Risk Factors for Arteriovenous Fistula Thrombus Development: A Systematic Review and Meta-Analysis

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Keywords
Arteriovenous fistula · Thrombus · Risk factor · End-stage renal disease · Meta-analysis

Abstract

\textbf{Background:} Risk factors like female sex, fistula location, hypertension, albumin, diabetes, arteriovenous graft (AVG), age, and other factors are related to arteriovenous fistula thrombus (AVFT), but the consistency and magnitude of their associations have not been confirmed by meta-analysis. \textbf{Objectives:} The purpose of this study was to provide a comprehensive and up-to-date synthesis of evidence on the association between potential risk factors and AVFT. \textbf{Methods:} In this systematic review and meta-analysis, PubMed, Embase, Cochrane Library, and Web of Science databases were searched for articles published up to April 20th, 2022, and cohort, cross-sectional, and case-control studies examining the association (odds ratio [OR]) between potential risk factors and AVFT were identified. The other inclusion criteria were sufficient data for analysis and nonoverlapping datasets, excluding reviews, meta-analyses, and articles with overlapping datasets. Extracted variables included first author, publication year, study type, sample size, percentage of women, vascular access type, risk or protective factors, and measure of association (adjusted estimates of effect of all risk factors). The study protocol is registered at PROSPERO (CRD42020201884) and followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. \textbf{Results:} Among the 27 identified studies, data from 24 cohort, 2 case-control, and 1 cross-sectional study were included in this review. When compared to non-AVFT, our data showed that the significant risk factors were AVG (pooled OR = 6.28, 95\% CI = 1.79–22.02, \(p = 0.004, I^2 = 87\%\)), age (pooled OR = 1.06, 95\% CI = 1.00–1.13, \(p = 0.05, I^2 = 98\%\)), female sex (pooled OR = 2.62, 95\% CI = 2.56–2.69, \(p < 0.00001, I^2 = 0\%\)), C-reactive protein (pooled OR = 1.18, 95\% CI = 1.08–1.30, \(p = 0.0005, I^2 = 90\%\)), fistula site (distal) (pooled OR = 3.64, 95\% CI = 1.74–7.62, \(p = 0.0006, I^2 = 47\%\)), hypertension (pooled OR = 1.21, 95\% CI = 1.00–1.47, \(p = 0.05, I^2 = 46\%\)), CD34\(^+\)KDR\(^+\) cell (pooled OR = 1.85, 95\% CI = 1.33–2.57, \(p = 0.0002, I^2 = 0\%\)), and eprex use (pooled OR = 5.36, 95\% CI = 1.82–15.77, \(p = 0.002, I^2 = 0\%\)). \textbf{Conclusions:} The meta-analysis suggests that AVG, Yuhan Zhang and Jing Yi made equal contributions to the design and writing of this article and should be considered co-first authors.

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age, female sex, CRP level, fistula site (distal), hypertension, CD34+KDR+ cell, and the use of eprex are independent risk factors for AVFT. Therefore, clinical medical staff should treat these risk factors carefully, identify them early, and prevent them early to reduce the occurrence of AVFT.

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Introduction

The number of patients being treated for kidney failure continues to increase every year at a significantly higher rate than that of the world population [1]. In Europe, for example, 592,779 patients received renal replacement therapy as of December 31, 2017. The number was 632,653 in China until 2019. The main renal replacement therapy was hemodialysis (HD) in 57% patients and peritoneal dialysis in 5% patients, while 37% patients underwent a functional kidney transplant [2].

Treating patients with kidney failure involves a large number of resources from national public and private funds. Arteriovenous fistula (AVF) designated by guidelines and initiatives as the “best” available vascular access (VA) for HD and in any condition [3, 4] has many advantages compared to arteriovenous graft (AVG) or central venous catheters [5]. The ultimate goal of angioaccess surgery is functional, durable access with a low complication rate [6]. The downside is that there are many complications, mainly related to thrombosis when AVF is applied. Complications such as thrombosis of VA remain the main problem for many patients with kidney failure [7]. Since 1994, prospective and case-control studies have explored the relationship between risk factors and arteriovenous fistula thrombus (AVFT) in patients undergoing HD [8]. Until now, these studies and reviews [9] have revealed that numerous risk factors are associated with AVFT. In particular, there is a debate whether female sex is a risk factor for AVFT. Despite the substantial and accumulating literature, no comprehensive meta-analysis of risk factors for AVFT has been published in the last 30 years.

Having robust, updated, publication bias-corrected estimates of these associations would advance the research on AVF, provide information for multivariable individualized risk prediction models, and facilitate identification of modifiable factors for potential preventive strategies. To address this knowledge gap, a systematic review and meta-analysis was conducted to quantify the consistency and magnitude of the associations between these risk factors and AVFT.

Methods

Search Strategy and Selection Criteria

With respect to this systematic review and meta-analysis, a multistep literature search was conducted. Web of Science, PubMed, Embase, and Cochrane library databases were first searched to identify original studies examining the association between risk factors and AVFT published in English from database inception to April 20, 2022. The search strategy for PubMed is as follows: ((Hemodialysis OR hemodialysis patients OR Regular hemodialysis OR Dialysis OR Chronic hemodialysis OR Maintenance hemodialysis OR HD OR MHD OR Dialyses, Renal OR Renal Dialyses OR Dialysis, Renal OR Hemodialyses OR Dialysis, Extracorporeal OR Dialyses, Extracorporeal OR Extracorporeal Dialyses OR Extracorporeal Dialysis) AND (Arteriovenous thrombosis OR Vascular access thrombosis OR Thromboses OR Arte- riovenous fistula thrombosis OR Thrombosis of dialysis arteriovenous fistulas OR Fistula thrombosis OR AVFT)) AND (Risk factor* OR Predict factor* OR Related factor OR Factor* OR Predict* OR Influence factor OR Associate factor OR risk* OR Relative)) AND (Cohort stud* OR Cross-sectional stud* OR Prospective stud* OR Retrospective stud* OR Longitudinal stud*) Sort by: Most Recent. Similar key terms were used for the other databases, and details of the search strategy of each database can be found in the online supplementary (for all online suppl. material, see www.karger.com/doi/10.1159/000526768). Following this, additional articles were identified through manual searches of the reference lists of the included articles.

Articles were initially screened based on titles and abstracts, and full-texts of potentially eligible articles were assessed based on the following inclusion criteria: (1) observational (case-control, cohort, or cross-sectional) primary studies published in peer-reviewed journals that examined the association between risk factors and AVFT; (2) subjects following the diagnostic criteria of fistula thrombosis: interruption or reduction of blood flow (BF); sudden, locally felt pain and a tender, hard thrombus in the fistula; detection of a thrombus mass in the internal fistula by ultrasonic examination; failure of contrast medium passage or the presence of narrow blood vessels filled with defects during angiography; (3) sufficient data available to complete the analyses (i.e., raw binary data or precalculated odds ratio [OR], risk ratio [RR], hazard ratio [HR], or continuous data); and (4) nonoverlapping datasets. The exclusion criteria included reviews, meta-analyses, renal transplantation patients, and study designs other than the aforementioned and overlapping datasets. When two articles presented overlapping datasets (i.e., analyses of the same patients or samples) on the same factor, the article with the largest dataset, the most similar risk factor or protective factor definition compared with other studies, or the longest follow-up period was retained for that risk factor.

Outcome Measures and Data Extraction

The literature search, data selection, and data extraction were performed independently by two investigators (P.Y. and M.Y.), and discrepancies were resolved via consensus after discussion with a senior researcher (Y.J.). The extracted variables included first author, publication year, study type, sample size, percentage of women, VA type, risk or protective factors, and measure of association (adjusted estimates of effect). Simultaneously, some factors were discarded and reported less than two times in all studies.
The preference for the measure of association was needed to calculate an OR. When not available, OR, RR, HR were extracted and reported (preferably unadjusted for any covariates) with 95% confidence intervals (CIs). Specifically, RR and HR were considered equivalent to OR when considering the low incidence of AVFT. No other imputations or transformations were performed, and risk or protective factor data were initially extracted, as defined in the original papers.

Bias was assessed using the Newcastle-Ottawa Scale for cohort and case-control studies. These were awarded a maximum of nine points on items related to the selection of the cohort or cases, comparability of exposed and nonexposed groups, ascertainment of exposure and outcome, and adequacy of follow-up. Cross-sectional studies used the observational research evaluation tool developed by the Agency for Healthcare Research and Quality (AHRQ).

Statistical Analysis
We performed meta-analyses using RevMan (version 5.3) and the metan package in Stata (version 16.0). For each risk factor (e.g., female) with data from at least two independent samples, a random-effects meta-analysis was employed to summarize the results since a high degree of heterogeneity emerged. The main outcome of the meta-analysis was the pooled OR of the risk or protective factor, thus estimating the 95% CI and the p value of the OR with significance set at \( p = 0.05 \). To evaluate heterogeneity between studies, the \( I^2 \) index was assessed (\( I^2 > 50\% \) is commonly considered to indicate serious heterogeneity), and the Q test was also performed \( (p < 0.05, \text{indicating potential heterogeneity}) \). The meta-analysis explored the origin of heterogeneity by conducting subgroup analyses according to study characteristics if there are enough data. Asymmetry in the funnel plots was performed to assess publication bias, adopting Duval and Tweedie’s trim-and-fill [10] method to estimate potential unpublished studies with negative results, and Egger’s test was performed [11] \( (p < 0.05 \text{ might indicate potential publication bias}) \). When the trim-and-fill method estimated one or more potential unpublished studies, the OR and its 95% CI were recalculated with these estimated studies.

The study protocol is registered at PROSPERO (CRD42020201884) and followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses [12, 13] guidelines. The details of Preferred Reported Items for Systematic Reviews ad Meta-Analyses checklist can be seen at online supplementary.

**Results**

**Search Results and Study Characteristics**
Figure 1 illustrates the study selection process and the consequences of the literature search. A total of 2,109 articles were identified in the database search, and an additional 20 articles were identified through other sources. One hundred and twenty were deemed duplicates and a further 1,864 failed to meet the inclusion criteria. One hundred and twenty-five full-text articles were screened, and 97 were subsequently excluded from the meta-analysis for various reasons (Fig. 1). The remaining 27 studies were published between 2003 and 2022 and comprised 49,688 participants (ranging from 41 to 42,244). The other basic characteristics of the included studies are listed in Table 1.

**Assessment of Methodological Quality**
The remaining 27 studies showed high-quality data (NOS/AHRQ score 6–7). Among them, 8 items of NOS scale can be used to evaluate the quality of cohort study or case-control study, and 11 items of AHRQ scale can be used to evaluate the quality of cross-sectional study. The quality assessment of the included cohort studies is presented in Table 1; detailed evaluation figure can be found.
| Author/year          | Country | Study          | N, female % | Age, mean | Gender | Outcome                                                                 | Follow-up time | Score | VA type |
|---------------------|---------|----------------|-------------|-----------|--------|---------------------------------------------------------------------------|----------------|-------|---------|
| Güven et al. 2021   | Turkey  | Cohort         | 162, 61.1   | 54.44     | Both   | Na, BUN, HDL-C                                                          | 2 years        | 7     | AVF     |
| Chou et al. 2011    | China   | Cohort         | 568, 54.2   | 56.70     | Both   | Atrial fibrillation, AVG, diabetes, hypertension age, CRP               | 10 years       | 7     | AVF/AVG |
| Androulakis et al.  | Greece  | Cohort         | 133, 39.09  | 64.05     | Both   | Increased APC-R, female                                                 | –              | 6     | –       |
| Luo et al. 2022     | China   | Cohort         | 761, 46     | 65.00     | Both   | Frail                                                                    | 3 years        | 7     | AVF/AVG |
| Brophy et al. 2009  | America | Case-control   | 101, 57.4   | 54.3      | Both   | Aspirin, statin                                                          | –              | 6     | Catheter/AVF/AVG |
| Chang et al. 2011   | America | Cohort         | 1,426, 54.8 | 57.4      | Both   | SBP                                                                      | 3.1 years      | 7     | AVF/AVG |
| Chen et al. 2016    | China   | Cohort         | 147, 57     | 68.3      | Both   | Lesion length, CRP, CD34+KDR+                                           | 3.91 years     | 6     | AVF     |
| Chou et al. 2006    | China   | Cohort         | 223, 55.2   | 59.54     | Both   | CRP                                                                      | 4 years        | 6     | AVF     |
| Chou et al. 2009    | China   | Cohort         | 576, 45.83  | 57.35     | Both   | Pulse pressure, CRP                                                     | 19 years       | 7     | AVF/AVG |
| Chuang et al. 2005  | China   | Cohort         | 483, 59.83  | 57.7      | Both   | Age, AVG, hepatitis C                                                   | 2 years        | 7     | AVF/AVG |
| Ernandez et al. 2005| Switzerland| Cohort    | 148, 59.45  | 58.15     | Both   | Location, female, diabetes, surgeon                                    | 5 years        | 7     | AVF     |
| Irvin et al. 2014   | UK      | Cohort         | 151, 39.7   | 67        | Both   | Warfarin, systolic BP                                                  | 2.75 years     | 7     | AVF     |
| Jamshid et al. 2003 | Iran    | Cohort         | 218, 33.5   | 52.03     | Both   | Fistula site, eprex                                                     | 1.16 years     | 7     | AVF     |
| Kirkpantur et al. 2008| Turkey   | Cohort       | 99, 50.50   | 54.00     | Both   | LDL-C, albumin, CRP, CCI                                               | 3 years        | 7     | AVF     |
| Klamothen et al. 2013| Germany   | Cohort       | 199, 42.7   | 59.6      | Both   | Thrombophilia                                                           | 0.5 years      | 6     | AVF/AVG |
| Knoll et al. 2005   | Canada  | Case-control   | 419, 37.71  | 62.65     | Both   | Thrombophilia                                                           | 2.3 years      | 7     | AVF/AVG |
| Mallamaci et al. 2005| Italy   | Cohort        | 205, –      | 59.4      | Both   | Age, homocysteine                                                       | 2.7 years      | 7     | AVF     |
| Hsieh et al. 2017   | China   | Cohort         | 269, 60.59  | 69        | Both   | CD34+ KDR+                                                              | 0.5 years      | 7     | AVF/AVG |
| Ozdemir et al. 2005 | Turkey  | Cohort         | 141, 43.26  | 43        | Both   | Snuffbox location, smoking, eosinophil                                  | –              | 7     | AVF     |
| Stolic et al. 2014  | Serbia  | Cohort         | 41, 54      | 65        | Both   | Diabetic nephropathy, MPO                                               | 2 years        | 7     | AVF     |
| Stolic et al. 2017  | Serbia  | Cohort         | 112, 34.8   | 59.4      | Both   | Magnesium, antiplatelet                                                 | 2 years        | 7     | AVF     |
| Roobeh et al. 2006  | Iran    | Cohort         | 181, 30.38  | 53        | Both   | Age, fistula site, eprex                                                | 1.16 years     | 7     | AVF     |
| Chen et al. 2006    | China   | Cohort         | 196, 50.51  | 64.7      | Both   | AVG, diabetes                                                           | 4 years        | 7     | AVF/AVG |
| Chen et al. 2016    | China   | Cohort         | 42,244, 86.6| –         | Both   | Male, age, diabetic, hypertension, coronary artery disease, DVT         | 7 years        | 7     | AVF/AVG |
| Stirbu et al. 2018  | Romania | Cohort         | 258, 39.93  | 59.7      | Both   | CRP, ADPKD, pre-emptive AVF                                             | 11 years       | 7     | AVF     |
| Gagliardi et al. 2012| Italy   | Cohort        | 84, –       | 67        | Both   | SBP, albumin, hemoglobin, CRP, waist circumference, waist/hip ratio     | 2.6 years      | 6     | AVF     |
| Shin et al. 2017    | Korea   | Cohort         | 143, 56.6   | 62.3      | Both   | MPV/P, diabetes, AVG Previous VAF                                       | 2.24 years     | 7     | AVF/AVG |
Risk Factors for AVFT

Fig. 2. Forest plot of each risk factor. Age (a), female (b), diabetes (c), hypertension (d), AVG (e), fistula site (distal) (f).
in online supplementary materials. The biggest limitation observed in all the included studies was the lack of any description of the nonexposed cohort. The three studies conducted in Greece, America, and Turkey did not report the length of follow-up required to produce relevant results.

**Main Results of the Meta-Analysis**

A total of 11 risk factors were combined in this study, and the final result showed that eight of them were statistically significant. Forest plots results are shown in Figures 2 and 3.
Table 2. Meta-analytic association between risk factors and AVFT

| Risk factors     | Study details | Effect measure | Heterogeneity | Publication bias |
|------------------|---------------|----------------|---------------|-----------------|
|                  | studies, n    | OR (95% CI)    | p value       | I², %           | Egger p value |trim-and-fill-imputed studies |trim-and-fill-adjusted OR (95% CI) |
| AVG              | 4             | 6.28 (1.79–22.02) | 0.004         | 87              | 0.896         |1 | 1.600 (0.323–8.523) |
| Age              | 5             | 1.06 (1.00–1.13) | 0.05          | 98              | 0.070         |2 | 1.002 (0.937–1.071) |
| Female           | 3             | 2.62 (2.56–2.69) | <0.00001      | 0               | 0.520         | – | – |
| Diabetes         | 6             | 1.49 (0.95–2.34) | 0.08          | 76              | 0.378         |2 | 1.288 (0.804–2.065) |
| CRP              | 6             | 1.18 (1.08–1.30) | 0.0005        | 90              | 0.324         |0 | – |
| Fistula site (distal) | 3 | 3.64 (1.74–7.62) | 0.0006        | 47              | 0.052         |0 | – |
| Hypertension     | 2             | 1.21 (1.00–1.47) | 0.05          | 46              | –             |1 | 1.149 (0.963–1.371) |
| SBP              | 3             | 0.94 (0.73–1.21) | 0.63          | 91              | 0.450         |0 | – |
| CD34*KDR+ cell   | 2             | 1.85 (1.33–2.57) | 0.0002        | 0               | –             |1 | 1.799 (1.372–2.359) |
| Eprex use        | 2             | 5.36 (1.82–15.77) | 0.002         | 0               | –             |1 | 4.050 (1.562–10.499) |
| Albumin          | 2             | 0.58 (0.21–1.56) | 0.28          | 46              | –             | – | – |

Demographic Data

There are five studies reporting the adjusted OR/HR/RRs for the association of age and the risk of AVFT in HD patients. Our results of random-effect meta-analysis indicated there was a significant association between age and AVFT (pooled OR = 1.06, 95% CI = 1.00–1.13, p = 0.05, I² = 97%, Fig. 2a). Besides, our result of Egger’s test for age is 0.070. Trim-and-fill method imputed 2 studies for age, and the trim-and-fill-adjusted OR is 1.002, as is shown in Table 2. Meanwhile, three studies reported the adjusted OR/HR/RRs for the association of females and the risk of AVFT in HD patients. Our results of random-effect meta-analysis indicated there was a significant association between female sex and AVFT (pooled OR = 2.62, 95% CI = 2.56–2.69, p = 0.00001, I² = 0%, Fig. 2b). Besides, our result of Egger’s test for female is 0.520. No study was imputed by trim-and-fill method.

Comorbid Conditions

There are six studies reporting the adjusted OR/HR/RRs for the association of diabetes and the risk of AVFT in HD patients. Our results of random-effect meta-analysis indicated there was no association between diabetes and AVFT (pooled OR = 1.49, 95% CI = 0.95–2.34, p = 0.08, I² = 76%, Fig. 2c). Result of Egger’s test for diabetes is 0.378. Trim-and-fill method imputed 2 studies for age, and the trim-and-fill-adjusted OR is 1.288, as is shown in Table 2. Two studies reported the adjusted OR/HR/RRs for the association of hypertension and the risk of AVFT in HD patients. Our results of random-effect meta-analysis indicated there was a significant association between hypertension and AVFT (pooled OR = 1.21, 95% CI = 1.00–1.47, p = 0.05, I² = 46%, Fig. 2d). Trim-and-fill method imputed 1 study for hypertension, and the trim-and-fill-adjusted OR is 1.149, as is shown in Table 2.

Fistula Situation

Four studies reported the adjusted OR/HR/RRs for the association of AVG and the risk of AVFT in HD patients. Our results of random-effect meta-analysis indicated there was a significant association between AVG and AVFT (pooled OR = 6.28, 95% CI = 1.79–22.02, p = 0.004, I² = 87%, Fig. 2e). Besides, our result of Egger’s test for AVG is 0.856. Trim-and-fill method imputed 1 study for AVG, and the trim-and-fill-adjusted OR is 1.60, as is shown in Table 2. Three studies reported the adjusted OR/HR/RRs for the association of fistula site (distal) and the risk of AVFT in HD patients. Our results of random-effect meta-analysis indicated there was a significant association between fistula site (distal) and AVFT (pooled OR = 3.64, 95% CI = 1.74–7.62, p = 0.0006, I² = 47%, Fig. 2f). Result of Egger’s test for fistula site (distal) is 0.052. No study was imputed by trim-and-fill method.

Clinical Index

Six studies reported the adjusted OR/HR/RRs for the association of CRP and the risk of AVFT in HD patients. Our results of random-effect meta-analysis indicated there was a significant association between CRP and AVFT (pooled OR = 1.18, 95% CI = 1.08–1.30, p = 0.0005, I² = 90%, Fig. 3a). Result of Egger’s test for CRP is 0.324. No study was imputed by trim-and-fill method. Three studies reported the adjusted OR/HR/RRs for the association of SBP and the risk of AVFT in HD patients. Our
results of random-effect meta-analysis indicated there was no association between SBP and AVFT (pooled OR = 0.94, 95% CI = 0.73–1.21, p = 0.63, $I^2 = 91\%$, Fig. 3b). Result of Egger’s test for SBP is 0.450. No study was imputed by trim-and-fill method. Two studies reported the adjusted OR/HR/RRs for the association of CD34⁺KDR⁺ cell and the risk of AVFT in HD patients. Our results of random-effect meta-analysis indicated there was a significant association between CD34⁺KDR⁺ cell and AVFT (pooled OR = 1.85, 95% CI = 1.33–2.57, p = 0.0002, $I^2 = 0\%$, Fig. 3c). Trim-and-fill method imputed 1 study for CD34⁺KDR⁺ cell, and the trim-and-fill-adjusted OR is 1.799, as is shown in Table 2. Two studies reported the adjusted OR/HR/RRs for the association of albumin and the risk of AVFT in HD patients. Our results of random-effect meta-analysis indicated there was no association between albumin use and AVFT (pooled OR = 0.58, 95% CI = 0.21–1.56, p = 0.28, $I^2 = 46\%$, Fig. 3d).

**Other Factors**

Two studies reported the adjusted OR/HR/RRs for the association of eprex use and the risk of AVFT in HD patients. Our results of random-effect meta-analysis indicated there was a significant association between eprex use and AVFT (pooled OR = 5.36, 95% CI = 1.82–15.77, p = 0.002, $I^2 = 0\%$, Fig. 3e). Trim-and-fill method imputed 1 study for eprex use, and the trim-and-fill-adjusted OR is 4.050, as is shown in Table 2. The results of two studies found that thrombophilia is related to the formation of AVFT, but because of the different definitions of thrombophilia in these two studies, we cannot merge the effect values. Klamroth [28] thinks that severe thrombophilia is related to the occurrence of AVFT (HR: 2.05; 95% CI: 1.42–2.96), and in his research, severe thrombophilia was defined as pathologies in at least one of the following factors: antithrombin, protein C, protein S, factor V mutation G1691A (homozygous), factor II mutation G2010A (heterozygous), lupus anticoagulant, IgG anticardiolipin antibodies. The results of study by Knoll [29] in 2005 found that AVFT was 2.42 times more likely to occur in patients with thrombophilic disorder than in patients without thrombophilic disorder. In his research, thrombophilic disorder was defined as follows: the presence of factor V Leiden, prothrombin gene mutation, or lupus anticoagulant; factor VIII level >90th percentile (>237 IU/dL); homocysteine ≥85th percentile (≥28.9 μmol/L); lipoprotein (a) ≥85th percentile (≥46.0 mg/dL); or anticardiolipin antibody level (IgG or IgM) ≥30 U/mL.

**Discussion**

This study is a comprehensive meta-analysis of risk factors for AVFT conducted in nearly 30 years. A total of 49,688 patients, 27 studies, and 11 risk factors or protective factors of contributing data were included. The data showed that AVG, age, female sex, CRP, fistula site (distal), hypertension, CD34⁺KDR⁺ cell, and eprex use were related to increased AVFT in HD patients.

There is ongoing debate on whether female sex is a risk factor for AVFT. Gjorgjievski et al. [41] found that females are more likely to develop AVFT because they have smaller average preoperative arterial diameters and are less likely to achieve adequate BF. After AVF construction for 4 weeks, 12% of the female participants and 63% of their male counterparts achieved adequate BF, defined as 600 mL/min (p = 0.001). This five-fold difference between men and women has been documented in the literature. However, Miller et al. [42] demonstrated that there was no significant difference in preoperative diameters of the arteries and veins that drain the AVF between patients with adequate and inadequate AVFs. Our results show that the OR of females was 2.62 with no heterogeneity ($I^2 = 0\%$). There was no publication bias, and the results were quite convincing. Although female sex is a risk factor for AVFT, in our result, its cause remains unclear. Kudze et al. [43] suggested that hemodynamic changes during AVF maturation play an important role in increasing AVF failure rates in females. Therefore, large, well-designed studies with an accurate assessment of both preoperative arterial diameters and hemodynamic changes during AVF maturation are essential to confirm this hypothesis. Furthermore, age was found to be highly related to AVFT. Age is a very common risk factor in patients with kidney failure and AVFT. Previous studies have indicated that the incidence of comorbidities (peripheral vascular diseases, diabetes, etc.) increases with age, and elderly patients are more likely to have thrombosis than other age groups [44].

In terms of fistula location, our data indicated that the OR of the forearm was 3.64 times than that of the upper arm. One hypothesis explaining this result is that unlike other veins in the arm, the basilic vein in the upper arm has the advantage of being free of damage caused by previous venipuncture and is often of good caliber since it is a deep vein [45]. In addition, there is evidence that upper arm fistulas involve larger superficial vessels and increase the velocity of the BF, thus reducing thrombosis risk [46]. However, this finding should be interpreted with caution as fewer upper arm sites were being used. The probability
of AVFT in AVG is significantly higher than that in AVF, which has been widely known, and our research results have once again verified this conclusion.

The widely acknowledged risk factor associated with AVFT is hypertension. The reason may be that the higher the blood pressure, the greater the pulse pressure difference, leading to the fluctuation or instability of blood pressure which causes damage to vascular endothelial cells, activates the body fluid regulation system including the renin-angiotensin system, enhances inflammatory reaction, and increases vascular permeability [47, 48]. Our results show that the OR of hypertension in HD patients was 1.21. In our results, however, it was not concluded that higher SBP is more likely to develop AVFT, probably owing to the scarcity of reported data. Therefore, it would be worthwhile to perform additional prospective studies for further exploration of SBP and AVFT. Diabetes is commonly acknowledged as a cause of systemic vascular endothelial injury and intimal hyperplasia, which affects hemodynamics and eventually leads to stenosis or embolism of the internal fistula [49–51]. This indicates that diabetes could be a significant predictor of AVFT development in patients with kidney failure. However, our results show that diabetes is not an independent risk factor for AVFT. Because of the heterogeneity of the merged results, it is found that the literature by Chen et al. [36] has a great influence on the results after deleting the included pieces of literature one by one. After deleting this document, it was found that the results were statistically significant.

The data found that a higher CRP level could indicate a higher likelihood of developing AVFT, possibly because CRP can promote tissue factor activity and antigen in patients undergoing HD. Tissue factor is a transmembrane glycoprotein with coagulation-promoting activity and is the key factor in the initiation of thrombosis [52], which leads to thrombosis of autologous AVF. Another reason may be the excessive expression or release of tissue factors that can activate the exogenous coagulation pathway, facilitate blood coagulation activity, and activate platelet adhesion and aggregation to form thrombi [53]. There are several hypotheses about albumin as a protective factor for AVFT. One hypothesis is that hypoalbuminemia leads to insufficient blood volume, blood concentration, and increased lipoprotein synthesis in the liver, which results in secondary hyperlipidemia and the formation of a hypercoagulable state of blood [54]. Simultaneously, hypoproteinemia promotes the synthesis of coagulation factors in the liver, leading to vascular endothelial injury and activation through a series of reactions including internal and external coagulation systems and thrombosis [55]. The secondary hypothesis is that serum albumin levels and the levels of TNF-α, IL-6, IL-10, and CRP were negatively correlated in inflammatory reactions [56]; thus, kidney failure patients were less likely to develop AVFT. However, the results show that albumin is not a protective factor for AVFT, and this conclusion should be treated with caution because only two articles are included, and there is no research to prove that albumin is a risk factor for AVFT.

More and more evidence shows that circulating endothelial progenitor cells (EPCs) derived from bone marrow can fuse at the site of endothelial injury and restore vascular function [57]. Circulating EPCs have been proved to reflect vascular repair ability and vascular function. However, the relationship between EPCs and AVFT has not been explored. Our results show that the decrease of circulating progenitor cells is significantly related to the risk of AVFT in HD patients. In addition, low CD34+KDR+ cell count may be helpful to identify high-risk patients with thrombosis after angioplasty. It will contribute to the treatment or monitoring plan, such as active monitoring, EPC adjustment intervention, or early surgical revision. Our results also show that erythropoietin is a risk factor for AVFT, but this conclusion should be treated with caution because only two studies that meet the standards are included, and more studies should be included in the future to confirm their accuracy. At present, it is believed that most thromboses are caused by potential anatomical abnormalities, such as the stenosis of the pathway caused by fibromuscular and intimal hyperplasia. However, access thrombosis can occur without anatomical abnormality, and it is unclear why some patients with anatomical abnormality have access thrombosis, while others do not. Thrombophilic disorders are the susceptibility of hereditary or acquired thrombosis, and it is considered as the possible cause of thrombosis in dialysis pathway. However, at present, due to the limited data, it is impossible to combine the effect values. It is suggested that the future research should conduct high-quality research on the premise of controlling other risk factors of AVFT to clarify the mechanism of thrombophilic disorders in AVFT.

These findings have several implications. First, these results might advance the understanding of AVFT and can be used as a starting point for future research in this field. For example, the significance and magnitude of the identified risk factors could form the basis of an updated assessment scale for collecting native AVF risk exposure information. Second, the measures of association provided by this evidence synthesis could be used to develop multivariable psychosis risk prediction models, which integrate the loading of several factors into prognostic.
tools. A third implication is that these results can advance preventive strategies.

The study has various limitations. The main limitation is that the number of each risk factor included is small and we cannot do subgroup analysis or meta-regression to find its heterogeneity. Second, the study design included prospective, retrospective, case-control, and cross-sectional studies, which may have caused heterogeneity. At the same time, one conference abstract was included for analysis, and this abstract did not have complete data available, so we cannot fully evaluate the quality. Third, we could not assess potentially important risk factors, such as puncture failure times, compression time after the puncture, high versus low flux, and hypotension because most primary studies did not report sufficient outcomes separately by such factors. Lastly, the risk factors of early internal fistula thrombosis were not distinguished from those of late internal fistula thrombosis, and future studies are needed to investigate this.

Conclusions

The study demonstrated that risk factors like AVG, age, female sex, CRP level, fistula site (distal), hypertension, CD34 “KDR” cell, and the use of eprex can be associated with AVFT, and this knowledge advances the understanding of AVFT, facilitates multivariable risk prediction profiling, and lays the foundation for future preventive strategies.

Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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Author Contributions

Yuhan Zhag and Yi Jing provided the manuscript design for this study. Yu Peng, Liyan Sha, Jianli Dong, and Rongzhi Zhang helped with the manuscript review.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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