Peer Review File

Reviewer A

This article evaluates the association of various clinical laboratory values with late failure of hemodialysis fistulas. This is a highly relevant study since finding a factor that predicts AVF failure may help identify patients at risk and even lead to new therapeutic strategies for prevention.

Several modifications and clarifications are needed throughout the manuscript.

Major:

Introduction, line 22-24. There is sufficient published evidence that questions the presumed association between intimal hyperplasia and early or late failure of AVFs. This association came from pure observation of resected AVF specimens that failed but without comparing with functional AVF samples. More recent studies have demonstrated that the vast majority of AVF present intimal hyperplasia regardless of outcomes. It is now believed that IH only leads to stenosis when combined with other wall characteristics like fibrosis that affects wall distensibility (and therefore makes IH occlusive).

Reply: Yes, we agree with you. However, IH indeed in some cases progress to stenosis, not every case.

Changes in the text: None.

Study Population, line 7-8: Was the angioplasty done to an already mature and functional fistula, or was it to facilitate maturation? Did any AVF require repeat angioplasties? If yes, was the target lesion the same? How were these cases treated in survival analyses?

Reply: We stated in the inclusion criteria that "patients with ESRD who underwent AVF angioplasty with mature AVF fistula and regular dialysis (2–3 times/week)".

Changes in the text: page 4, line 7: we added "first" in that sentence: (I) patients with ESRD who underwent first AVF angioplasty with mature AVF fistula and regular dialysis (2–3 times/week)

Results, lines 9-16: this paragraph needs reorganization. Specifically, the third sentence should be inserted after "…accounting for 34.5%." and before "Baseline patient data…".

Reply: We revised this paragraph.

Changes in the text: page 5, line 9-16: A total of 137 subjects were included in this study. In 61 patients over 60 years, there were 29 (47.5%) AVF failure, while in 76 patients ≤60 years, there were 23 (30.3%) AVF failure (P<0.05). The AVF failure group included 50

patients (64% male, 36% female), with an average age of 57.8±10.4 years. There were 87 cases in the success group (56% male, 44% female), with an average age of 52.4±13.6 years old. The most common primary disease was chronic nephritis, accounting for 34.5%. The most common primary disease was diabetic nephropathy, accounting for 38.0%. Baseline patient data is reported in Table 1.

Results, Fig 1. There are several discrepancies between this figure and Table 1 that need to be explained. In the table, CRP was around 2-4 in all individuals but the cutoff chosen for figure 1 was 20? Same issue for iPTH, approximately 50-60 in the table but a cutoff of 300 in the figure? Is this number even correct? Indicate units for values in the figure. How were those cutoffs selected? You need to show the events in the survival curves and the number of individuals at risk and censored at the time of each event under the graphs.
Reply: Sorry, we made some mistakes in figure 1. For CRP, 20 should be 2; for iPTH, 300 should be 30.
Changes in the text: We revised figure 1.

Similarly, Table 1 indicates that iPTH was significantly higher with failure; however, high iPTH was associated with better survival in the figure and in Table 2. There must be an error somewhere.
Reply: Sorry, we made a mistake. We revised the value of iPTH in table 1.
Changes in the text: Please refer to table 1, line (iPTH).

Similar to comment above, for full interpretation of Table 3 and Figure 2 you need to provide a table of numbers at risk and censored.
Reply: We added numbers in table 3. Thanks.
Changes in the text: Please refer to table 3.

Discussion, page 7 line 32-33. You need to tone down this statement. I suggest writing "Patients with low ALB may be more prone"… since you didn't actually demonstrate the rest of the statement.
Reply: Thank you for your suggestion. We added "be more" in that sentence.
Changes in the text: page 7 line 32-33: Patients with low ALB are more be more prone to AVF failure due to upregulation of procoagulant factors…

Discussion, page 7 line 2-3, in reference 22 they didn't measure venous stenosis.
Reply: Thanks. We replaced "venous stenosis" with " vascular dysfunction".
Changes in the text: page 7, line 1-3: In ESKD patients, chronic inflammation is associated with arterial intimal hyperplasia and vascular dysfunction in AVF (22).

Discussion, page 7 line 12-15 – atherosclerosis is not relevant to AVF failure

Reply: We revised these sentences.

Changes in the text: page 7, line 12-15: Several studies have shown that serum CRP concentrations were strongly associated with vascular lesions (20). Chronic inflammation is a main cause of vascular aging and calcification in CKD patients (17,25)…

Table 1 – indicate units for ALB, TC, TG ,and Hb

Reply: We added the units.

Changes in the text: table 1:

| ALB (g/L) |
| TC (mmol/L) |
| TG (mmol/L) |
| Hb (g/L) |

Table 2 – What do p-values in this table refer to?

Reply: We added a description in the footnote of table 1.

Changes in the text: page 14, line 1: *, compared with failure group, P<0.05.

Minor:

Intro, line 22 – intubation or cannulation?

Reply: cannulation. Thanks.

Data collection, line 24 – C-reactive protein

Reply: Revised. Thanks.

Results, line 21 – should be "between the AVF outcome groups".

Reply: Revised. Thanks.

1) First, the title needs to indicate the other focus of this study, cumulative patency rates of AVF.

   Reply: We added patency rates in the title. Thanks.

   Changes in the text: page 1, line 3-4: Analysis of risk factors for late arteriovenous fistula failure and patency rates after angioplasty in hemodialysis patients: a retrospective cohort study

2) Second, the abstract is not adequate. The background did not indicate the potential clinical significance of this research focus. The methods did not describe the inclusion of subjects,

the measurements of potential factors, follow up procedures, and criteria for diagnosing failed AVF and cumulative patency rates of AVF. The results need to summarize the baseline clinical characteristics of the study cohort and report the incidence rate of failed AVF. The conclusion needs comments for the clinical implications of the findings, not to repeat the findings again.

Reply: We revised some contents in the abstract. Since abstract has words limitaion, we cannot decribe those information in detail. Thanks.

Changes in the text: page 2, line 5-page 3, line 6:

Background: The incidence of chronic kidney disease (CKD) and end-stage kidney disease (ESKD) is increasing worldwide. Hemodialysis (HD) is the mainstay of renal replacement therapy for patients with ESKD. Risk factors associated with late arteriovenous fistula (AVF) failure in HD patients are poorly investigated. Therefore, the aim of this study was to identify factors associated with late AVF failure in HD patients.

Methods: Patients with end-stage renal disease (ESRD) who underwent forearm or upper arm AVF angioplasty at Honghui Hospital between September 2009 and August 2018 were included. Patients were followed up for 36 months. Baseline characteristics were collected using electronic medical records (EMRs). Variables associated with late AVF failure were identified using Cox proportional hazards models.

Results: There were 137 patients (64% male, 36% female) included in this study, with 50 (36.5%) experiencing AVF failure. Univariable log-rank analysis showed that age, C-reactive protein, erythrocyte sedimentation rate (ESR), intact parathyroid hormone (iPTH), albumin (ALB), and AVF patency rate were significantly different between patients who did and did not experience AVF failure. Cox regression analysis showed that C-reactive protein [P=0.002, hazard ratio (HR) =2.719, 95% confidence interval (CI) for HR: 1.432–5.164], ESR (P=0.030, HR =2.431, 95% CI: 1.088–5.434), iPTH (P=0.013, HR =0.325, 95% CI: 0.133–0.793), and ALB (P=0.040, HR =0.539, 95% CI: 0.299–0.972) were independently associated with AVF failure. Kaplan-Meier survival analysis showed that the cumulative patency rates of AVF at 6, 12, 18, 24, 30, and 36 months were 84%, 74%, 69%, 64%, 64%, and 64%, respectively.

Conclusions: C-reactive protein, ESR, iPTH, and ALB were associated with AVF failure and should be used as reference in clinical practice.

3) Third, in the introduction of the main text, an extensive review on factors associated with failed AVF and comments on the limitations and knowledge gaps are needed.

Reply: Dear reviewer, we discussed this point in discussion section.

Changes in the text: None.

4) Fourth, in the methodology of the main text, please describe the sample size estimation and follow up procedures. In statistics, please further clarify the methods for the selection of related factors in the multiple Cox regression analysis.

Reply: Dear reviewer, this is a retrospective cohort study, we did not do sample size **extimation. Factors for Cox were selected according to P<0.05 in univariable analysis. Changes in the text: None.**

5) Finally, please consider to review and cite some related papers: 1. Li X, Reddy SN, Clark TWI, Vance AZ. Endovascular creation of hemodialysis arteriovenous fistulae: the current status and future perspective—a literature review. Cardiovasc Diagn Ther 2023;13(1):173-189. doi: 10.21037/cdt-21-600. 2. Li Y, Cui W, Wang J, Zhang C, Luo T. Factors associated with dysfunction of autogenous arteriovenous fistula in patients with maintenance hemodialysis: a retrospective study. Ann Palliat Med 2021;10(4):4047-4054. doi: 10.21037/apm-20-2196. 3. Gonzalez TV, Bookwalter CA, Foley TA, Rajiah PS. Multimodality imaging evaluation of arteriovenous fistulas and grafts: a clinical practice review. Cardiovasc Diagn Ther 2023;13(1):196-211. doi: 10.21037/cdt-22-439.

Reply: Sure. We used 2 and 3 as reference 41 and 43 in the text. Thanks.

Changes in the text: page 13, line 4-7, and line 11-13.