

Pathophysiology of High Output Arteriovenous Fistula with Heart Failure: A Systematic Review and Meta-analysis

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ABSTRACT

Introduction: Arteriovenous Fistula (AVF) is extensively used as vascular access for haemodialysis patients. It induces a high output state, which is associated with cardiac remodeling. With High Output Heart Failure (HOHF), the AVF occupies a low pressure; reduced vascular resistance and increased venous return. The High Output Arteriovenous Fistula with Heart Failure (HOHF-AVF) patients often undergo a comprehensive assessment of type of underlying diseases, the degree of vasodilatation along with laboratory investigations and cardiac imaging. Hence identification of the pathophysiological determinants of HOHF-AVF is intriguing.

Aim: To identify the pathophysiological determinants of HOHF-AVF.

Materials and Methods: This systematic review was conducted from May 2021 to December 2021 at the Department of Cardiovascular Surgery, Imperial College, United Kingdom. Randomised Controlled Trials (RCTs), cohort, case-control, cross-sectional and descriptive studies, conducted on adult patients who underwent AVF creation or ligation and addressed the pathophysiological determinants of HOHF-AVF were included. Studies conducted among Paediatric cases, case reports, and case series were excluded. Medline (PubMed), EMBASE, ProQuest, and the Cochrane database were searched, by utilising the key words [{"HOHF" OR "High output heart failure"}] AND [{"AVF" OR "Arteriovenous fistula"}] AND [{"LV parameters" OR "Structural Characteristics" OR "Echocardiographic indices"}]. The searches were restricted from January 2000 to October 2021 with studies published in

the English language. All the included studies were subjected to critical appraisal using the "Cochrane risk of bias assessment tool" for RCTs, and the "Joanna Briggs Institute (JBI) checklist" for cohort, case-control, cross-sectional and descriptive studies. For meta-analysis Mantel-Haenszel Odds Ratio (M.H. O.R.) with its 95% Confidence Interval (C.I), Mean Difference (M.D) with its 95 % C.I were computed. The Review Manager Software (Rev Man 5, Cochrane collaboration, Oxford, England) was used for data analytics.

Results: Overall, 115 citations were identified from the initial search, of which 29 studies were retrieved. Later, 14 studies were excluded. Of the remaining 15 studies, 12 were subjected to meta-analysis. There was a change in Left Ventricular (LV) end diastolic diameter (M.D=2.0; $p<0.001$; 95% C.I=1.13 to 2.86), and cardiac index (M.D=0.63; $p<0.001$, 95% C.I=0.46 to 0.79) from baseline to atleast three months of postsurgery among HOHF-AVF patients. According to the AVF flow, there was a change in LV systolic diameter (M.D=-18.90; $p<0.01$; 95% C.I=-22.84 to -14.96), cardiac index (M.D=0.50; $p=0.007$; 95% C.I=0.14 to 0.86) and tricuspid annular plane systolic excursion (M.D=3.90; $p=0.03$; 95% C.I=0.30 to 7.50).

Conclusion: Left ventricular end diastolic diameter and cardiac index were found to be the major determinants for a HOHF-AVF. The left ventricular mass index, ejection fraction, posterior wall thickness, interventricular septum were not associated with HOHF-AVF. Left ventricular systolic diameter, cardiac index and tricuspid annular plane systolic excursion were the determinants of AVF flow.

Keywords: Cardiac index, Cardiac remodeling, Echocardiographic indices, Ejection fraction, Structural characteristics

INTRODUCTION

The Arteriovenous Fistula (AVF) can cause or exacerbate heart failure, ventricular hypertrophy or dysfunction, pulmonary hypertension, and Coronary Artery Disease (CAD). Chances of having pre-existing adverse cardiac events are higher among haemodialysis patients [1]. In order to maintain vascular perfusion, the increase in cardiac output and blood flow through an AVF (one to two litres per minute) must be atleast equal [2]. Dyspnoea, decreased exercise tolerance, peripheral oedema, and fatigue were common among HOHF patients [2,3]. Thus, a comparison of the pathophysiological characteristics of persistence versus systematic closure of AVF is important to evaluate the cardiac impact of a functioning AVF and echocardiographic abnormalities.

The symptomatic fistula with HOHF should be subjected to either reconstruction or ligation. The AVF flow (800 mL/min) or AV graft (1200 mL/min) were the diagnostic marker for HF resulted from the high flow vascular access [4]. However, vascular access closure among kidney allograft recipients was limited. The successful transplantation can be followed a safe closure of an aneurysmatic fistula. It can lead by

the occurrence of steal syndrome, cosmetic defects, inflammation, oedema, and the risk of HF [5]. The flow restriction procedure of AVF involves the creation of a surgical stenosis within the venous access site to curtail the radius. It involves the ligation of fistula and then attaching it distally with the jump grafts [2].

The requirement for fistula repair or the creation of a new AVF is a challenge, especially if there is a contraindication for high flow graft or when HF develops along with allograft nephropathy. Fistula ligation among the stable kidney allograft recipient may not yield any beneficial effect on cardiac structure and function in patients without the history of HF. High cardiac output maintains the ejection fraction and hence the surgical closure of an AVF in a patient with New York Heart Association class IV heart failure may result in adverse cardiac events [6,7].

In order to permit maturation, it is recommended to construct an AVF atleast six months prior to dialysis; and a graft can be used after three to six weeks [8]. Creation of a temporary vascular access should be preferred as the last option for first time access in HOHF-AVF patients [8]. After AVF creation, the

chances of increase in cardiac output are higher due to the reduction in peripheral vascular resistance and rise in right ventricular preload. In patients on haemodialysis, conversion from AVF to catheter was followed, but use of the catheter as mode of vascular access carries high-risk of infection [9]. The detrimental effects of high flow AVF are the predictors of mortality, morbidity and adverse cardiac events. Thus, the surgical blood flow reduction is recommended as an elective to reduce the effect of a high flow on the heart, and it enhances the survival rate of a functioning AVF [9]. The creation or persistence of AVF followed by its closure resulted from HF, limb swelling, cosmetic complications, fatigue, and palpitations may result the AVF to progress the hypertrophy and high cardiac output [2,10]. Thus, an identification of pathophysiological determinants of HOHF-AVF is important to evaluate the cardiac impact of a functioning AVF and echocardiographic abnormalities.

This systematic review and meta-analysis was conducted to identify the pathophysiological determinants of HOHF-AVF.

MATERIALS AND METHODS

This systematic review was conducted from May 2021 to December 2021 including the English literature from January 2000 to October 2021 at Department of Cardiovascular Surgery, Imperial College, London, United Kingdom.

Inclusion criteria: Randomised Controlled Trials (RCTs), cohort, case-control, cross-sectional, and descriptive studies, which made an attempt to address the pathophysiological determinants of HOHF-AVF were the inclusion criteria. The studies conducted on adult patients who underwent AVF creation or ligation irrespective of study setting and regions were included in the study.

Exclusion criteria: Studies conducted among paediatrics, case reports, and case series were excluded. If the outcome measure (pathophysiological determinants of HOHF-AVF) was not reported or was impossible to extract or calculate from the available results, then such studies were excluded from the study.

Medline (PubMed), EMBASE, ProQuest, and the Cochrane database were searched, by utilising a combination of the relevant Medical Subject Heading (MeSH) terms and the key words [{"HOHF" OR "High output heart failure"}] AND [{"AVF" OR "Arteriovenous fistula"}] AND [{"LV parameters" OR "Structural Characteristics" OR "Echocardiographic indices"}]. In the Cochrane database the search was limited by the term "clinical trial". The searches were restricted from January 2000 to October 2021 with studies published in the English language. Citations were screened at the title or abstract level and retrieved as a full report if they were clinical studies, addressed structural or echocardiographic characteristics of HOHF-AVF. PRISMA guidelines were followed in this systematic review.

Search strategy: Screening criteria in preliminary search were the pathophysiological determinants associated with HOHF-AVF. In the second phase full manuscripts of all the studies qualified the screening criteria, were obtained. Selection criteria were applied to each of these studies and valid studies were subjected for final data extraction.

Methods used to collect the data: The keywords [{"HOHF" OR "High output heart failure"}] AND [{"AVF" OR "Arteriovenous fistula"}] AND [{"LV parameters" OR "Structural Characteristics" OR "Echocardiographic indices"}] were entered into different database and year-wise search was conducted. Titles or abstracts were screened for the content and full manuscripts of the studies were obtained. All the downloaded articles were studied and subjected for eligibility criteria and a list of selected studies was obtained. They were further subjected for inclusion and relevant data were extracted.

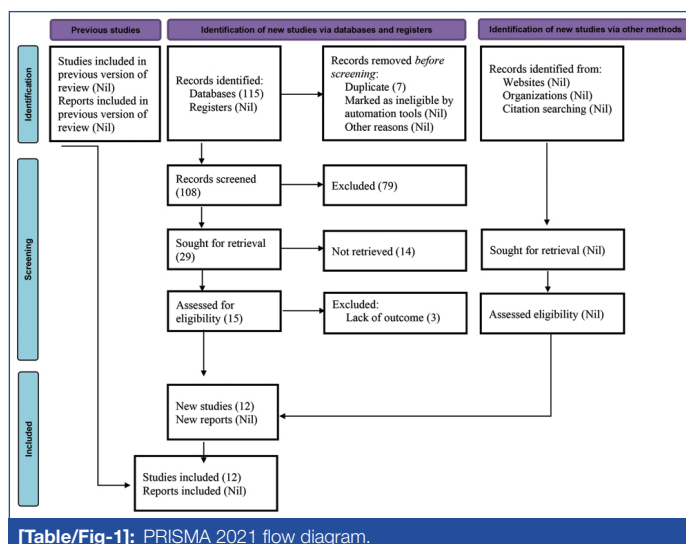
Quality assessment: All the included studies for meta-analysis were subjected to methodological quality appraisal using the "Cochrane risk of bias assessment tool for RCTs", and the "Joanna Briggs Institute (JBI) checklist for case-control, cross-sectional, cohort and descriptive studies" [11,12]. For each item the response was recorded as "yes" or "no" and a credit point of "one" was assigned for "yes" and "zero" for "no".

Data analysis: For meta-analysis Mantel-Haenszel Odds Ratio (M.H. O.R.), mean difference (M.D), and 95% Confidence Interval (C.I) were computed by using the fixed effect model. The Chi-square and I² statistic were used to test heterogeneity [13]. The Review Manager Software (Rev Man 5, Cochrane collaboration, Oxford, England) was used for data analytics [14].

[Table/Fig-1] shows the PRISMA flow diagram. Total counts of all points for appraisal were obtained and higher counts indicate well appraisal [Table/Fig-2].

RESULTS

Overall, 115 citations were identified from the initial search, of which 29 studies were retrieved. Later, 14 studies were excluded. Of the remaining 15 studies [15-29], 12 were subjected to meta-analysis in the second phase [15-26] [Table/Fig-2].



[Table/Fig-1]: PRISMA 2021 flow diagram.

Author	Year of publication	Design	Sample size	Appraisal score ^{*,#}
Van Duijnhoven EC et al., [15]	2001	Cohort	20	8/12
Unger P et al., [16]	2002	Cohort	23	7/12
Sheashaa H et al., [17]	2004	Cohort	51	9/12
Unger P et al., [18]	2004	Cohort	25	8/12
Cridlig J et al., [19]	2008	RCT	76	5/7
Unger P et al., [20]	2009	Cohort	16	9/12
Gorgulu N et al., [21]	2011	Cohort	109	8/12
Głowiński J et al., [22]	2012	Cohort	18	8/12
Soleimani MJ et al., [23]	2012	Cohort	40	7/12
Dundon BK et al., [24]	2014	RCT	18	4/7
Papasotiriou M et al., [25]	2019	Cohort	99	8/12
Rao NN et al., [26]	2019	Cohort	54	8/12
Mailik J et al., [27]*	2021	Cohort	26	7/12
Saleh MA et al., [28]*	2018	Descriptive	100	7/10
Salehi T et al., [29]*	2021	Descriptive	45	8/10

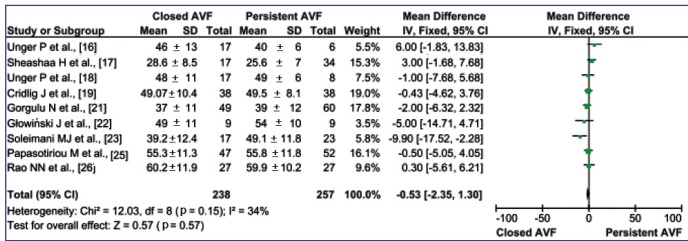
[Table/Fig-2]: Critical appraisal of the studies [15-29].

*:Excluded from meta-analysis

**Cochrane risk of bias assessment tool (RCTs)

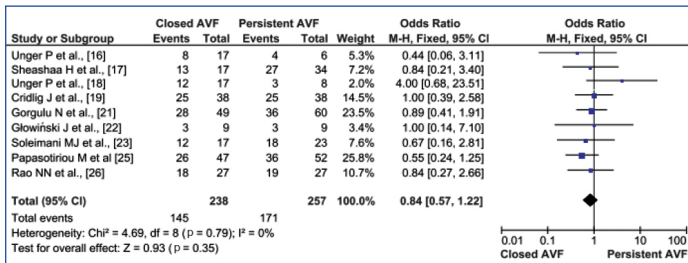
#Joanna Briggs Institute (JBI) checklist (cohort, case-control, cross-sectional and descriptive studies)

The studies selected for meta-analysis contributed a sample size 549. It included 292 (53.19%) closed AVF cases and 257 (46.81%) with persistent AVF (failure of complete healing of the AVF for more than six months followed by the surgery). Three studies had patients with closed AVF (n=54) and there was no comparison (persistent AVF) group [15,20,24]. Mean age of the study population of the closed AVF group was 46.61±11.17 years and in the persistent AVF group it was 46.14±9.21. Thus, age was homogeneous (M.D=-0.53; p=0.57; 95% C.I.=-2.35 to 1.30) between the two groups of AVF [Table/Fig-3] [16-19,21-23,25,26].



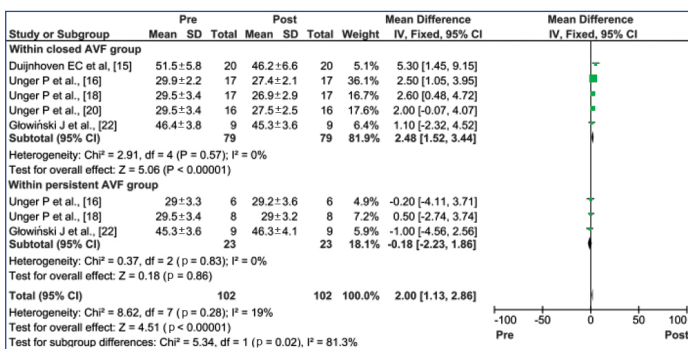
[Table/Fig-3]: Comparison of age [16-19,21-23,25,26].

The Majority of the study population were males 145 (60.92%) in the closed AVF group and 171 (66.53%) in persistent AVF. Gender was not associated (M.H. O.R=0.84; p=0.35; 95% C.I.=0.57 to 1.22) with the AVFs [Table/Fig-4].



[Table/Fig-4]: Comparison of gender (Male) [16-19, 21-23,25,26].

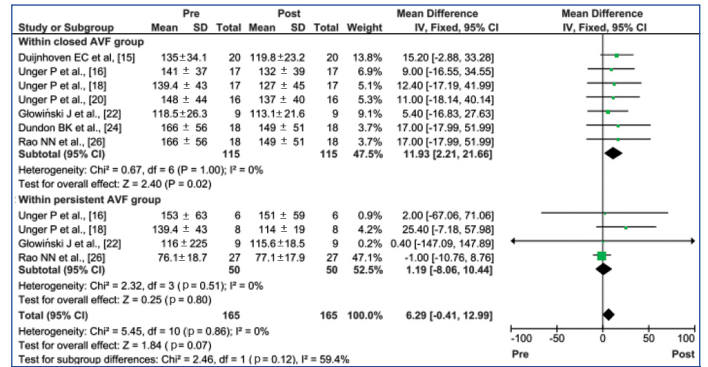
There was a difference in Left Ventricular (LV) end diastolic diameter (mm) within the closed (M.D=2.48; p<0.001; 95% C.I.=1.52 to 3.44) AVF group. In a persistent AVF group of patients, there was no difference (M.D=-0.18; p=0.86; 95% C.I.=-2.23 to 1.86) in LV End Diastolic Diameter (LVEDD). The pooled estimate of LVEDD differed (M.D=2.0; p=0.02; 95% C.I.=1.13 to 2.86) from baseline (pre) to at least three months of postsurgery. It indicates that Left Ventricular end diastolic diameter was one of the determinants for AVF among HOHF patients [Table/Fig-5].



[Table/Fig-5]: Comparison of the left ventricular end diastolic diameter (mm) [15,16,18,20,22].

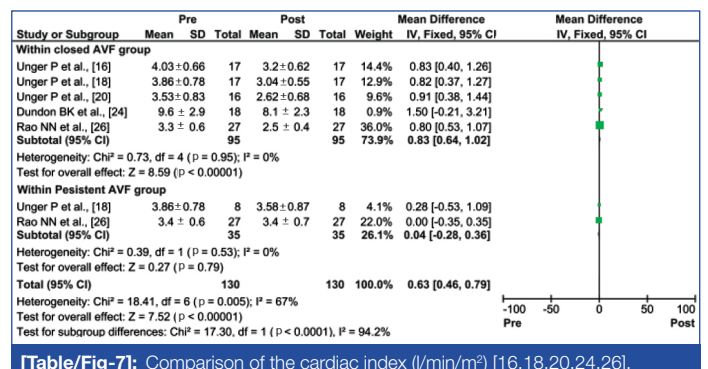
The Left Ventricular Mass Index (LVMI) within the closed AVF group from (M.D=11.93; p=0.02; 95% C.I.=2.21 to 21.66) pre to post measurements exhibited a change. Among the patients with a persistent AVF, there was no change (M.D=1.19; p=0.80; 95% C.I.=-8.06 to 10.44) in LVMI. Also, there was no difference (M.D=6.29; p=0.07; 95% C.I.=-0.41 to 12.99) in the pooled estimate of LVMI [Table/Fig-6].

For cardiac index, there was no difference within the closed (M.D=0.83; p<0.001; 95% C.I.=0.64 to 1.02) AVF group as well



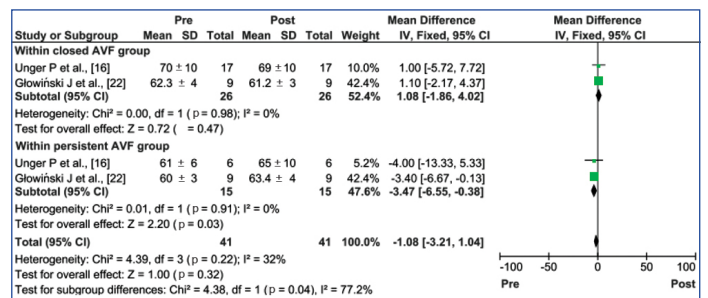
[Table/Fig-6]: Comparison of the left ventricular mass index (g/m²) [15,16,18,20,22,24,26].

as a persistent AVF group (M.D=0.04; p=0.79; 95% C.I.=-0.28 to 0.36). The combined estimate of cardiac index changed (M.D=0.63; p<0.001; 95% C.I.=0.46 to 0.79) from baseline (pre) to at least three months of postsurgery. It indicates that cardiac index was a determinant for AVF [Table/Fig-7].



[Table/Fig-7]: Comparison of the cardiac index (l/min/m²) [16,18,20,24,26].

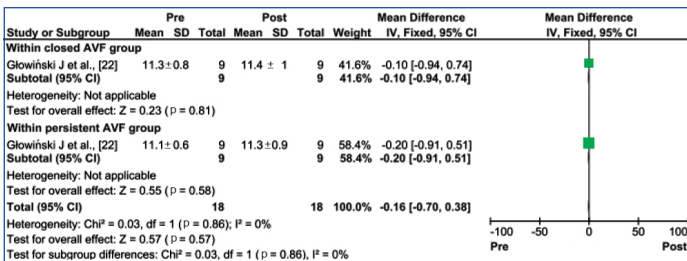
Among the patients with a closed AVF, there was no difference (M.D=1.08; p=0.47; 95% C.I.=-1.86 to 4.02) in the ejection fraction (%) and for the persistent AVF group, there was a difference (M.D=-3.47; p=0.03; 95% C.I.=-6.55 to -0.38) in Ejection Fraction (EF) from baseline (pre) to at least three months of postsurgery. There was no difference (M.D=-1.08; p=0.32; 95% C.I.=-3.21 to 1.04) in the overall estimates of EF and hence it was not associated with HOHF-AVF [Table/Fig-8].



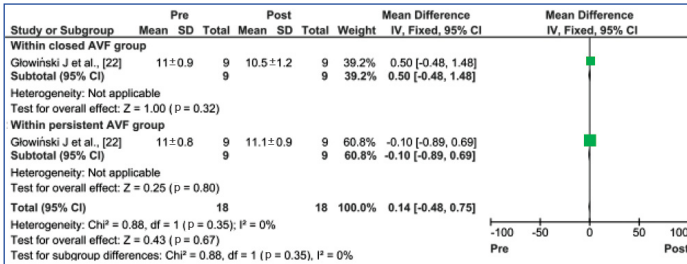
[Table/Fig-8]: Comparison of ejection fraction (%) [16,22].

The posterior wall thickness (mm) within closed (M.D=-0.10; p=0.81; 95% C.I.=-0.94 to 0.74) AVF group as well as a persistent AVF group (M.D=-0.20; p=0.58; 95% C.I.=-0.91 to 0.51) was consistent. There was no difference (M.D=-0.16; p=0.86; 95% C.I.=-0.70 to 0.38) in the pooled estimate of Posterior Wall Thickness (PWT) during the AVF procedures. Hence PWT was not associated with the AVF [Table/Fig-9].

Interventricular septum (mm) within the closed (M.D=0.50; p=0.32; 95% C.I.=-0.48 to 1.48) AVF group as well as persistent AVF group (M.D=-0.10; p=0.80; 95% C.I.=-0.89 to 0.69) exhibited no change. There was no difference (M.D=0.14; p=0.35; 95% C.I.=-0.48 to 0.75) in the combined estimate of Interventricular Septum (IVS) during AVFs and hence IVS was not associated with the AVFs among HOHF patients [Table/Fig-10].

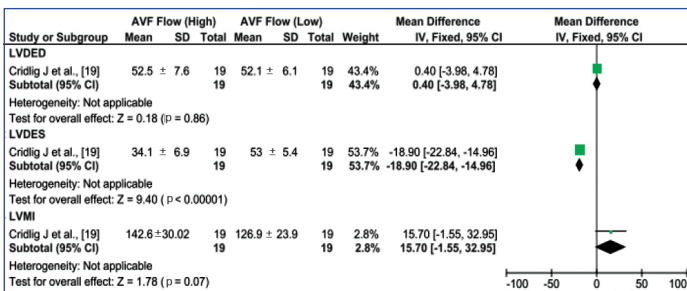


[Table/Fig-9]: Comparison of posterior wall thickness (mm) [22].



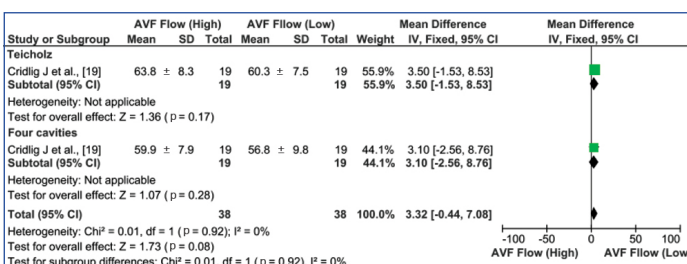
[Table/Fig-10]: Comparison of the Inter ventricular septum [22].

In this study, an AVF with flow rate >680 mL/minutes was considered as high flow fistula and <680 mL/minutes as low flow. This stratification of flow rate was reported in one study among the nine studies included in meta-analysis. There was a difference (M.D=-18.90; p<0.001; 95% C.I.=-22.84 to -14.96) in left ventricular systolic diameter according to the flow rate and hence the LV systolic diameter was associated with AVF flow. However, there was no association between LV diastolic diameter (M.D=0.40; p=0.86; 95% C.I.=-3.98 to 4.78), LV mass index (M.D=15.70; p=0.07; 95% C.I.=-1.55 to 32.95) and the AVF flow [Table/Fig-11].

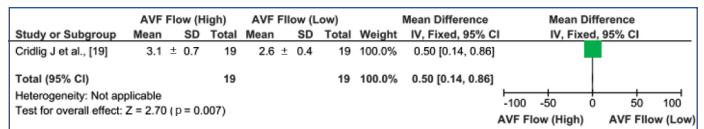


[Table/Fig-11]: Left ventricular end diastolic/systolic diameter, LVMI (g/m²) according to AVF flow [19].

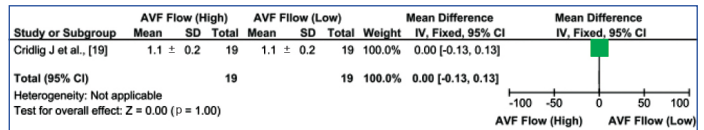
According to AVF flow, there was a difference (M.D=0.50; p=0.007; 95% C.I.=0.14 to 0.86) in cardiac index and tricuspid annular plane systolic excursion (M.D=3.90; p=0.03; 95% C.I.=0.30 to 7.50). Ejection fraction (M.D=3.32; p=0.92; 95% C.I.=-0.44 to 7.08), E/A ratio (M.D=0.0; p=1.00; 95% C.I.=-0.13 to 0.13), left atrial diameter (M.D=2.10; p=0.24; 95% C.I.=-1.37 to 5.57), pulmonary arterial pressure (M.D=2.20; p=0.17; 95% C.I.=-0.92 to 5.32), AVF Area (M.D=0.79; p=0.07; 95% C.I.=-1.40 to 2.98), time deceleration of the "E" wave (M.D=1.80; p=0.90; 95% C.I.=-25.67 to 29.27) were consistent with respect to AVF flow [Table/Fig-12-17].



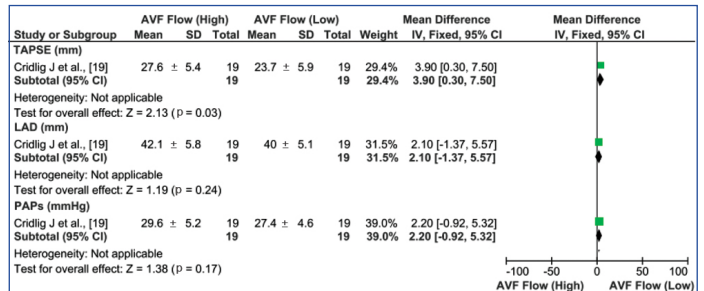
[Table/Fig-12]: Comparison of ejection fraction (%) according to AVF flow [19].



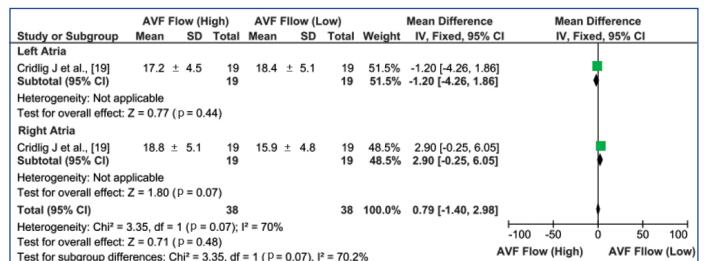
[Table/Fig-13]: Comparison of cardiac index (l/min/m²) according to AVF flow [19].



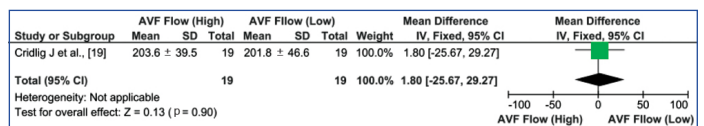
[Table/Fig-14]: Comparison of E/A ratio according to AVF flow [19].



[Table/Fig-15]: Comparison of tricuspid annular plane systolic excursion (TAPSE), left atrial diameter (LAD), pulmonary arterial pressure (PAPs) according to AVF flow [19].



[Table/Fig-16]: Comparison of AVF Area (cm²) according to AVF flow [19].



[Table/Fig-17]: Comparison of time deceleration of the E wave (TDCE) according to AVF flow [19].

DISCUSSION

Left Ventricular (LV) hypertrophy or dilatation and systolic dysfunction were common among chronic kidney disease patients [30]. AVF is a surgically created form for the chronic vascular access in haemodialysis therapy. Venous stenosis and thrombosis are associated with the failure of AVF and remains a major determinant for hospitalisation and morbidity among the haemodialysis cases [31]. Ligation of the AVF followed by renal transplantation may result the decrease in LV mass, LV and left atrial volumes, and hence there was a higher chance of reversibility of the cardiac adaptive remodeling [32]. The structural cardiac changes associated with AVF are adaptive and reversible.

In this study, the left ventricular end diastolic diameter from baseline to atleast three months of postsurgery (follow-up) differed and hence LVEDD (mm) was associated with HOHF-AVF. The combined estimate of cardiac index differed from baseline to follow-up and it indicates that cardiac index was a determinant for a HOHF-AVF. There was no difference in the overall estimates of ejection fraction (EF), PWT, and IVS. Hence, the EF (%), PWT, and IVS were not associated with the HOHF-AVF. Upper arm AVFs (flows >2000 mL/min) were associated with an increased risk of HOHF and lower peripheral resistance [33-35]. High flow within the AVF may underlie the onset of HOHF and it was characterised by a cardiac index more than 3.9 l/min/m² [27,35].

In this study, the LV systolic diameter, cardiac index and tricuspid annular plane systolic excursion were associated with AVF flow. There was no association between LV diastolic diameter, LV mass index, Ejection fraction, E/A ratio, left atrial diameter, pulmonary arterial pressure, AVF Area, and time deceleration of the "E" wave; and the AVF flow. The venous return (excessive) to the heart by high-flow AVF can provide the myocardial protection through cardiopulmonary bypass. Aortic Stenosis (AS), aortic regurgitation, mitral regurgitation and tricuspid regurgitation were common among patients on haemodialysis with a prevalence of 39-43%. However, the AVF-associated volume load of patients with valvular heart disease was limited to patients with AS [36,37].

Increased oxygen demand, structure of artery bypass graft, and CABG were the contributing factors for an AVF. Even though AVF closure is not routinely performed in patients with stable renal allograft function, it is associated with cardiac functions and survival of allograft. However, spontaneous or planned AVF closure may not yield favourable results on echocardiographic indices [37].

Limitation(s)

There is a paucity of evidence about the body mass index or obesity, signs of HOHF-AVF, and duration of AVF use. Haemodynamic stabilisers such as dietary restriction (salt and water), diuretics and vasoconstrictor adrenergic drug use have been demonstrated an effect on the creation or closure of AVF and its follow-up. However, the present findings suggest that there is a need for more clinical studies on the treatment regimens of HOHF.

CONCLUSION(S)

Left ventricular end diastolic diameter and cardiac index were found to be the major determinants for a HOHF-AVF. The left ventricular mass index, ejection fraction, posterior wall thickness, interventricular septum were not associated with HOHF-AVF. Left ventricular systolic diameter, cardiac index and tricuspid annular plane systolic excursion were the determinants of AVF flow. The ejection fraction, left atrial diameter, "E/A" ratio, pulmonary arterial pressure, AVF area, time deceleration of the "E" wave were consistent with respect to AVF flow.

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