Original Investigation

Systemic Profile of Cytokines in Arteriovenous Fistula Patients and Their Associations with Maturation Failure

Laisel Martinez,1 Mikael Perla,1 Marwan Tabbara,1 Juan C. Duque,2 Miguel G. Rojas,1 Nieves Santos Falcon,1 Simone Pereira-Simon,1 Loay H. Salman,3 and Roberto I. Vazquez-Padron1,4

Key Points
- Seven of 74 cytokines profiled were elevated in patients with AVF maturation failure compared with participants with successful maturation.
- G-CSF, MDC, RANTES, SDF-1, and TGFβ demonstrated significant incremental associations with AVF maturation failure by logistic regression.
- This investigation may open the doors for future therapeutics and markers for risk stratification.

Abstract

Background Systemic cytokines are elevated in patients with chronic kidney disease (CKD) and on hemodialysis compared with the general population. However, whether cytokine levels interfere with vascular remodeling, increasing the risk of arteriovenous fistula (AVF) failure, remains unknown.

Methods This is a case-control study of 64 patients who underwent surgery for AVF creation (32 with AVF maturation failure and 32 matching controls with successful maturation). A total of 74 cytokines, including chemokines, interferons, interleukins, and growth factors, were measured in preoperative plasma samples using multiplex assays. Sixty-two patients were included in the statistical analyses. Associations with AVF failure were assessed using paired comparisons and conditional logistic regressions accounting for paired strata.

Results Seven cytokines were significantly higher in patients with AVF maturation failure than in matching controls (G-CSF, IL-6, MDC, RANTES, SDF-1α/β, TGFβ, and TPO). Of these, G-CSF (odds ratio [OR] 5 1.71; 95% confidence interval [95% CI], 1.05 to 2.79 per 10 pg/ml), MDC (OR 5 1.60, 95% CI, 1.08 to 2.38 per 100 pg/ml), RANTES (OR 5 1.55, 95% CI, 1.10 to 2.17 per 100 pg/ml), SDF-1α/β (OR 5 1.18, 95% CI, 1.04 to 1.33 per 1000 pg/ml), and TGFβ (OR 5 1.39, 95% CI 1.003, 1.92 per 1 pg/ml) showed an incremental association by logistic regression.

Conclusions This study identified a profile of plasma cytokines associated with adverse maturation outcomes in AVFs. These findings may open the doors for future therapeutics and markers for risk stratification.

Introduction

CKD and hemodialysis treatments are associated with a heightened state of systemic inflammation (1,2). Plasma levels of various cytokines and growth factors are known to influence vascular function and postoperative remodeling (3–8). However, whether these components of the systemic inflammatory milieu modify venous remodeling after arteriovenous fistula (AVF) creation and contribute to access failure remains largely unknown.

There are multiple sources of inflammation that lead to elevated cytokines in patients with CKD and on hemodialysis. These include central venous catheters and dialysis itself (2,9,10), underlying comorbidities and autonomic imbalance (11,12), increased gut permeability and dysbiosis (13–15), and symptomatic or subclinical infections of various etiologies (16,17). Additional triggers include cellular senescence, oxidative stress, insulin resistance, fluid and sodium overload, hypoxia, metabolic acidosis, and bone mineral disorders (18–24). This proinflammatory state is further aggrivated by insufficient clearance of uremic toxins and cytokines by both the kidneys and hemodialysis treatments (25–28). The relationship between CKD and systemic inflammation was further demonstrated by the association between lower eGFR and higher cystatin C and albuminuria.

1DeWitt Daughtry Family Department of Surgery, Leonard M. Miller School of Medicine, University of Miami, Miami, Florida
2Katz Family Division of Nephrology, Department of Medicine, University of Miami, Miami, Florida
3Division of Nephrology, Albany Medical College, Albany, New York
4Bruce W. Carter VA Medical Center, Department of Veterans Affairs, Miami, Florida

Correspondence: Dr. Roberto I. Vazquez-Padron, Division of Vascular Surgery, University of Miami Miller School of Medicine, 1600 NW 10th Avenue, RMSB 1048, Miami, FL 33136. Email: rvazquez@med.miami.edu

www.kidney360.org Vol 3 April, 2022 Copyright © 2022 by the American Society of Nephrology
with increasing circulating levels of IL-6, TNFα, high-sensitivity C-reactive protein (hs-CRP), serum albumin, and fibrinogen (29,30). A high proinflammatory cytokine profile (high in IL-1, IL-6, and TNFα; low in IL-2, IL-4, IL-5, IL-12, total complement, and T-cell counts) was also associated with lower survival in patients on hemodialysis (31).

The vasculature is a direct target of systemic inflammation. Systemic cytokines and other inflammatory elements underlie endothelial dysfunction (32), synthetic transformation of smooth-muscle cells (SMCs) (33–36), fibroblast activation (37,38), and vascular immune cell infiltration (39,40). Clinical studies have demonstrated significant associations between low albumin and cholesterol levels, and high CRP and fibrinogen with AVF failure (41–44), but these associations have not remained significant in meta-analyses (45). Recently, elevated panel reactive antibodies, as a measure of immune system reactivity, have been found associated with AVF nonmaturation (46). Animal AVF models also support a role for IL-6, monocyte chemoattractant protein-1, and regulated on activation, normal T cell expressed and secreted (RANTES) protein in intimal thickening and reduced outward remodeling (47–50). However, whether specific cytokines and growth factors are associated with human AVF outcomes remains unknown.

In this study, we evaluate the relationship between systemic cytokines and AVF maturation failure. Our findings may open the doors to new therapeutic approaches, personalized medicine, and improved risk stratification and vascular access planning in patients on hemodialysis.

**Materials and Methods**

**Study Design**

This was a case-control study to analyze the associations between plasma cytokines and AVF maturation outcomes. Patients with CKD aged ≥21 years and scheduled for AVF creation surgery at Jackson Memorial Hospital and University of Miami (UM) Hospital from February 2018 to March 2020 were invited to participate in the study. Following our surgical protocol, we used the most peripheral vein with an internal luminal diameter ≥3.5 mm, the brachial artery if ≥4 mm, or the radial artery if ≥2.5 mm (51). Blood was collected from 96 consented individuals at the time of AVF creation using EDTA Vacutainer tubes (Becton, Dickinson and Company, Franklin Lakes, NJ) and centrifuged at 2000 g for 15 minutes at 4°C for plasma isolation (Figure 1). Plasma samples were stored at –80°C. All patients with anatomic AVF maturation failure were retrospectively selected (N=32) from the cohort. Anatomic maturation failure was defined as an AVF that never achieved an internal luminal diameter ≥6 mm as determined during postsurgical follow-up and/or transposition surgeries (51). Blood was collected from 96 consented individuals at the time of AVF creation using EDTA Vacutainer tubes (Becton, Dickinson and Company, Franklin Lakes, NJ) and centrifuged at 2000 g for 15 minutes at 4°C for plasma isolation (Figure 1). Plasma samples were stored at –80°C. All patients with anatomic AVF maturation failure were retrospectively selected (N=32) from the cohort. Anatomic maturation failure was defined as an AVF that never achieved an internal luminal diameter ≥6 mm as determined during postsurgical follow-up and/or transposition surgeries (51). All AVF that failed required endovascular and/or surgical salvage procedures or ligation. An equal number of patients with successful maturation was retrospectively selected from the cohort using propensity score matching on the basis of patient age, sex, ethnicity, diabetes, and predialysis status. One-to-one matches were generated by applying a greedy algorithm and Mahalanobis distance. The study was performed according to the ethical principles of the Declaration of Helsinki and regulatory requirements at Jackson Memorial Hospital and UM. The ethics committee and UM Institutional Review Board approved the study.

**Multiplex Cytokine/Chemokine and hs-CRP Assays**

Undiluted plasma samples were profiled using the 71-plex Human Cytokine/Chemokine Discovery Assay (catalog no. HD71) and the 3-plex TGFβ Array (catalog no. TGFB1–3) by Eve Technologies Corporation (Calgary, Canada). For the purposes of statistical analysis, values below the quantification limit (QL) were assigned the minimum
Table 1. Baseline characteristics of the study cohort

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Matured (N=31)</th>
<th>Failed (N=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yr, mean±SD</td>
<td>58.16±12.37</td>
<td>59.06±13.30</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>11 (35)</td>
<td>14 (45)</td>
</tr>
<tr>
<td>Hispanic, n (%)</td>
<td>15 (48)</td>
<td>14 (45)</td>
</tr>
<tr>
<td>Black, n (%)</td>
<td>11 (35)</td>
<td>12 (39)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>5 (16)</td>
<td>5 (16)</td>
</tr>
<tr>
<td>Comorbidities and laboratory values</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>31 (100)</td>
<td>27 (87)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>20 (65)</td>
<td>18 (58)</td>
</tr>
<tr>
<td>CHF, %</td>
<td>8 (26)</td>
<td>6 (19)</td>
</tr>
<tr>
<td>ASCVD, n (%)</td>
<td>14 (45)</td>
<td>13 (42)</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>19 (61)</td>
<td>14 (45)</td>
</tr>
<tr>
<td>History of smoking, n (%)</td>
<td>10 (32)</td>
<td>14 (45)</td>
</tr>
<tr>
<td>BMI, kg/m², mean±SD</td>
<td>27.64±5.21</td>
<td>27.35±5.36</td>
</tr>
<tr>
<td>WBC count, 10³/µl, mean±SD</td>
<td>7.62±2.63</td>
<td>6.92±2.58</td>
</tr>
<tr>
<td>Fasting plasma glucose, mg/dl, median (IQR)</td>
<td>109 (89.8–175.5)</td>
<td>129.5 (88.3–173)</td>
</tr>
<tr>
<td>hs-CRP, mg/L, median (IQR)</td>
<td>6.82 (1.49–13.35)</td>
<td>15.68 (4.29–31.42)</td>
</tr>
<tr>
<td>Vascular access and HD history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predialysis, n (%)</td>
<td>4 (13)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Previous AVF, n (%)</td>
<td>5 (16)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>HD vintage, mo, median (IQR)</td>
<td>4.27 (2.40–6.46)</td>
<td>4.60 (2.33–7.82)</td>
</tr>
<tr>
<td>High-flux dialyzer use, n (%)</td>
<td>25/27 (93%)</td>
<td>24/27 (89%)</td>
</tr>
<tr>
<td>AVF features</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BC, n (%)</td>
<td>10 (32)</td>
<td>11 (35)</td>
</tr>
<tr>
<td>BB, n (%)</td>
<td>13 (42)</td>
<td>13 (42)</td>
</tr>
<tr>
<td>BBr, n (%)</td>
<td>2 (6)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Other anastomosis, n (%)</td>
<td>6 (19)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Left arm, n (%)</td>
<td>27 (87)</td>
<td>23 (74)</td>
</tr>
<tr>
<td>Preaccess vein diameter, mm, median (IQR)</td>
<td>4 (4–4)</td>
<td>4 (4–4)</td>
</tr>
</tbody>
</table>

ASCVD, atherosclerotic cardiovascular disease; AVF, arteriovenous fistula; BB, brachiobasilic; BBr, brachiobrachial; BC, brachiocephalic; BMI, body mass index; CHF, congestive heart failure; HD, hemodialysis; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; WBC, white blood cell. ASCVD was defined as having a history of coronary artery disease, peripheral arterial disease, transient ischemic attack, or stroke.

Statistical Analyses

Statistical analyses were performed using GraphPad Prism v8.4 (GraphPad Software, San Diego, CA) and the “survival” package in R (52). Statistical differences between the failure and maturation groups were assessed using Wilcoxon matched pairs signed rank tests and paired t tests. The Benjamini–Hochberg method (also known as FDR) was used to correct for multiple testing (53). An FDR<0.1 was considered statistically significant. Odds ratios (OR) were calculated using conditional logistic regressions accounting for paired strata.

Results

Demographics, Clinical, and AVF Characteristics of the Study Population

The preoperative plasma levels of 74 cytokines were quantified in a case-control study of 64 patients who underwent surgery for AVF creation (32 with AVF maturation failure and 32 matching controls with successful maturation; Figure 1). One pair of patients was excluded from the statistical analyses due to undetectable cytokine levels in 46 out of 74 tests in one of the samples. The baseline characteristics of the remaining 31 pairs are included in Table 1. Patients in both the failed and matured subgroups had a mean age of 58–59 years, 35%–45% were women, and they were predominantly of Hispanic (45%–48%) and Black ancestry (35%–39%). Comorbidities were similarly represented in both subgroups, including hypertension (87%–100%), diabetes (58%–65%), congestive heart failure (19%–26%), atherosclerotic cardiovascular disease (42%–45%), hyperlipidemia (45%–61%), and history of smoking (32%–45%). Both study arms also had similar distributions of body mass index (P=0.82), fasting plasma glucose (P=0.59), white blood cell count (P=0.27), and hs-CRP (P=0.35).

Thirteen percent of the patients were still in predialysis, whereas 13%–16% had a history of a previous AVF. Dialysis vintage was similar between the groups (P=0.76). In addition, at least 89%–93% of those already on hemodialysis and followed by our team used either the Optiflux quantification limit value. High-sensitivity CRP was measured by ELISA (catalog no. RAB0096–1KT; Sigma–Aldrich, St. Louis, MO) in 1:20,000 diluted plasma according to the manufacturer’s recommendations.
F160NR or F180NR high-flux dialyzers. The types of AVF created and the diameter of the native vein selected for surgery were also similar in both arms of the study (Table 1). Lastly, none of the study participants were on hemodialysis at the time of AVF creation or during the period of maturation.

Preoperative Cytokines Levels and Association with AVF Failure

Plasma cytokine levels in the patient population ranged from ≤1 pg/ml (IL-2, IL-4, IL-10, vascular endothelial growth factor A) to ≥10,000 pg/ml (MIG/CXCL9, PDGF-AB/BB, SDF-1α/β, TGFβ1; Figure 2A, Supplemental Table 1). For the most part, there were no significant correlations between cytokines in circulation or with respect to hs-CRP (Figure 2B), suggesting different cell sources, clinical characteristics, or disease processes responsible for their elevation. Exceptions included a cluster of growth factors (PDGF-AA, PDGF-AB/BB, TGFβ1, and TGFβ2) and small groups of interleukins and other cytokines (sCD40L and ENA-78; IL-3 and IL-4; IL-1β, IL-17A, and IFN-α2; IL-13, TNFβ, and monocyte chemotactant protein-3; IL-2 and IFN-γ). An extreme outlier was detected in 27 out of 74 tests (Grubb’s test alpha=0.0001; Figure 1A), and this pair was removed from the corresponding linear regression models and comparative analyses.

Seven cytokines were significantly higher in individuals with AVF maturation failure than in matching controls (Figure 3A, Supplemental Table 1), including highly abundant factors with median levels ≥500 pg/ml (MDC, RANTES, and SDF-1α/β). Five cytokines (G-CSF, MDC, RANTES, SDF-1α/β, and TGFβα) also demonstrated an incremental association by logistic regression (Table 2), which remained significant after adjusting for hs-CRP and dialysis vintage, with the exception of TGFβa. This suggests that the higher these factors are found in blood, the higher the likelihood of AVF maturation failure.

Interestingly, higher plasma levels of G-CSF were significantly associated with women (β coefficient 0.430 [95% confidence interval 0.140 to 0.720]), smoking history (0.359 [0.066 to 0.651]), and predialysis status (0.433 [0.155 to 0.710]; Figure 3B). The latter was also associated with increased IL-6 (0.335 [0.053 to 0.618]) and MDC (0.343 [0.052 to 0.635]). Increased thrombopoietin (TPO) levels were associated with smoking history (0.323 [0.044 to 0.638 to...
likely reflecting reduced liver function in older individuals. Lastly, higher levels of both RANTES (0.355 [0.062 to 0.647]) and SDF-1α/β (0.346 [0.050 to 0.642]) were significantly associated with dialysis vintage. The lack of significant correlations between these cytokines (Figure 2B) and the different effects of baseline covariates on their plasma concentrations (Figure 3B) highlight the complexity of clinical factors in the hemodialysis population and the multifactorial mechanisms that may contribute to AVF failure.

Discussion
Systemic inflammation is considered a catalyst for postoperative vascular complications. Various inflammatory cytokines have shown significant associations with vascular proliferative processes such as restenosis after percutaneous coronary interventions and vein graft failure (3,4,54). Therefore, it is plausible to hypothesize a positive relationship between systemic cytokine concentrations and increased risk of AVF failure. Herein, we identified a group of circulating cytokines with preoperative levels significantly elevated in patients with AVF maturation failure (G-CSF, IL-6, MDC, RANTES, SDF-1α/β, TGFα, and TPO). Out of these, G-CSF, MDC, RANTES, SDF-1α/β, and TGFα also showed an incremental association in logistic regressions (i.e., the higher the cytokine level, the higher the risk of failure).

Failure of the AVF happens secondary to a combination of wall fibrosis and excessive intimal expansion (55). However, the mechanisms that initiate or contribute to maladaptive remodeling early after AVF creation remain unknown (56). We have found cytokines associated with AVF failure that have been previously implicated in adverse vascular remodeling. IL-6, for instance, activates endothelial cells (ECs) and fibroblasts, induces SMC proliferation and migration, and enhances immune cell infiltration (57). PBMCs from patients with AVF failure produce more IL-6 than dialysis age-matched controls (58). Interestingly, activation of the IL-6 receptor in ECs of the adventitial neovasculature is commonly found in stenotic AVFs (58). TGFα, in turn, is proangiogenic and serves as a transducer of mechanosensitive NFκB proinflammatory

---

**Figure 3.** Plasma cytokines associated with AVF maturation failure. (A) Cytokines and chemokines significantly elevated in plasma of individuals with arteriovenous fistula maturation failure (cases) compared with matched controls (successful maturation) at a false discovery rate of <0.1. Groups were compared using Wilcoxon matched pairs signed rank tests or paired t tests. Unadjusted P values are shown. (B) Associations of significant cytokines with baseline characteristics using multivariate general linear regression models. Dots represent the β coefficient; whiskers mark the confidence interval.
signaling in response to high blood pressure (59–61). G-CSF increases proliferation and migration of ECs and SMCs, inhibits nitric oxide signaling, and is chemotactic for immune cells (8,62,63). There is also increasing evidence of SMCs, inhibits nitric oxide signaling, and is chemotactic for immune cell in veins that failed to mature after AVF creation (65), suggesting a potential synergistic effect in maturation failure.

Along with the above factors, the remaining failure-related cytokines have also shown pleiotropic effects on vascular remodeling. For example, SDF-1 promotes recruitment of EC and SMC progenitors, increases proliferation and collagen production of SMCs and fibroblasts, and increases platelet aggregation (66–71). RANTES plays critical roles in EC and SMC recruitment for neovascularization (72,73), increases immune cell infiltration (74), and induces SMC phenotypic switching from the contractile to the synthetic phenotype (75). Macrophage-derived chemokine also contributes to immune cell infiltration (76) and platelet aggregation (71), whereas TPO is the chief regulator of platelet production and priming with proangiogenic activity (77,78).

Despite the lack of correlation between the plasma levels of all of these factors, they share potential vascular effects in common such as immune cell infiltration, neovascularization, and platelet aggregation. The role of immune cell infiltration in early AVF remodeling is not clear at the moment (56). However, an exaggerated response to injury may affect the proper healing of the vascular wall. Adventitial vascularization increases significantly after access creation (79), but how much it contributes to wall remodeling is also an open question. Animal studies support a role for hypoxia-driven angiogenic signaling in intimal expansion (80,81), but prominent vascularization of the intima is not evident in human two-stage AVFs (79). Nonetheless, excessive vascularization early after surgery (and that resolves later on) may be linked to myofibroblast activation and fibrotic remodeling as a response to oxidative stress. Early thrombosis is a relatively infrequent complication (2%–5%) after AVF creation surgery, but it can occur in association with small vein diameter, stenosis, and poor intraoperative thrill (82,83).

The sources and triggers of these circulating factors are not clear at the moment because many of them are ubiquitously produced by hematopoietic and nonhematopoietic cells (58,59,70,76,84–86). Immune cell phenotyping studies are needed to assess activation of leukocyte populations

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Odds Ratio (Confidence Interval)a</th>
<th>Odds Ratio (Confidence Interval)b</th>
<th>Main Cellular Sourcesc</th>
<th>Potential Vascular Effectsc</th>
</tr>
</thead>
<tbody>
<tr>
<td>G-CSF</td>
<td>1.71 (1.05 to 2.79)</td>
<td>1.64 (1.02 to 2.64)</td>
<td>Monocytes/macrophages, bone marrow stromal cells, endothelial cells, fibroblasts</td>
<td>Hematopoietic stem cell mobilization, endothelial cell activation, proangiogenic, prothrombotic</td>
</tr>
<tr>
<td>IL-6</td>
<td>1.15 (0.98 to 1.36)</td>
<td>1.14 (0.96 to 1.36)</td>
<td>Monocytes/macrophages, endothelial cells, smooth muscle cells, fibroblasts</td>
<td>Proinflammatory, immune cell recruitment, endothelial cell activation and dysfunction, proinflammatory, proangiogenic</td>
</tr>
<tr>
<td>MDC</td>
<td>1.60 (1.08 to 2.38)</td>
<td>1.76 (1.12 to 2.78)</td>
<td>Dendritic cells, macrophages, NK cells, B cells, T cells</td>
<td>Proinflammatory, platelet aggregation, immune cell recruitment</td>
</tr>
<tr>
<td>RANTES</td>
<td>1.55 (1.10 to 2.17)</td>
<td>1.45 (1.03 to 2.06)</td>
<td>T cells, macrophages, platelets, adipocytes</td>
<td>Proinflammatory, proangiogenic, immune cell recruitment, SMC proliferation and synthetic switch</td>
</tr>
<tr>
<td>SDF-1α/β</td>
<td>1.18 (1.04 to 1.33)</td>
<td>1.31 (1.07 to 1.60)</td>
<td>Bone marrow stromal cells, monocytes, liver</td>
<td>Progenitor cell mobilization, proangiogenic, platelet aggregation, profibrotic, SMC proliferation and chemotaxis</td>
</tr>
<tr>
<td>TGFα</td>
<td>1.39 (1.003 to 1.92)</td>
<td>1.34 (0.98 to 1.83)</td>
<td>Monocytes/macrophages, epithelial cells</td>
<td>Proangiogenic, endothelial cell migration, mechanosensitive signaling</td>
</tr>
<tr>
<td>TPO</td>
<td>1.10 (0.97 to 1.25)</td>
<td>1.08 (0.96 to 1.22)</td>
<td>Liver, kidney</td>
<td>Platelet priming, proangiogenic</td>
</tr>
</tbody>
</table>

CI, confidence interval; G-CSF, granulocyte colony-stimulating factor; IL-6, interleukin 6; MDC, macrophage-derived chemokine; OR, odds ratio; RANTES, regulated on activation, normal T cell expressed and secreted; SDF-1α/β, stromal cell-derived factor 1 alpha and beta; TGFα, transforming growth factor alpha; TPO, thrombopoietin.

a ORs and CIs indicate increased risk per 1 pg/ml increment of IL-6 and TGFα; 10 pg/ml increment of G-CSF; 100 pg/ml increment of MDC, RANTES, and TPO; and 1000 pg/ml increment of SDF-1α/β.

b Adjusted by high-sensitivity C-reactive protein and hemodialysis vintage.

c References for cellular sources and vascular effects are cited in the Discussion.
and the balance of inflammatory and regulatory cells. Hemodialysis treatments can also affect circulating cytokines in both directions. Recent dialyzer and membrane innovations can potentially allow for better clearance of cytokines during treatment (87,88). On the other hand, hemodialysis may contribute to maintaining inflammation through increases in oxidative imbalance and acetatemia; absorption, back-diffusion/filtration, or nonelemiation of proinflammatory molecules; and direct or indirect stimulation of monocytes via endotoxins and other pyrogens or complement activation (2,89,90). Attempts at increasing cytokine clearance with newer hemodialysis modalities have been inconsistent, which highlights the complexity of cytokine production and clearance in this population (27,28,91,92). More than 85% of patients in our study were already on hemodialysis before AVF creation but were equally represented in both study arms. In addition, the vast majority of those already on hemodialysis were using high-flux dialyzers. Three of the cytokines associated with failure had a positive association with predialysis status (G-CSF, IL-6, and MDC), suggesting that they may be removed with treatment. In contrast, RANTES and SDF-1 were positively associated with dialysis vintage. Future studies with a larger number of predialysis patients and with plasma collected at different time points after dialysis may help clarify the role of hemodialysis on cytokines that are associated with AVF failure.

The identification of blood inflammatory markers associated with AVF maturation failure can have significant implications for the design of preventive therapies, risk stratification of patients, and vascular access planning. Analysis of these cytokines in a larger and more diverse study population would pave the way toward the development of a much-needed biomarker to help stratify preoperative risk and choose the best hemodialysis access for patients on the basis of an individual benefit-risk assessment. Confirmatory associations in study participants with postoperative parameters of AVF remodeling (AVF diameter, blood flow, stenosis), such as the Hemodialysis Fistula Maturation cohort (93), would lend support to a causative relationship that can be further explored in preclinical models. Lastly, a detailed analysis of the net effect of dialysis on causative cytokines (elevation versus clearance) would allow planning of AVF creation with respect to initiation or schedule of RRT.

The limitations of this study include the small number of patients, retrospective design, and single-center enrollment of study participants, all of which could affect the generalizability of our findings. Despite these limitations, to our knowledge, this is the first clinical study to screen for more than 70 cytokines and chemokines in patients with CKD and their associations with AVF failure.

Scientific Reports, and has other interests/relationships with the National Institutes of Health and American Heart Association study sections. All remaining authors have nothing to disclose.

Funding
This study was supported by the National Institutes of Health (grant R01-DK098511 to L.H. Salman and R.I. Vazquez-Padron, grant R01-DK121227 to R.I. Vazquez-Padron, and grant K08-HL151747 to L. Martinez) and the VA Merit Award (grant IBX004658 to R.I. Vazquez-Padron).

Author Contributions
J.C. Duque, L. Martinez, L.H. Salman, and R.I. Vazquez-Padron conceptualized the study; J.C. Duque, L. Martinez, M. Perla, L.H. Salman, M. Tabbara, and R.I. Vazquez-Padron were responsible for the investigation and reviewed and edited the manuscript; L. Martinez, M.G. Rojas, and N. Santos Falcon curated the data; L. Martinez, M.G. Rojas, and R.I. Vazquez-Padron conducted the formal analysis; L. Martinez and R.I. Vazquez-Padron were responsible for funding acquisition, project administration, and supervision; L. Martinez, S. Pereira-Simon, M.G. Rojas, N. Santos Falcon, M. Tabbara, and R.I. Vazquez-Padron were responsible for the methodology; L. Martinez and M.G. Rojas were responsible for visualization; L. Martinez and M. Perla wrote the original draft of the manuscript; S. Pereira-Simon was responsible for validation; and M. Tabbara and R. Vazquez-Padron were responsible for resources.

Data Sharing Statement
All data are included in the manuscript and/or supporting information.

Supplemental Material
This article contains the following supplemental material online at http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.000602021/./DCSupplemental.

Supplemental Table 1. Statistical comparisons of 74 cytokines and chemokines by arteriovenous fistula maturation outcome.

References


