.014). • There were no significant differences between 2.5 and 5 cm needle distances in the amount of EID (P=0.139). | Good |
| Reyes, 2016 (31) | Philippines | 1. RCT<br>2. 20 (10/10)<br>3. Antegrade vs. retrograde cannulation<br>4. N/A<br>5. N/A<br>6. 0 | N/A | N/A | Arterial needles in AVFs were implanted in this group as antegrade. | • URR<br>• Kt/V<br>• AR | N/A | • The URR in antegrade cannulation was significantly higher than in retrograde cannulation (P<0.05).<br>• The Kt/V in antegrade cannulation was significantly higher than in retrograde cannulation (P<0.05).<br>• There was no significant difference between antegrade and retrograde cannulation in the amount of AR (P>0.05). | Good |
| Elias et al., 2018 (11) | France | 1. Quasi-experimental<br>2. 14<br>3. Antegrade vs. retrograde cannulation in distance between needles 2.5 cm<br>4. N/A<br>5. N/A<br>6. 0 | 57.14/42.86 | 62.30 (15.57) | Participants underwent HD three times with arterial needles in antegrade cannulation and then with arterial needles in retrograde cannulation. | • Kt/V<br>• AR | • Non-parametric paired test<br>• Signed rank test | • There was no significant difference between the antegrade and retrograde cannulation with a 2.5 cm distance between needles in the amount of Kt/V (P=0.20).<br>• There was no significant difference between the antegrade and retrograde cannulation with a 2.5 cm distance between needles in the amount of AR (P>0.05). | Fair |

**Table 1:** Basic characteristics of the studies included in this systematic review

| First Author/year | Location | Study characteristics* | Male/ Female ratio (%) | Age (year) mean(SD) | Control group | Tool characteristics | Specific statistical tests | Key results | JBI Score |
|---|---|---|---|---|---|---|---|---|---|
| Lim et al., 2018 (17) | South Korea | 1. Quasi-experimental<br>2. 30<br>7. Antegrade vs. retrograde cannulation with distance between needles 7 cm vs. 5 cm<br>4. 3 weeks<br>5. N/A<br>6. 0 | 43.33/56.67 | 55.50 (13.21) | N/A | AR | ANOVA | There was no significant difference between the antegrade and retrograde cannulation and their needle distance in the amount of AR (P=1.00). | Fair |
| Vahedi et al., 2018 (13) | Iran | 1. RCT<br>2. 22<br>8. Antegrade vs. retrograde cannulation with distance between needles 3 cm vs. 6 cm<br>4. N/A<br>5. 4 hours<br>6. 0 | 54.55/45.45 | 53.00 (16.75) | N/A | AR | • Generalized estimating equations<br>• Odds ratio | The AR in antegrade cannulation and 3 cm needles distance was significantly higher than in retrograde manner and 6 cm needles distance (P<0.05). | Good |

RCT: Randomized clinical trial; HD: Hemodialysis; AR: Access recirculation; EID: Effective ionic dialysance; URR: Urea reduction rate; ANOVA: Analysis of variance; JBI: Joanna Briggs Institute; Kt/V: k is the dialyzer urea clearance, t, the duration of dialysis, and V, the volume of distribution of urea; AVF: arteriovenous fistula; N/A: not available.
*:1. Design; 2. Sample Size (I/C); 3. Intervention; 4. Duration of study; 5. Duration of intervention; 6. Duration of follow-up.

# 3. Results

## 3.1. Study selection

As shown in figure 1, after a thorough search of electronic databases, 2,228 articles were obtained. After deleting 402 duplicate articles, 1,826 articles remained. After reviewing the titles and abstracts of the articles, 1,634 articles were excluded from the study due to discrepancies with the research purpose. Then another 126 articles were excluded due to their non-experimental design. Full-text evaluation of the remaining 56 articles led to the elimination of another thirty-four due to poor design and results.

Another fifteen articles were excluded due to a lack of appropriate information. Finally, this systematic review and meta-analysis utilized seven studies (10, 11, 13, 17, 29-31).

## 3.2. Study characteristics

As mentioned in tables 1 & 2, a total of 294 HD patients entered this systematic review and meta-analysis in seven studies (10, 11, 13, 17, 29-31). Their mean age was 55.67 (SD = 15.27) years. 53.69% of the patients were male, and 96.60% were in the intervention group. Four studies (11, 17, 29, 30) had non-RCT, and three (10, 13, 31) had RCT designs. Of the studies in this systematic review, two (17, 30) reported an average study duration of 5.5 weeks. Two studies (13, 29) also reported a duration of intervention that averaged 4 hours. To assess HD adequacy, six studies (10, 11, 13, 17, 29, 31) used AR, 4 articles (11, 29-31) used KT/V, one study (10) used blood access flow rate, while one other study (10) used effective ionic dialysance (EID). Also, one study (31) used urea reduction rate (URR). The studies included in this review were conducted in Brazil (29), France (11), Iran (13), the Philippines (31), South Korea (17), Turkey (30), and the UK (10). Three studies (10, 11, 31) had control groups.

## 3.3. Methodological Quality assessment of eligible studies

As shown in figures 2 and 3, of the seven studies (10, 11, 13, 17, 29-31), two (10, 11) had a good quality level, while five (13, 17, 29-31) had an acceptable quality level.

## 3.4. Effect of needle direction in AVF cannulation on HD adequacy based on KT/V

Four studies (11, 29-31) (one RCT (31) and three non-RCTs (11, 29, 30)) reported the effects of direction on HD adequacy based on KT/V. The RCT study (31) indicated that antegrade direction improved HD adequacy. This study did not report a standard deviation (31). Therefore there was insufficient data to report the effects of direction on KT/V and AR based

**Table 2:** Interventions of the studies included in the systematic review

| First Author/ year | Intervention Program | Description |
|---|---|---|
| Dias et al., 2008 (29) | Antegrade and retrograde cannulation | Patients undergoing HD were divided into the following five groups:<br>• Group 1: The placement of the needles in this group was retrograde, with the arterial set toward the extremity of the arm and the venous set toward the heart. The distance of the needles from each other in this group was 5 cm or more.<br>• Group 2: The placement of the needles in this group was retrograde, with the arterial set toward the extremity of the arm and the venous set toward the heart. The distance of the needles from each other in this group was less than 5 cm.<br>• Group 3: The placement of the needles in this group was antegrade, with both arterial and venous sets pointing toward the heart. The distance of the needles from each other in this group was 5 cm or more.<br>• Group 4: The placement of the needles in this group was antegrade, with both arterial and venous sets pointing toward the heart. The distance of the needles from each other in this group was less than 5 cm.<br>• Group 5: In this group, patients had a temporary double lumen catheter.<br>To evaluate Kt / V, five blood samples of 3 to 5 ml were taken before and after HD. Also, to evaluate AR, three blood samples were taken from arterial and venous sets and limb contralateral to VA. |
| Ozmen et al., 2008 (30) | Antegrade and retrograde cannulation | Participants underwent two different interventions for HD, as follows:<br>• Month 1: The placement of the needles was retrograde, with the arterial set toward the extremity of the arm and the venous set toward the heart.<br>• Month 2: The placement of the needles was antegrade, with both arterial and venous sets pointing toward the heart.<br>Blood samples were taken before and after HD in the middle of the treatment week and four times a month in each direction. |
| Rothera et al., 2011 (10) | Antegrade cannulation | The distance between the two needles in five consecutive HD sessions was 5 cm in half of the participants and 2.5 cm in the same number of HD patients. In the other Overall, a maximum of 60 HD sessions were performed for each group.<br>During each HD, AR was measured as a percentage, EID as an ml/min, and blood flow rate as an ml/min. EID was measured in the first half hour, one and a half hours, and the last half hour of HD. AR and blood flow rate were measured in the first half hour of HD. |
| Reyes, 2016 (31) | Antegrade and retrograde cannulation | Patients participating in this study were divided into two groups, as follows:<br>• Intervention group: The placement of the needles was retrograde, with the arterial set toward the extremity of the arm and the venous set toward the heart.<br>• Control group: The placement of the needles was antegrade, with both arterial and venous sets pointing toward the heart.<br>Blood samples were taken before HD, the first 30 minutes of HD, and after HD.<br>URR, Kt / v, and AR were used to evaluate the adequacy of HD. |
| Elias et al., 2018 (11) | Antegrade and retrograde cannulation | Participants underwent HD three times with arterial needles in antegrade cannulation and then with arterial needles in retrograde cannulation. The distance between HD needles was 2.5 cm.<br>In general, a maximum of 84 HD sessions were performed on these patients.<br>AR was measured in the first 30 minutes of HD and Kt / V in the last 30 minutes of HD. |
| Lim et al., 2018 (17) | Antegrade and retrograde cannulation | Participants underwent three different interventions for HD, as follows:<br>• Week 1: The placement of the needles was antegrade, with both arterial and venous sets pointing toward the heart. The distance of the needles from each other was 7 cm.<br>• Week 2: The placement of the needles was retrograde, with the arterial set toward the extremity of the arm and the venous set toward the heart. The distance of the needles from each other was 5 cm.<br>• Week 3: The placement of the needles was retrograde, with the arterial set toward the extremity of the arm and the venous set toward the heart. The distance of the needles from each other was 7 cm. |
| Vahedi et al., 2018 (13) | Antegrade and retrograde cannulation | Participants underwent four different interventions for HD, as follows:<br>• Session 1: The placement of the needles was retrograde, with the arterial set toward the extremity of the arm and the venous set toward the heart. The distance of the needles from each other was 3 cm.<br>• Session 2: The placement of the needles was antegrade, with both arterial and venous sets pointing toward the heart. The distance of the needles from each other was 3 cm.<br>• Session 3: The placement of the needles was retrograde, with the arterial set toward the extremity of the arm and the venous set toward the heart. The distance of the needles from each other was 6 cm.<br>• Session 4: The placement of the needles was antegrade, with both arterial and venous sets pointing toward the heart. The distance of the needles from each other was 6 cm.<br>To assess AR, a blood sample was taken 30 minutes after the start of HD, after the device was turned off, a blood sample was taken from the arterial line and a blood sample was taken from the venous line of the filter. |

HD: Hemodialysis; EID: Effective ionic dialysance; Kt/V: k is the dialyzer urea clearance, t, the duration of dialysis, and V, the volume of distribution of urea; AR: Access recirculation; VA: vascular access; URR: Urea reduction rate.

**Table 3:** Grade of Recommendation, Assessment, Development, and Evaluation (GRADE) approach summary for this study

| -Outcome -Number of included effect sizes -Number of participants | Risk of bias | Consistency | Directness | Precision | Publication bias | Summary of findings (effect size) | Quality |
|---|---|---|---|---|---|---|---|
| -AR<br>-3<br>-182 | Non-RCT studies were included analysis | Considerable heterogeneity | + | - | Was not detected* | -0.64 (-1.94, 2.65) | Low |
| -KT/V<br>-4<br>-226 | Non-RCT studies were included analysis | Considerable heterogeneity | + | - | Was not detected * | 0.44 (-0.38,1.27) | Low |

*: Number of studies was less than 10. RCT: randomized clinical trial; AR: Access recirculation; Kt/V: k is the dialyzer urea clearance, t, the duration of dialysis, and V, the volume of distribution of urea.

on RCT studies. The Results of three non-RCT studies (11, 29, 30) showed that retrograde direction decreased KT/V more than antegrade direction.

However, this difference was statistically insignificant (ES: 0.44, 95%CI: -0.38 to 1.27, Z=1.05, I2:87.0%, P=0.29, Figure 4).

### *3.5. Effect of needle direction in AVF cannulation on HD adequacy based on AR*

Five studies (11, 13, 17, 29, 31) (two RCTs (13, 31) and three non-RCTs (11, 17, 29)) reported the effects of direction on HD adequacy based on the AR. The results of two studies (one RCT and one non-RCT) (13, 29) showed that AR in the retrograde cannulation method is less than in the antegrade cannulation method. Also, three studies (one RCT and two non-RCT) (11, 17, 31) did not show a significant difference in AR in the two antegrade and retrograde cannulation methods. One RCT study (13) did not report sufficient data. Therefore meta-analysis was not performed based on RCTs. Also, the results of three non-RCT studies (11, 17, 29) showed that the antegrade direction decreased AR when compared to the retrograde direction, but it was not statistically significant (ES: -0.64, 95%CI: -1.94 to 0.67, Z=0.96, I2:92.5%, P=0.34, Figure 5).

### *3.6. Effect of needles' distance in AVF cannulation on HD adequacy based on KT/V*

Of the studies included in this review, one non-RCT study (29) reported the effect of needle distance in AVF cannulation on HD adequacy based on KT/V. This study (29) suggested that a distance of 5 cm or more between arterial and venous needles had greater adequacy than a distance of less than 5 cm.

### *3.7. Effect of needles' distance in AVF cannulation on HD adequacy based on AR*

Of the studies included in this review, four studies (10, 13, 17, 29) reported the effect of needle distance in AVF cannulation on HD adequacy based on AR. Two studies (one RCT and one non-RCT) (13, 29) demonstrated that a distance of 5 cm or more between arterial and venous needles had greater adequacy and lower AR than a distance of less than 5 cm. However, one RCT study (10) showed that a distance of 2.5 cm between arterial and venous needles had greater adequacy and lower AR than a distance of 5 cm. One non-RCT study (17) did not show a significant difference between 5 cm and 7 cm needle distances in HD adequacy based on AR.

### *3.8. Publication bias*

Funnel plots indicated asymmetric views (Figure 6); however, the results of the Egger's test did not confirm the presence of publication bias for effect sizes of AR (P=0.99) and KT/V (P=0.74).

### *3.9. Sensitivity analysis*

Sensitivity analysis showed that pooled effect size regarding the effect of directions on the KT/V was not dependent on a single study (95% CI: -0.62 to 1.77). In addition, pooled effect size regarding the effect of directions on the AR was not dependent on a single study, either (95% CI: -3.32 to 2.37).

### *3.10. Certainty of the evidence*

The body of evidence assessed using the GRADE approach received an overall certainty rate of low for both outcomes (Table 3).

## 4. Discussion

Meta-analysis showed that retrograde direction decreased KT/V more than antegrade, but it was not statistically significant. Also, the antegrade direction decreased AR compared to the retrograde; however, this was not statistically significant.

One cross-sectional study showed that antegrade cannulation increases KT/V in HD patients (32). Another cross-sectional research found that the frequency of AR in the retrograde cannulation method was higher than in the antegrade method (33). In a study with 7,058 patients, Parisotto et

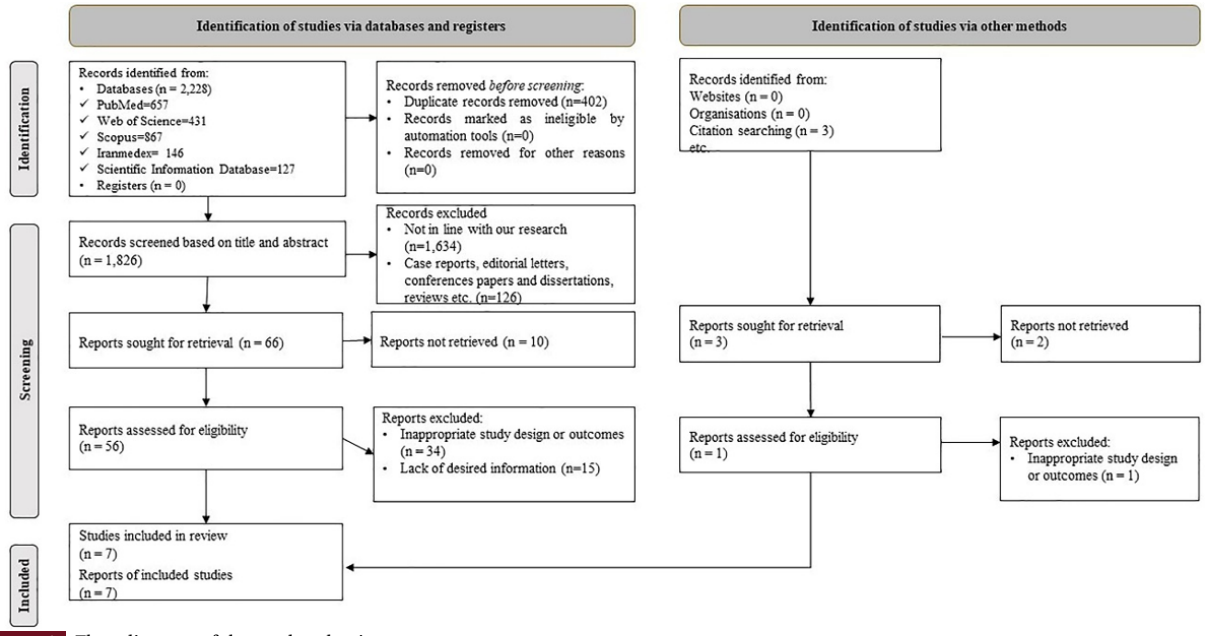


**Figure 1:** Flow diagram of the study selection process.

| | | Rothera et al., 2011 | Reyes, 2016 | Vahedi et al., 2018 |
|---|---|---|---|---|
| RCT | Was true randomization used for assignment of participants to treatment groups? | Y | Y | Y |
| | Was allocation to treatment groups concealed? | U | U | U |
| | Were treatment groups similar at the baseline? | Y | Y | Y |
| | Were participants blind to treatment assignment? | N | N | N |
| | Were those delivering treatment blind to treatment assignment? | N | N | N |
| | Were outcomes assessors blind to treatment assignment? | N | N | N |
| | Were treatment groups treated identically other than the intervention of interest? | Y | N | Y |
| | Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed? | N | N | N |
| | Were participants analyzed in the groups to which they were randomized? | Y | Y | Y |
| | Were outcomes measured in the same way for treatment groups? | Y | Y | Y |
| | Were outcomes measured in a reliable way? | Y | Y | Y |
| | Was appropriate statistical analysis used? | Y | Y | Y |
| | Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial? | Y | Y | Y |

**Figure 2:** Methodological quality assessment of randomized clinial trial (RCT) studies using Joanna Briggs Institute (JBI) checklist.

al. (2014) indicated that the retrograde cannulation method would increase the risk of failure in HD (34).

These findings were in line with the results of the current meta-analysis. Another study found that most HD staff used the antegrade direction to access AVF (35). The two RCT studies included in the study showed controversial results. However, the results of other studies showed that direction has some impact on HD adequacy. Therefore, the recommendation to use one particular direction is unsettled due to a lack of definitive evidence and guidelines on VA give little importance to cannulation techniques . More studies with good-quality designs such as RCTs are suggested. RCT study design, after meta-analysis and systematic review studies, produce valid and reliable findings and researchers should con-

| | | Dias et al., 2008 | Ozmen et al., 2008 | Lim et al., 2018 | Elias et al., 2018 |
|---|---|---|---|---|---|
| Quasi-Experimental | Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)? | Y | Y | Y | Y |
| | Were the participants included in any comparisons similar? | Y | Y | Y | Y |
| | Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest? | Y | Y | Y | Y |
| | Was there a control group? | N | N | N | N |
| | Were there multiple measurements of the outcome both pre and post the intervention/exposure? | Y | Y | N | N |
| | Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed? | N | N | N | N |
| | Were the outcomes of participants included in any comparisons measured in the same way? | Y | Y | Y | Y |
| | Were outcomes measured in a reliable way? | Y | Y | Y | Y |
| | Was appropriate statistical analysis used? | Y | Y | Y | Y |

**Figure 3:** Methodological quality assessment of quasi-experimental studies using Joanna Briggs Institute (JBI) checklist.

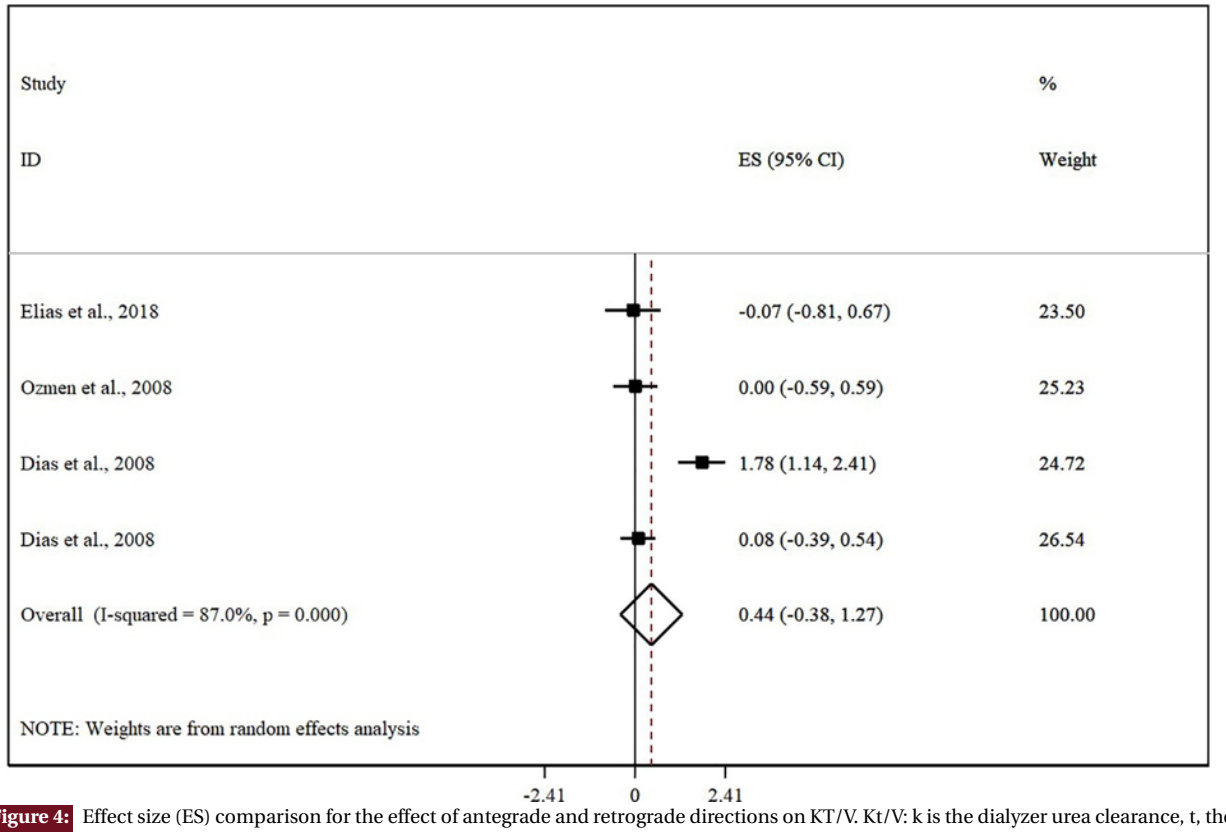


**Figure 4:** Effect size (ES) comparison for the effect of antegrade and retrograde directions on KT/V. Kt/V: k is the dialyzer urea clearance, t, the duration of dialysis, and V, the volume of distribution of urea; CI:confidence interval.

sider this characteristic. However, when there is limited evidence in studies with RCT design, assessment of other designs, such as non-RCT, becomes inevitable.

We did not perform quantitative analysis to evaluate the ef-

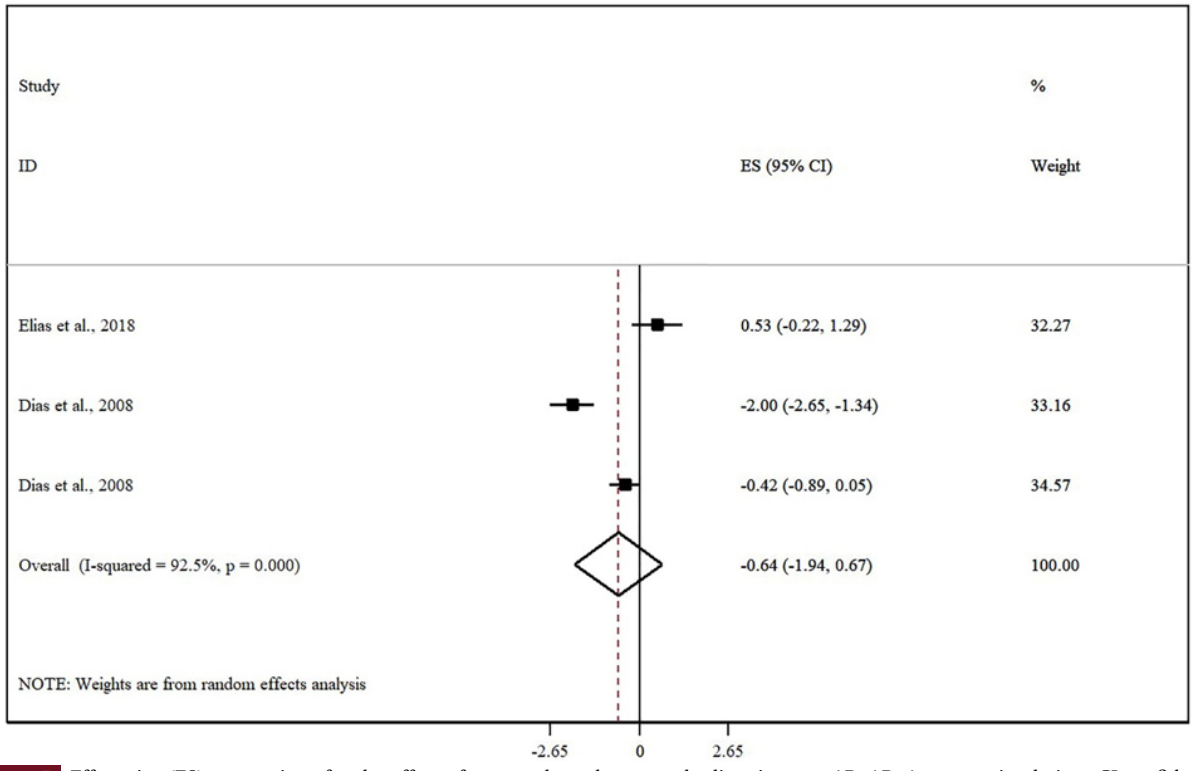


**Figure 5:** Effect size (ES) comparison for the effect of antegrade and retrograde directions on AR. AR: Access recirculation; CI:confidence interval.

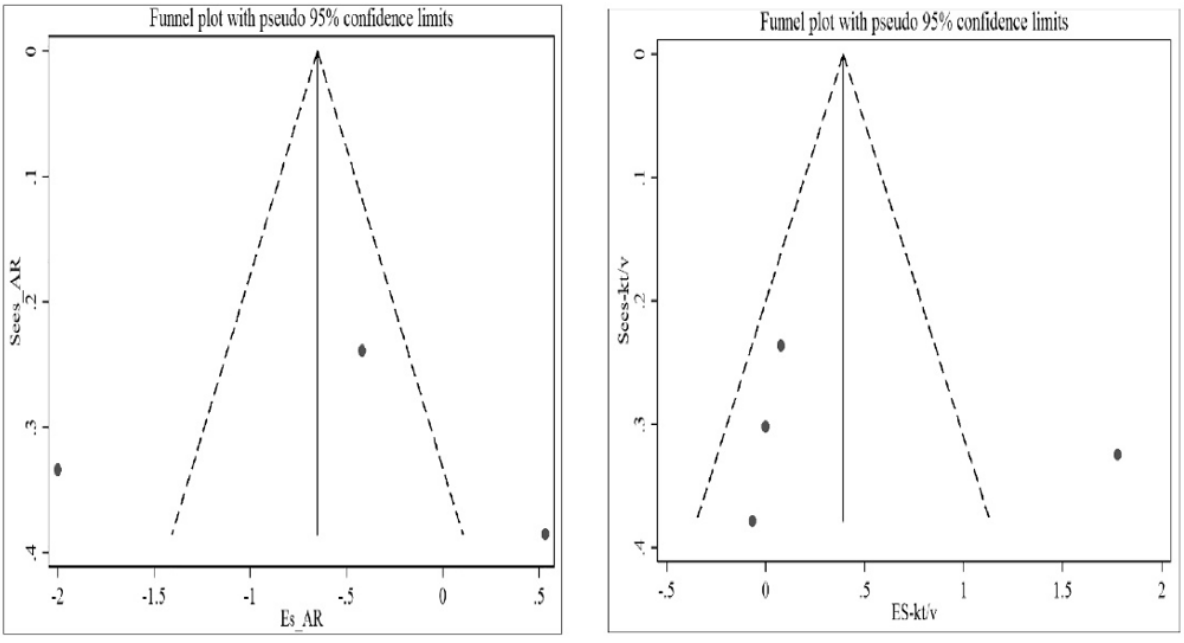


**Figure 6:** Funnel plots of effect sizes (ES) for AR (left) and KT/V (right). AR: Access recirculation; Kt/V: k is the dialyzer urea clearance, t, the duration of dialysis, and V, the volume of distribution of urea.

fect of distance on dialysis adequacy criteria due to insufficient data in the articles. However, qualitative comparison of the results of the two RCT and two Non-RCT studies indicated contradictory findings. One cause of AR is the lack of

correct placement of AVF, so reducing the distance between two needles can increase returning of dialyzed blood to the arterial line and thereby decrease HD adequacy (33). One cross-sectional study in Iran showed that cannulation with a needle distance less than 5 cm had more AR and lower HD adequacy than other methods (33).

Heterogeneity between studies was considered significant based on I2 value. The source of heterogeneity can be related to the distance of needles, the number of sessions, and patients' demographic characteristics in each study. Certainty of evidence was evaluated and found to be at a low level based on the GRADE approach. Results related to AR and KT/V based on the non-RCTs studies showed that there are heterogeneity and wide confidence interval between studies. This finding again confirms the need for vigorous studies to better adjudicate the effects of distance and direction of the needle on HD adequacy.

One of the most common ways of accessing blood vessels in patients with HD is an AVF (36). Patients under HD require VA with proper functioning to survive (37). Incorrect procedures in AVF cannulation can reduce HD adequacy and increase AR (38). The current study showed that there are ambiguous issues about the effects of direction and distance of AVF cannulation in HD patients. As a result, it is recommended that researchers pay more attention to this vital issue.

### *4.1. Limitations*

This study had some limitations. Meta-analysis was performed on the effects of direction on KT/V and AR based on non-RCT studies since some of the included RCT studies had insufficient data. We described the result of RCTs qualitatively. Although only seven articles were included in the review and analysis, this study can attract the attention of researchers and motivate them to conduct more studies with higher-quality designs on this topic. Despite a comprehensive search of databases, not all studies on this subject may have been found, so it may have reporting bias. Finally, only studies in English and Persian were included in the present study, so it may have language bias.

### *4.2. Implications for health managers and policymakers*

Although the results of the meta-analysis suggested antegrade was more effective than retrograde, making any definitive recommendation based on this finding is problematic because of the low strength of the evidence. Also, findings showed controversy and uncertainty about the effect of needle distance on HD adequacy outcomes. More RCT studies and more data are required to make better evidence-based decisions regarding the effect of needle direction on HD efficacy.

### *4.3. Implications for future research*

Due to the heterogeneous nature of the results in this systematic review, it is suggested that researchers conduct more interventional studies to investigate the effect of antegrade and retrograde cannulation methods and needle distance on HD adequacy and AR.

## 5. Conclusion

Overall, the findings from this study are inconclusive and support the uncertainty regarding the effects of directions and distances of AVF cannulation. However, a meta-analysis based on non-RCTs showed that antegrade direction had insignificant positive effects on HD adequacy, decreasing AR and improving KT/V. Future RCT studies are suggested to increase knowledge about the issue of needle direction and distances and their impacts on AVF cannulation.

## 6. Declarations

### *6.1. Acknowledgments*

None.

### *6.2. Conflict of interest*

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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### *6.4. Authors' contribution*

All authors have agreed on the final version of this manuscript. Those listed as authors are qualified for authorship according to the following criteria: They have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; been involved in drafting the manuscript or revising it critically for important intellectual content; and have given final approval of the version to be published. Each author participated sufficiently in the work, has taken public responsibility for appropriate portions of the content, and has agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

### *6.5. Ethics approval*

This review study has not been registered in the international prospective register of systematic reviews (PROSPERO) database.

### *6.6. Data availability*

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

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