Frailty score before admission as risk factor for mortality of renal patients during the first wave of the COVID pandemic in London

L'epidemia Covid-19: diario di bordo di una emergenza

Dr. Aegida Neradova[1,2], Dr. Gisele Vajgel[3,4,5], Heidy Hendra[1,3], Dr. Marilina Antonelou[1,3], Dr. Ioannis D. Kostakis[6], David Wright[1], Dr. Philip Masson[1], Sarah E. Milne[1], Dr. Gareth Jones[1], Prof. Dr. Alan Salama[1,3], Prof. Dr. Andrew Davenport[1], Prof. Dr. Áine Burns[1]


Aegida Neradova

1 Department of Nephrology & Transplantation, Royal Free London NHS Foundation Trust, UK
2 Dianet Amsterdam, Amsterdam UMC Department of Nephrology, Amsterdam, The Netherlands
3 Department of Renal Medicine, Royal Free Campus, UCL, Rowland Hill Street, London, UK
4 Nephrology Department, Hospital das Clinicas - Federal University of Pernambuco (HC-UFPE), Brazil
5 Laboratório Imunopatologia Keizo Azami - Federal University of Pernambuco (LIKA/UFPE), Brazil
6 Department of HPB Surgery and Liver Transplantation, Royal Free Hospital, Royal Free London NHS Foundation Trust, London, UK

Contact details:
Aegida Neradova
Dianet Amsterdam, Amsterdam UMC Department of Nephrology
Meibergdreef 7
1105 AZ Amsterdam, The Netherlands
Tel/Fax 0031205669111, 0031208888729
E-mail: a.neradova@amsterdamumc.nl

ABSTRACT

Background: Frailty is a known predictor of mortality and poor outcomes during hospital admission. In this large renal retrospective cohort study, we investigated whether frailer COVID-19 positive renal patients had worse outcomes.

Design: All SARS-Cov-2 positive renal patients aged ≥18 years who presented to the emergency department at the Royal Free Hospital or at the satellite dialysis centres from 10th of March until the 10th of May 2020, with recent data on frailty, were included. The follow up was until 26th of May 2020. Age, gender, ethnicity, body mass index, chronic kidney disease stage, modality of renal replacement therapy, co-morbidities, Rockwood clinical frailty score (CFS), C reactive protein and the neutrophil-to-lymphocyte count were collected at presentation. The primary outcome was the overall mortality rate following COVID-19 diagnosis. Secondary outcomes included the need for hospital admission.

Results: A total of 200 renal patients were SARS-Cov-2 positive. In the 174 patients who had a CFS recorded, the age was 65.4 years ± 15.8 (mean ± SD) and 57,5% were male. At the end of follow up, 26% had died. Frail patients (CFS 5-7) were more than three times more likely to die compared to less frail patients (CFS of 1-4) (odds ratio (OR) 3.3, 95% confidence interval (CI) 1.0-10.6). 118 patients (68%) required admission, but there was no difference in hospital admission rates for frail vs non-frail patients (OR 0.6, CI 0.3-1.7).

Conclusions: Frailty is a better predictor of mortality than age and co-morbidities in COVID-19 positive renal patients.

KEYWORDS: frailty, renal patients, SARS-Cov-2

Introduction

Frailty is defined as a biologic syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems and causing vulnerability to adverse outcomes [1].

In a recent systematic review of 32 articles (36,076 participants) the prevalence of frailty ranged from 7% in chronic kidney disease (CKD) stages 1-4 up to 73% in patients on haemodialysis and was associated with increased risk of mortality and hospitalisation [2].

Frailty is not only a challenge for the elderly on renal replacement therapy (RRT). In a prospective cohort of 146 haemodialysis patients, 56.2% were younger than 65 years and 35% were frail, described as a combination of weight loss, weakness, exhaustion and slowed walking speed. In the whole cohort, frailty was associated with a higher risk of death, 2.60-fold (95% CI: 1.04-6.49, *P*=0.041), and a higher chance of hospitalisation [3]. Clinical frailty scale (CFS) is a clinical scale ranging from one (very fit) up to nine (terminally ill) [4].

In the National Institute for Health and Care Excellence (NICE) guideline for COVID-19 positive patients, the use of CFS is recommended to guide the decision-making process on whether to admit a patient to the intensive care unit or not [5]. According to this guideline, frailty score was associated with in-hospital mortality in a retrospective cohort of 1564 patients [6].

The CFS has been recorded since 2016 for the renal patients at the Royal Free Hospital, so frailty data were available for most patients admitted with COVID-19 infection. The aim of this study was to determine whether preexisting frailty was a risk factor for hospital admissions and mortality in renal patients in the first wave of the COVID pandemic.

Material and methods

Ethics statement

This study was conducted in accordance with the principles of the Declaration of Helsinki. This study was approved by the NHS ethics committee 20/SW/0077.

Individual patient consent was waved, and data anonymised.

Study population

All SARS-Cov-2 positive renal patients (dialysis 88.5%, CKD patients 7.5% and transplant recipients 4%) aged ≥18 years who presented to the emergency department at the Royal Free Hospital or at the satellite dialysis centres between 10th of March and the 10th of May 2020 and with prior data on frailty were included in the analysis.

Patient outcomes were followed until 26th of May 2020.

Data collection and measurements

Age, gender, ethnicity, body mass index (BMI), CKD stages, modality of renal replacement therapy (including kidney transplantation), history of diabetes, hypertension, coronary artery disease, chronic lung disease, historical clinical frailty scale (CFS), C-reactive protein (CRP) and the neutrophil-to-lymphocyte count (NLR) were collected at presentation.

Quantitative real-time PCR (RT-PCR) assay of nasopharyngeal swab were utilised for detection of SARS-Cov-2, using a UK Public Health Authority approved assay. CRP and the neutrophil-to-lymphocyte count (NLR) were measured by standard laboratory techniques.

Outcomes

The primary outcome was the overall mortality rate following a COVID-19 diagnosis. Secondary outcomes included the need for hospital admission due to respiratory failure.

Statistical Methods

Patients were divided in two groups according to their frailty score (group 1: score 1-4, non-frail; group 2: score 5-7, frail). There were no patients with a frailty score >7.

Normality of data distribution was assessed using the Shapiro-Wilk test. Comparisons among these two groups were performed using the analysis of variance (ANOVA) or the Kruskal-Wallis test for quantitative parameters and the Chi-squared test or the Fisher's exact test for qualitative parameters.

Logistic regression analysis was performed in order to assess how much each of the included parameters affects the need for admission and mortality. All the tests were two-tailed.

The 25th edition of the Statistical Package for Social Sciences (SPSS) (IBM Corporation, Armonk, NY, USA) was used for the statistical analysis. The statistical models were adjusted for gender, age, ethnicity, presence of obesity, diabetes mellitus, hypertension, coronary heart disease and chronic lung disease, renal treatment group (CKD, dialysis, transplant), as well as NLR and CRP on presentation.

Results

200 SARS-Cov-2 positive renal patients were admitted during the study period. 174 patients had a prior CFS score recorded (Figure 1). There were 154 dialysis patients, 13 patients with CKD and 7 kidney transplant recipients. Of the 26 patients who did not have a frailty score recorded 16 (61.5%) had CKD, 2 (7.7%) were on dialysis and 8 (30.8%) were transplant recipients.

The majority of patients were >65-year-old and male (57.5%); 37.4% were black (Table I).

The most common comorbidities were hypertension (82.8%) and diabetes (55.2%). Obesity was considered as a BMI ≥30 and was present in 35.3%. The mean CFS was 4.8 ± 1.5 (mean ± SD). Patients with a frailty score of 5-7 were older, had more diabetes, coronary disease, chronic pulmonary disease and a higher CRP levels compared to those patients with a frailty score of 1-4 (Table I).

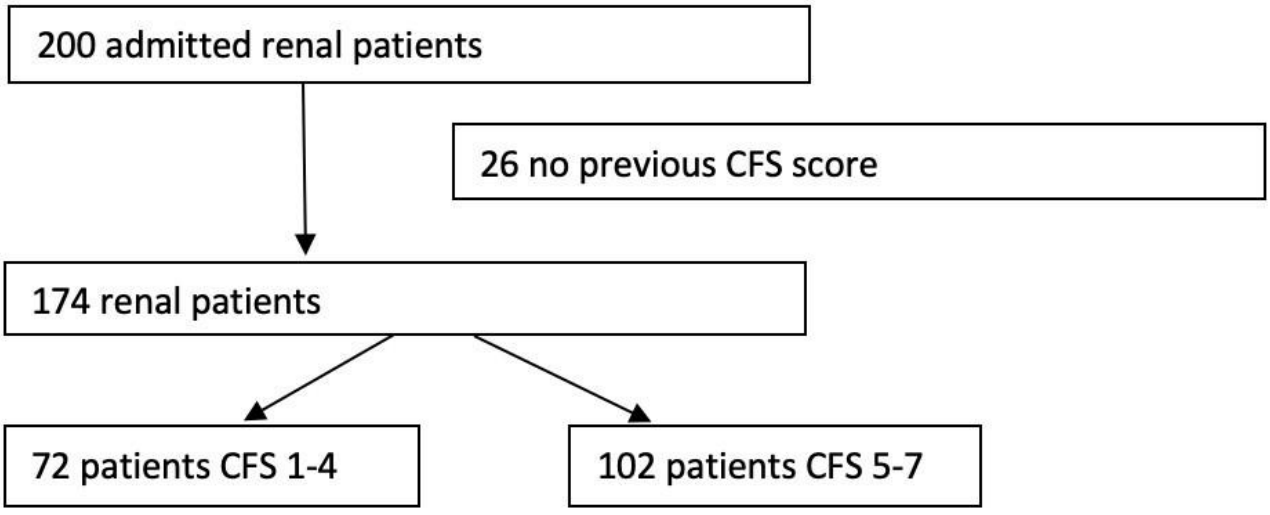

Figure 1: Number of patients in the cohort

Parameter	All patients	Frailty score 1-4 (N=72)	Frailty score 5-7 (N=102)	P-value
Gender				
Male	100 (57.5%)	42 (58.3%)	58 (56.9%)	
Female	74 (42.5%)	30 (41.7%)	44 (43.1%)	0.847
Age (years)				
Mean ± SD	65.4 ± 15.8	56.3 ± 14.5	71.5 ± 13.6	
Median (min-max)	67 (20-99)	55 (20-86)	73 (29-99)	**<0.001**
Ethnicity				
White	61 (35.1%)	27 (37.5%)	34 (33.3%)	
Black	65 (37.4%)	32 (44.4%)	33 (32.4%)	
Asian	48 (27.6%)	13 (18.1%)	35 (34.3%)	0.052
Obesity				
No	110 (64.7%)	48 (66.7%)	62 (63.3%)	
Yes	60 (35.3%)	24 (33.3%)	36 (36.7%)	0.647
Renal group				
CKD	13 (7.5%)	4 (5.6%)	9 (8.8%)	
Dialysis	154 (88.5%)	62 (86.1%)	92 (90.2%)	
Transplant	7 (4%)	6 (8.3%)	1 (1%)	0.052
Diabetes mellitus				
No	78 (44.8%)	41 (56.9%)	37 (36.3%)	
Yes	96 (55.2%)	31 (43.1%)	65 (63.7%)	**0.007**
Hypertension				
No	30 (17.2%)	15 (20.8%)	15 (14.7%)	
Yes	144 (82.8%)	57 (79.2%)	87 (85.3%)	0.292
Coronary disease				
No	120 (69%)	57 (79.2%)	63 (61.8%)	
Yes	54 (31%)	15 (20.8%)	39 (38.2%)	**0.015**
Chronic lung disease				
No	151 (86.8%)	67 (93.1%)	84 (82.4%)	
Yes	23 (13.2%)	5 (6.9%)	18 (17.6%)	**0.04**
NLR				
Mean ± SD	8.2 ± 10.8	6.9 ± 7.4	9.1 ± 12.5	
Median (min-max)	5.5 (0.3-78.8)	5.4 (0.8-50.2)	5.7 (0.3-78.8)	0.437
CRP				
Mean ± SD	93.7 ± 86.4	71.7 ± 78.5	108.5 ± 88.7	
Median (min-max)	62.5 (1-402)	40 (1-402)	82 (3-346)	**0.002**
Frailty score				
Mean ± SD	4.8 ± 1.5			
Median (min-max)	5 (1-7)			

Table I: Patient characteristics and analysis frailty scores

Mortality

At the end of follow up, 26% (44/174) of the patients had died. Except for 2 patients, all died within 28 days of follow up. The crude odds ratio (OR) for mortality was 5.3 (95% CI 2.2-12.7; p <0.001) for CFS 5-7 compared with CFS of 1-4.

Compared to patients younger than 65 years, the crude OR was 2.6 (95% CI 1.2-5.7; p=0.013) for those aged 65-80 years and 4.5 (95% CI 2.0-10.4; p <0.001) for those aged >80. The presence of coronary disease, chronic lung disease, NLR >10 and CRP >50 mg/L at presentation were also associated with increased mortality in the unadjusted analysis (Table II). After adjusting for other

factors, frailty was associated with mortality for CFS 5-7 OR 3.3 (95% CI 1.0-10.6) compared with CFS 1-4. The only other factors that remained statistically significant were a NLR >10 and CRP >50 mg/L (Table II). There was no significant difference between the number of admissions to the intensive care unit for the frail (4.9%) versus the non-frail (12.5%) patients (p=0.07).

Parameter	Unadjusted			Adjusted		
	OR	95% CI	P-value	OR	95% CI	P-value
Frailty score (reference: 1-4)						
5-7	5.286	2.197-12.717	**<0.001**	3.311	1.033-10.607	**0.044**
Gender (reference: male)						
Female	0.612	0.316-1.188	0.147	0.828	0.302-2.266	0.713
Age (reference: ≤65)						
65-80	2.635	1.226-5.665	**0.013**	0.731	0.223-2.395	0.604
>80	4.527	1.972-10.392	**<0.001**	3.162	0.773-12.94	0.109
Ethnicity (reference: White)						
Black	0.591	0.271-1.292	0.188	0.737	0.239-2.273	0.595
Asian	1.164	0.547-2.474	0.693	0.808	0.246-2.657	0.726
Obesity (reference: no)						
Yes	0.583	0.277-1.228	0.156	0.786	0.269-2.303	0.661
Renal group (reference: CKD)						
Dialysis	0.633	0.271-1.478	0.291	5.172	0.47-56.913	0.179
Transplant	0.691	0.174-2.738	0.599	4.788	0.137-167.752	0.388
Diabetes mellitus (reference: no)						
Yes	1.213	0.643-2.29	0.552	0.97	0.331-2.836	0.955
Hypertension (reference: no)						
Yes	0.898	0.411-1.962	0.788	1.365	0.336-5.549	0.663
Coronary disease (reference: no)						
Yes	2.552	1.321-4.93	**0.005**	2.607	0.875-7.762	0.085
Chronic lung disease (reference: no)						
Yes	3.017	1.278-7.123	**0.012**	1.524	0.442-5.252	0.504
NLR (reference: ≤10)						
>10	6.776	2.866-16.023	**<0.001**	4.87	1.376-17.24	**0.014**
CRP (reference: ≤50)						
>50	6.502	2.846-14.855	**<0.001**	4.442	1.556-12.676	**0.005**

Table II: Mortality

Hospital admission

118 patients (68%) required hospital admission. All patients were admitted within one week of the positive COVID test except for 3 (respectively after 8, 9, and 15 days). The crude OR for hospital admission for CFS 5-7, compared with CFS of 1-4, was 1.6 (95% CI 0.85-3.0; p=0.15). Hospital admission was greater for those aged 65-80 years compared to patients younger than 65 (crude OR was 1.6 (95% CI 0.8-3.2; p=0.168)) and even higher for those aged >80 (OR 12.6 (95% CI 2.9-55.1; p=0.001)).

NLR >10 and CRP >50 mg/L were also associated with a greater need for hospital admission, as was treatment by haemodialysis.

However, the dialysis group was the largest, and the frailty scores were higher. After adjusting for other covariates, only age >80 years and CRP >50 mg/L remained independent factors associated with hospital admission (Table III).

Parameter	Unadjusted			Adjusted		
	OR	95% CI	P-value	OR	95% CI	P-value
Frailty score (reference: 1-4)						
5-7	1.602	0.845-3.038	0.149	0.693	0.287-1.676	0.416
Gender (reference: male)						
Female	0.736	0.398-1.36	0.327	0.943	0.411-2.166	0.89
Age (reference: ≤65)						
65-80	1.616	0.817-3.194	0.168	1.292	0.52-3.212	0.581
>80	12.559	2.864-55.08	**0.001**	19.292	2.107-176.623	**0.009**
Ethnicity (reference: White)						
Black	0.503	0.241-1.049	0.067	1.026	0.378-2.785	0.959
Asian	0.811	0.364-1.808	0.609	1.018	0.344-3.01	0.975
Obesity (reference: no)						
Yes	0.72	0.38-1.366	0.315	0.967	0.404-2.315	0.94
Renal group (reference: CKD)						
Dialysis	0.066	0.009-0.495	**0.008**	0.5	0.031-8.146	0.626
Transplant	0.143	0.013-1.516	0.106	1.532	0.041-57.719	0.818
Diabetes mellitus (reference: no)						
Yes	1.696	0.919-3.128	0.091	1.768	0.682-4.581	0.241
Hypertension (reference: no)						
Yes	0.925	0.426-2.007	0.843	0.687	0.212-2.221	0.53
Coronary disease (reference: no)						
Yes	2.022	0.981-4.167	0.056	1.53	0.53-4.418	0.432
Chronic lung disease (reference: no)						
Yes	2.406	0.788-7.344	0.123	1.569	0.327-7.532	0.574
NLR (reference: ≤10)						
>10	5.637	1.287-24.684	**0.022**	2.829	0.517-15.47	0.23
CRP (reference: ≤50)						
>50	4.596	2.287-9.236	**<0.001**	3.877	1.688-8.902	**0.001**

Table III: Need for admission

Discussion

This paper reports on the impact of pre-existing frailty in COVID-19 positive renal patients with CKD, kidney transplant and on renal replacement therapy, and the positive association with mortality. The prevalence of frailty, defined as CFS >4, was 58.6% in our cohort of patients compared to 49.9% from a retrospective study of 1564 patients admitted to European hospitals with COVID-19 [6]. We report a mortality of 26.0% in our cohort, which included CKD, kidney transplant recipients and patients receiving renal replacement therapy. This is comparable to the mortality reported in a UK study of 20133 participants, 26% [7] and with that reported in a cohort of 1564 admitted patients in Italy, 27.2% [6]. These populations, however, were quite different to our cohort with respect to CKD. The first cohort had 16% patients with CKD and the second one 36.4% CKD (eGFR <60 mL/min per 1.73 m^2).

As for two smaller studies reporting exclusively on COVID-19 positive patients receiving renal replacement therapy, Valeri et al. reported a mortality of 31% in 59 patients [8] and Goicoechea et al. of 30.5% in 39 hemodialysis patients [9]. The small differences could be due to the fact that our cohort was more mixed, included CKD patients as well as kidney transplant recipients and was younger (65.4 +/- 15.8) compared to the cohort of Goicoechea et al. (mean age 71 +/- 12). Similar

data on mortality, as compared to our cohort, were reported in 44 patients on maintenance haemodialysis in Paris: 27.3% [10]. The most common comorbidities in our cohort were hypertension (82.8%) and diabetes (55.2%). This was quite similar to the other 3 cohorts: in the cohort by Valeri et al. 98% had hypertension and 69% had diabetes [8]; 97% had hypertension and 64% had diabetes in the cohort by Goicoechea et al. [9]; 97.7% had hypertension and 50% diabetes mellitus in the cohort by Tortonese et al. [10]. Two of the tree studies analysed only admitted patients [8,9]. Only in the French study the admission rate was reported 93.2% [9] compared to 67% in our cohort. Explanations for this phenomenon could be a more mixed group in our study and relatively more comorbidity, especially chronic cardiac disease (38.6%) and respiratory (27.3%) diseases, in the French cohort compared to our cohort (31% and 13,2% respectively).

A part of our cohort has already been described by Hendra et al. [11]. 148 out of 746 hemodialysis developed symptomatic COVID-19, 93 of whom (62.8%) required hospital admission. Frailty was a predictor for mortality, however no comparison between frail and the non-frail group was performed.

Data on frailty are available from the ERACODA (European Renal Association COVID-19 Database) [12]. Of the 1073 patients with a previous frailty score enrolled 305 (28%) were kidney transplant and 768 (72%) received dialysis. The 28 days mortality was 21.3% for kidney transplant recipients and 25% for dialysis patients. Advanced age and frailty (CFS >4) were predictors for mortality in dialysis patients. While hypertension, diabetes mellitus, coronary artery disease, heart failure and chronic lung disease did not emerge as independent risk factors. These findings are comparable to ours. No formal analysis for the difference between frail and non-frail patients was however performed.

The strengths of our study are the large number of renal patients included and the pre-existing frailty score. There are no data available yet on pre-existing frailty in renal patients and COVID-19 positive patients from other studies. The main limitation is, of course, that this is a single centre retrospective experience.

Conclusions

Frailty is a better predictor of mortality than age and co-morbidities in COVID-19 positive renal patients. Frailty is associated with death and hospitalisation in dialysis patients [2,3].

Since there has been a 13-fold increase of ESRD patients aged >75 in the past 3 decades [13] we need to be aware that common renal practice has shifted from general nephrology to the field of geriatric nephrology and, as such, frailty has become a better predictor of mortality compared to age, gender, ethnicity, or comorbidities. In the future, frailty could be used as a prognostic factor and interventions could be designed to reduce the burden that comes with it.

REFERENCES

1. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001 Mar; 56(3):M146-56. https://doi.org/10.1093/gerona/56.3.m146
2. Chowdhury R, Peel NM, Krosch M, et al. Frailty and chronic kidney disease: A systematic review. Arch Gerontol Geriatr 2017 Jan-Feb; 68:135-42. https://doi.org/10.1016/j.archger.2016.10.007
3. McAdams-DeMarco MA, Law A, Salter ML, et al. Frailty as a novel predictor of mortality and hospitalization in individuals of all ages undergoing hemodialysis. J Am Geriatr Soc 2013 Jun; 61(6):896-901. https://doi.org/10.1111/jgs.12266
4. Dalhousie University, Clinical Frailty Scale. https://www.dal.ca/sites/gmr/our-tools/clinical-frailty-scale.html
5. National Institute for Health and Care Excellence. COVID-19 rapid guideline: critical care in adults. 2020. https://www.nice.org.uk/guidance/ng159
6. Hewitt J, Carter B, Vilches-Moraga A, et al. The effect of frailty on survival in patients with COVID-19 (COPE): a multicentre, European, observational cohort study. Lancet Public Health 2020 Aug; 5(8):e444-51. https://doi.org/10.1016/S2468-2667(20)30146-8
7. Docherty AB, Harrison EM, Green CA, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ 2020 May 22; 369:m1985. https://doi.org/10.1136/bmj.m1985
8. Valeri AM, Robbins-Juarez SY, Stevens JS, et al. Presentation and Outcomes of Patients with ESKD and COVID-19. J Am Soc Nephrol 2020 Jul; 31(7):1409-15. https://doi.org/10.1681/ASN.2020040470
9. Goicoechea M, Sánchez Cámara LA, Macías N, et al. COVID-19: clinical course and outcomes of 36 hemodialysis patients in Spain. Kidney Int 2020 Jul; 98(1):27-34. https://doi.org/10.1016/j.kint.2020.04.031
10. Tortonese S, Scriabine I, Anjou L, et al. COVID-19 in Patients on Maintenance Dialysis in the Paris Region. Kidney Int Rep 2020 Sep; 5(9):1535-44. https://doi.org/10.1016/j.ekir.2020.07.016
11. Hendra H, Vajgel G, Antonelou M, et al. Identifying prognostic risk factors for poor outcome following COVID-19 disease among in-centre haemodialysis patients: role of inflammation and frailty. J Nephrol 2021 Jan 30; 34:315-23. https://doi.org/10.1007/s40620-020-00960-5
12. Hilbrands LB, Duivenvoorden R, Vart P, et al. COVID-19-related mortality in kidney transplant and dialysis patients: results of the ERACODA collaboration. Nephrol Dial Transplant 2020 Nov 1; 35(11):1973-83. http://doi.org/10.1093/ndt/gfaa261
13. Vandecasteele SJ, Tamura MK. A Patient-Centered Vision of Care for ESRD: Dialysis as a Bridging Treatment or as a Final Destination? J Am Soc Nephrol 2014 Aug; 25(8):1647-51. https://doi.org/10.1681/ASN.2013101082