Malnutrition-inflammation score and quality of life in hemodialysis patients

Tadic, Djordje

UNIVERSITY OF SPLIT

SCHOOL OF MEDICINE

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Diploma thesis

Academic year:

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Firstly, I would like to express gratitude to my mentor Assist. Prof. Josko Bozic, MD, PhD for the consistent help, guidance and immense knowledge, throughout my thesis. I could not have completed by thesis to the standard I did without the help of Josipa Bukic, MPharm, who clarified, simplified and who significantly helped me with my task.

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1. INTRODUCTION

1.1. Chronic kidney disease

Wide spectrum of pathophysiological processes that are associated with abnormal kidney function are known as chronic kidney disease (CKD). A cornerstone feature of CKD is a decline in glomerular filtration rate (GFR). There is a strong link between the glomerular filtration rate and the amount of albuminuria with the risk of CKD progression. GFR levels are used to determine the stage of the kidney disease, as presented in Figure 1 (1).

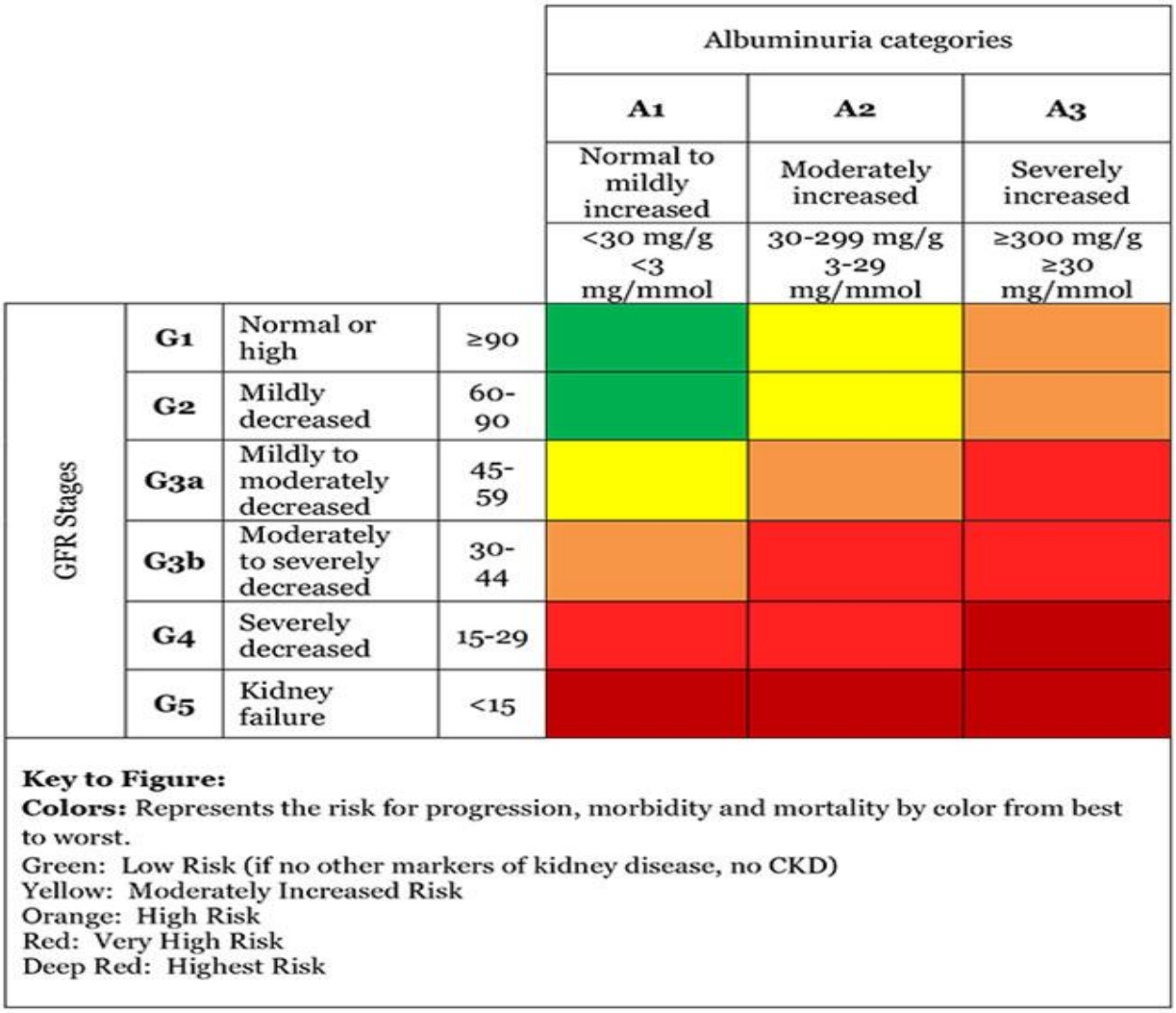

Figure 1. Relationship between the GFR and the risk for progression, morbidity and mortality of CKD

Source: The National Kidney Foundation 2019 [Internet]. Available online: https://www.kidney.org/atoz/content/gfr

End stage renal disease, like the name suggests, is the final stage of CKD where all the electrolytes, toxins and fluid that are excreted in a healthy kidney accumulate in the patient. This leads to morbidity and death if left untreated (2). End stage renal disease imposes sever limitations to the quality of life of afflicted patents. Every aspect of life is impaired and restricted. End stage renal disease is a prevalent and important health issue around the world. Furthermore, current prediction is that by the year 2020 there will be an increase of almost 60% of patients suffering from end stage renal disease when compared to 2005 (3, 4).

The signs and symptoms that occur as a result of end stage renal disease are known collectively as uremic syndrome. Urea and creatinine are used to estimate kidney function, however, their accumulation in the body alone does not cause uremic syndrome. A vast number of different toxins that build up in the kidney during end stage renal disease are all implicated in uremic syndrome (5). Uremic syndrome is not limited to the accumulation of toxins but also, multiple organ dysfunction and gut microbiota dysbalance. Uremic syndrome can thus be considered a disturbance of inter-organ and inter-organism (host–microbiota) communication (5).

The consequences of uremic syndrome include anemias, malnutrition due to dysfunctional metabolism of proteins, fats and carbohydrates. As a result of decreased excretion, reduced degradation and aberrant regulation plasma levels of various hormones including glucagon, insulin, steroid hormones; vitamin D and prolactin are abnormal (2).

Importantly, end stage renal disease has an association with a rise in systemic inflammation. Levels of acute phase reactants such as C-reactive protein are raised. Negative acute phase reactants such as fetuin and albumin are decreased. This chronic inflammation is a catalyst in the malnutrition-inflammation-atherosclerosis cycle, which adds fuel to the flames and accelerates comorbidities associated with end stage renal disease. To summarize, uremic syndrome is due to losses in the kidneys excretory function, hormonal and metabolic function and progressive systemic inflammation (2, 5). Complications of end stage renal disease are not only limited to direct consequences of uremic syndrome but also an increased risk of associated complications such as aortic stenosis (6). Furthermore, patients with CKD have dramatically increased risk of cardiovascular events (7).

1.1.1. Etiology and epidemiology

The global rise in the number of patients with CKD is threatening to reach epidemic proportions, and only a minor number of countries have a robust economies capable to meet challenges presented (8). This growing burden of CKD is mainly driven by population ageing (9). Population data estimates that approximately 6% of the adult population in the United States has CKD between stages 1 and 2. In addition to this, 4.5% of the United States population is estimated to have stages 3 and 4 CKD (2). There is a large amount of patients who suffer from early stages of kidney disease (CKD stages 1-3), and yet are unaware of their condition and do not have a diagnosis (10).

Data that was collected from the European Renal Association − European Dialysis and Transplant Association indicates that the overall prevalence of CKD is expected to increase, this is due to the following reasons, improved dialysis and transplant survival, increase in the relative prevalence of transplants and overall improvements in survival and treatment. As a whole, the European rate has risen from 124 patients per million in 2010 to 133 patients per million in 2014 (11). On the other hand the incidence of renal replacement therapy for diabetic nephropathy in Europe has stabilized at approximately ∼32 ppm , this is in part due to improved prophylactic treatments for CKD (12). Furthermore, in the general population, a healthy 60-year-old individual can expect to live an additional 20 more years, however the life expectancy of a 60-year-old hemodialysis patient is only 4 or 5 years (11).

The ratio of incidence to prevalence is high, this reflects a high mortality rate particularly in older patients. In the past, the country with the highest incidence for end stage kidney disease was Mexico followed by the United States, Taiwan and Japan. Prevalence was highest in Taiwan, Japan and U.S. The rankings reflect the universal health care provided for patients which keeps them alive. The country with the lowest prevalence reported was the Philippines (12).

The five most common causes of CKD are diabetic nephropathy, glomerulonephritis, hypertension-associated CKD, autosomal dominant polycystic kidney disease and other cystic and tubulointerstitial nephropathy. Together, these five causes account for approximately 90% of all cases of CKD. Of the aforementioned causes, the most common cause in the United States and Europe is diabetic nephropathy, a complication of diabetes mellitus type 2. Furthermore, diabetic nephropathy is the leading cause of renal failure in developed countries (2, 13). Certain areas in

the world are still burdened with higher rates of diabetic kidney disease, whereas other parts of the world are experiencing a decrease in the prevalence and mortality. Screening is proposed as valuable tool in mitigating the rising problem of diabetic nephropathy in regions of high-risk (12). Further, annual monitoring of urinary albumin-to-creatinine ratio, estimated GFR, and blood pressure is recommended in diagnosed diabetes patients (14). Among diabetes patients, a higher mean glycemic exposure (HbA_{1c}) was found to be the strongest modifiable risk factor associated with kidney disease development (15).

Hypertension is often found in patients with newly diagnosed CKD and augmented cardiovascular disease is a frequent complication of renal diseases. With no evidence for primary renal parenchymal disease hypertension becomes the most likely cause (16). There are two categories these patients fall under. Patients with subclinical primary glomerulopathy such as focal, segmental or glomerular sclerosis, are one category i.e. the kidney is the primary cause of the pathology. The second group of patients are those that have systemic vascular disease which in turn affects the kidney. These vascular pathologies often involve large and small vessels and involve the heart and brain too. The second category of patients tend to be elderly. It should be stated that while increased survival of the elderly is a major factor in the increased incidence of CKD, most elderly patients in the early stages of CKD succumb to complications of the heart or brain before they progress into end stage kidney disease (2).

Further, data collected from the European Renal Association − European Dialysis is the large difference between European countries in the incidence of renal replacement therapy, ranging from 23 patients per million in the Ukraine compared to the highest value of 237 patients per million in Portugal. (17).

1.1.2. Pathophysiology of chronic kidney failure

As a result of kidney failure, numerous disorders develop including disrupted electrolytes, acid base misbalance, fluid overload, a drop-in hematopoiesis of red blood cells and more. End stage kidney disease is an important cause of premature death of patients (18).

Stress to the blood vessels of the kidney glomerulus leads to the accumulation and activation of inflammatory cells which in turn activate and cause the dysfunction of mesangial

cells. Under the influence of various inflammatory cytokines (of note transforming growth factor β1 - TGFβ) mesangial cells regress into mesangioblasts. These mesangioblasts produce an excess of extracellular matrix resulting in a mesangial expansion. This is an early sign of glomerulosclerosis (8, 19).

Decreased TGFβ signaling activity has been proven in several animal studies to have beneficial effects on renal outcomes. On the other hand, because of its pleiotropic nature, complete inhibition of the TGFβ signaling pathway would likely lead to harmful side effects. Thus, an improved understanding of this pathway, and the modulating molecules, is necessary for development of practical real world therapeutic strategies in the treatment of CKD (20).

Another pathophysiological mechanism of kidney damage is the stretching of podocytes leaving areas of denuded glomerular basement membrane which in turn leads to the formation of Bowman's capsule adhesions. Moreover, disorders of podocyte architecture results in the retraction of foot processes and proteinuria and both appear to be shared consequences in the development of acquired glomerular disease. (21).

The aforementioned pathophysiological basis of kidney damage is presented in Figure 2.

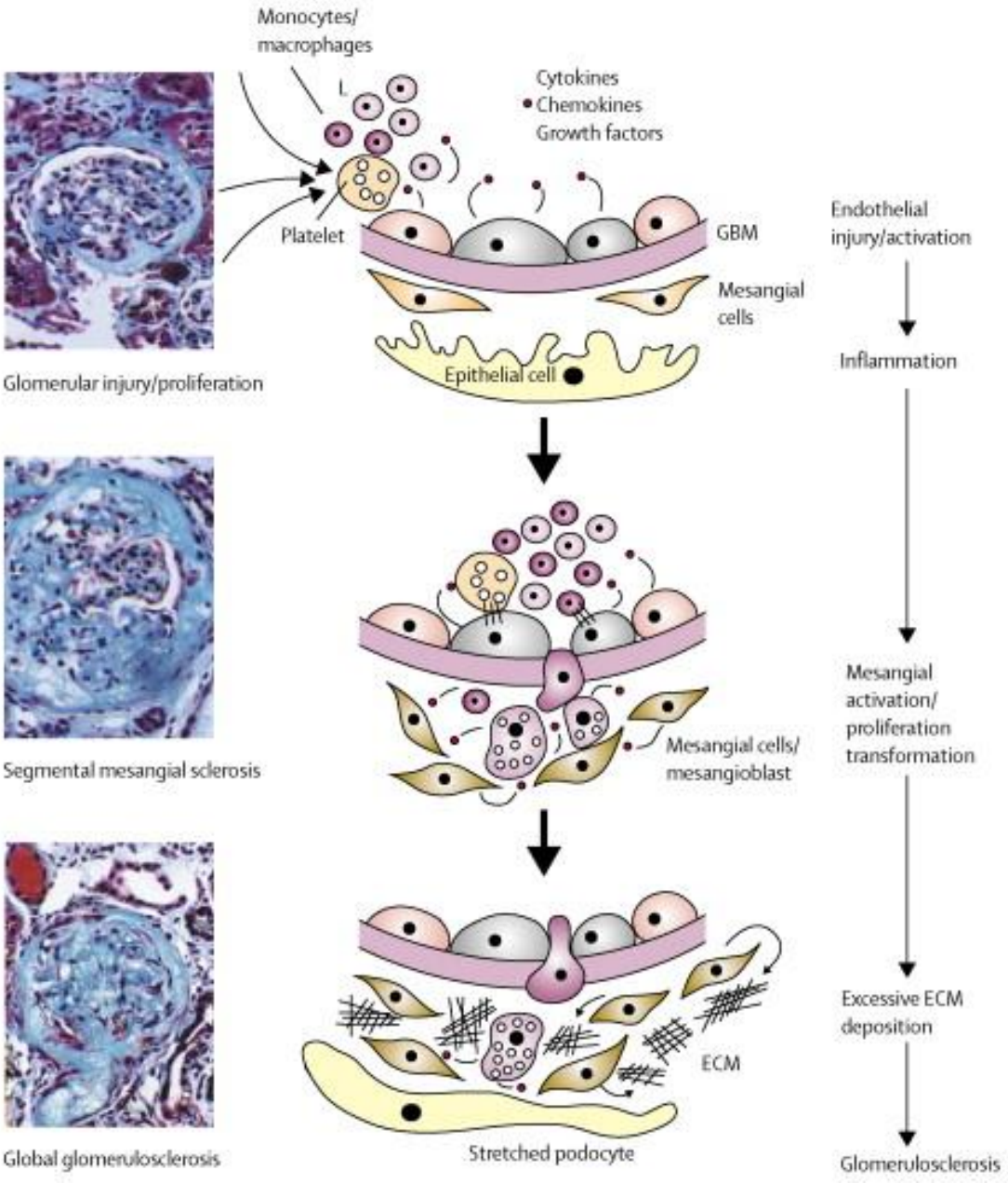

Figure 2. Stages of glomerulosclerosis

Source: Meguid El Nahas A, Bello AK. Chronic kidney disease: the global challenge. Lancet. 2005;365(9456):331-40.

There are two main pathophysiological mechanisms in CKD. The first is based on the primary etiology that initially caused the CKD. This could be developmental, caused by immune complex deposits, glomerular nephritis or toxin exposure (2). The most common primary causes of end stage renal disease, that initiate the first pathophysiological mechanism, are diabetes mellitus and

hypertension. These conditions are associated with increased cardiac morbidity and mortality as well (22). The second mechanism is a consequence of the first one. The remaining undamaged nephrons begin to hypertrophy and filter a larger amount of fluid. This compensatory action actually leads to further decline in kidney function (8).

Initially GFR is maintained as short term adaptations allow normal kidney function, despite a decrease in the number of nephrons. However, this increased pressure and flow begins to change the architecture of the glomeruli. Further changes that happen include abnormal podocyte function. An increase in the activity of renin-angiotensin system appears to contribute to the compensatory hyperfiltration and also to the consequential hypertrophy and sclerosis of the remaining nephrons. This is why reduced renal mass, due to the pathology, can over many years lead to a steady decrease in the function of renal parenchyma (2). End stage, stage 5 CKD, renal disease is the dramatic end to all kidney functions and results in the development of uremic syndrome (23). It should be acknowledged that kidney transplantation is ultimate treatment with the greatest survival rate, quality of life and cost effectiveness for patients with end stage renal disease (24).

1.2. Dialysis and extracorporeal therapies

1.2.1. Hemodialysis

Hemodialysis (HD) is a medical procedure where blood is moved out of the patient into extracorporeal circulation and then back the vasculature. It is the most common method of treatment for end stage renal disease. HD was a necessary procedure to sustain the lives of an estimated 2.6 million end stage patients around the globe in 2010 with this figure expected to double by 2030. Without HD, death from uremic syndrome can be expected in a few weeks (25, 26). The goal of HD is to replace the kidneys excretory function. Unwanted solutes including urea, potassium, phosphorus etc. are diffused into the dialysate. The dialysate circuit allows a hydrostatic pressure gradient to diffuse excess water from the blood thus maintain normovolemia. Replacement of kidney hormone function is a secondary goal (2).

During extracorporeal transit the blood is filtered. This is performed with an electrochemical concentration gradient using osmotic principles. Blood is separated from a solution called dialysate which contains necessary electrolytes to restore balance in the kidney

failure patient. The advent of hemodialysis has made the rapidly terminal diagnosis of kidney failure and subsequent uremic syndrome a thing of the past (2). A concentration gradient between the blood and dialysate is maintained with a counter current flow i.e. the dialysate flows in the opposite direction to the blood. The dialysate allows potassium, urea, phosphates and waste products to diffuse out of the blood, the concentration of sodium and chloride is the same in the dialysate as the blood thus preventing a change in blood concentration of these electrolytes. Bicarbonate is added in higher concentrations to the dialysate solution to restore normal blood pH (27).

The temperature of dialysate is kept between 35° and 37° C. At a constant temperature of 37° C the dialysate will cause the patients core temperature to paradoxically rise. It is not understood why, but one theory is that as a result of the bodies perceived loss of blood from the vessels and into the extracorporeal HD system, there is compensatory vasoconstriction, which in turn decreases any heat loss (28-30).. As the temperature increases, a reflex dilation occurs in the peripheral blood vessels causing decreased peripheral vascular resistance and a drop in the intradialytic pressure (hypotension).

Of the vascular access routes available for initiating HD the arteriovenous (AV) fistula is the most preferred. This type of fistula is made by connecting an artery with an adjacent vein. Different types of fistulas are presented in Figure 3. Things to consider when deciding lumen size are patient size, comorbidities like diabetes and obesity. Preoperative ultrasonographic imaging of the veins called vein mapping is useful in outlying the specific patient anatomy and may increase the rate of successfully establishing an AV fistula when distal fistulas fail or distal vessels are inadequate the alternative becomes the upper arm veins (31-33).

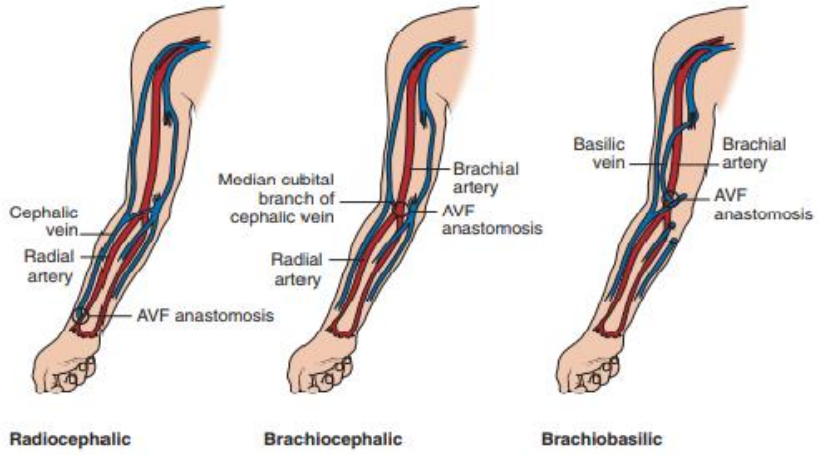

Figure 3. Varieties of upper arm fistulas

Source: Pereira B, Sayegh M, Blake P. Chronic kidney disease, dialysis, and transplantation. 2nd ed. Philadelphia: Saunders; 2005.

The cephalic and basilica can both be used to create an AV fistula. The basilica however, requires the additional procedure up and out from its anatomical position deep within the fascia. The brachiobasilic fistula can be made in several stages, firstly transposioned and then secondly anastomosed. Procedure can be advantages in adults and children. The basilic vein can also successfully be transposioned to the forearm. Meta-analysis of over 12,000 patients found that over time the failure rate for fistulas could be increasing, and this leads to concerns whether fistulas as a first step in HD therapy could be an overdone and unnecessary approach (33, 34). Further, in patients who exhaust all options for arteriovenous access in upper extremities an arteriovenous thigh graft is a potential vascular access (35).

It has been acknowledged that fistula creation is necessary in order to avoid the use of central venous catheters. However, it is still unclear which timing of fistula creation is preferable in order to minimize catheter use. In study by Clarke *et al.* patients' outcomes of predialysis (fistula attempt prior to initiation of the dialysis) and postinitiation (fistula attempt after starting dialysis) strategies were compared. The study involved 1091 patients, and the results showed that predialysis fistula attempts are associated with higher chance of catheter free use. However, catheter use was still common for both strategies of fistula creation (36).

Polytertrafluroethaline (ePTFE) is now the most widely used material for AV vascular access, and it secured its place as the most popular material by being easy to place and not taking a lot of time to do so. The recognized advantage of an AV graft is that it does not require an adequate vein in the forearm, but still provides an access for placement. One major advantage of these grafts is its low rate of thrombosis early on; however, this does not last and the patency rate of 12 months is only approximately 50 %. Graft material is at high risk of infection, infected grafts can be salvaged if the infected section is resected and the artificial material is replaced (39).

The AV graft initiates a biological response inside the lumen and in the distal part of the native vein. A number of different immune responses occur, amongst these is cellular growth inside and distal to the lumen itself. The consequent hyperplasia results in a high incidence of stenosis which is the number one cause of graft failure (38). Most stenosis develops at the venous anastomosis. Stents are often used to reduce the incidence of stenosis in grafts, the use of drug eluting stents, and its effectiveness is at this point undetermined. However, drug eluting graft material has shown promise in animal model (39) The future of grafts is a totally biological system, artificial materials will be just the skeleton on which autologous fibroblasts will be grown, after this endothelial cells will be seeded inside the lumen. This technology would provide grafts that are less likely to be affected by infections and thrombosis (40).

1.2.1.1. Complications of hemodialysis

Hypotensive events may occur in 15-30 but up to even 50% of all HD patients. Risk factors for this complication, among others, are female gender, older age and comprised heart function (41). Another complication, dialysis disequilibrium syndrome, is characterized by altered mental status, generalized seizures and coma. The occurrence of this syndrome has declined partly due to the earlier initiation of maintenance HD therapy. A less severe form of the syndrome includes symptoms of nausea and vomiting, headaches, fatigue and restlessness, and this form is still prevalent among HD patients (42).

It has been stated that available guidelines have discouraged the use of central venous catheters. Furthermore, one of the reasons that this is the case is because this route has been associated with higher incidence of complications. For instance, bacteremia occurs more frequent in this patient group, and it is their leading cause of hospitalization. However, some patients have

inadequate vessels for fistula creation, and they are only accessible to catheters. Therefore, the risks of catheters should be communicated to patients in order to prevent future complications (43).

An important symptom that reduces the health-related quality of life in HD patients are common muscle cramps. They can occur both during HD and in intradialytic periods, and are fairly painful. The cramps during HD could be due to exaggerated fluid removal, hypotension or perhaps shifts in electrolytes, but the cause is not precisely identified at this point. Another theory is that the accumulation of uremic solutes could account for intradialytic cramping. At this point in time there is no universal preventative measures that would reduce the duration or the frequency of patients cramps during HD. However, in some cases, changes in the frequency or duration of dialysis could be helpful. A number of different substances may have the ability to reverse intradialytic muscle cramps, and these include most commonly saline bolus followed by hypertonic infusions or dextrose solution. A meta-analysis results have suggested that L-carnitine administration could be helpful. Furthermore, vitamin E has showed variable efficacy in decreasing muscle cramps as well (44,45).

The most severe complications that can occur in HD patients are arrhythmias, myocardial stunning and death as their consequence. Concomitant heart disease predisposes patients to arrhythmias and possibly cardiac arrest during HD. Furthermore, HD causes a shift in solutes from intracellular to extracellular fluid, especially when the rate of removal is fast, and this is another predisposing factor to increased risk of arrhythmias. Change in the level of serum potassium is another important factor in arrhythmia occurrence, as are the changes in magnesium, calcium and pH serum values. Patients who use medicine that affect potassium, for instance digoxin, have even more complicated potassium control as this drug further affects electrolyte disbalance. For high risk patients, a computer programmed potassium removal (potassium modeling) could be beneficial. Moreover, the most feared occurrence in outpatient HD is a cardiac arrest. Despite external defibrillators, that are simple to use, the survival rate after one year for those patients is only approximately 15%. Furthermore, patients with internal defibrillators have a 2.7 times higher chance of death when on HD compared to the general population (46-49).

1.3. Quality of life in hemodialysis patients

Quality of life is an ambiguous term that can refer to the experience an individual has of the objective living conditions the individuals find themselves in. It is thus a very subjective term. People who have disabilities can describe their quality of life as excellent and people who are healthy can describe their quality of life as poor. Generally, quality of life is the degree of which an individual is in good health, comfort and able to enjoy events in their own life. In medicine, quality of life is a multidimensional term which encompasses wealth, social, physical and emotional wellbeing of an individual. The majority of medical procedures are based on objective findings. However, it should be acknowledged that the often neglected aspect, the subjective experience of patient, can have major influence on the disease course (50).

For HD to be effective, patients require the procedure approximately 3 times a week. This means that their whole lives need to revolve around their schedule, which imposes restrictions on every aspect of their living. This specificity of HD, among other factors, is what influences patients' quality of life the most. Therefore, observing patient-reported outcomes, to capture HD influences on health-related quality of life, has been recognized as an important factor for the improvement of health and individual care in CKD patients. Further, several questionnaires were developed in order to evaluate quality of life impairment in CKD patients. Short form health survey appeared to be the most used questionnaire in the studies of quality of life in end stage renal disease patients. A more specific questionnaire adopted to CKD patients is Kidney Disease Quality of Life Questionnaire-Short Form. A limitation of the quality of life questionnaires is the absence of assessment of family satisfaction, despite the fact that this is a crucial aspect of patients' lives (51-53).

Assessing the quality of life in HD patients not only has value in measuring the effectiveness of the therapy, but it also can be predictive of the outcome. Health-related quality of life has been found to have a significant predictive value on the survival and hospitalization of patients with chronic kidney disease. Moreover, quality of life places a role in deciding when a patient begins HD therapy. Needless to say, the most important factor that is taken into consideration when making the decision to initiate HD is the stage of the kidney disease and clinical picture. However, another important factor to consider is the patient's life style and the role they play in family and community. A patient who is very involved in the community may

forego HD initiation (disease permitting) for a while longer when compared to a retired patient at a similar stage of disease. This patient specific approach to decision making can be supplemented with information about patients' quality of life (51, 53, 54).

2. OBJECTIVES

The aims of this study are:

1. To evaluate quality of life in male and female hemodialysis patients
2. To determine malnutrition-inflammation score in male and female hemodialysis patients
3. To analyze connection between malnutrition-inflammation score and quality of life in hemodialysis patients.

Hypothesis:

1. There will be no differences in quality of life between male and female hemodialysis patients.
2. There will be no differences in malnutrition-inflammation score between male and female hemodialysis patients.
3. There will be a negative correlation between malnutrition-inflammation score and the quality of life in hemodialysis patients.

3. SUBJECTS AND METHODS

3.1. Study design

This cross-sectional study was conducted at Department of Nephrology, University Hospital of Split and Department of Pathophysiology, University of Split School of Medicine. Study was performed from August 2018 till December 2018.

3.2. Ethics approval and consent to participate

The included participants were informed about the procedures and the aim of this study, and their written informed consent was obtained. This study was approved by the Ethics Committee of the University Hospital of Split. Every procedure performed during this study was in accordance with the ethical standards of the institutional or national research committee and with 1964 Helsinki declaration, or its later amendments.

3.3. Study participants

Fifty hemodialysis (HD) patients were included in the presented study (26 male and 24 female patients). Inclusion criteria were outpatients who had been undergoing HD treatment for at least 6 months, who were 18 years or older and who signed the approved consent form. Patients with acute infections or an anticipated life expectancy of less than 6 months (e.g. due to a metastatic malignancy) were excluded.

A validated questionnaire Medical Outcomes Study Short Form-36 (SF-36) was used in the present study to assess participants' health-related quality of life. SF-36 is a multifunctional, non-disease specific, 36-question health survey that evaluates 8 domains of health providing an overall assessment of health-related quality of life. All questions are scored on a scale from 0 to 100, with 100 representing the highest level of functioning possible. Health aspects that are being valued are physical functioning, physical role limitations, bodily pain, general health perception, social functioning, emotional role limitations, emotional well-being and vitality. The scores from those questions that address each specific area of functional health status are then averaged together, for a final score within each of the 8 dimensions measured (55).

Body weight assessment and anthropometric measurements were performed according to the conventional medical standards within 5 to 20 minutes after termination of the treatment. Detailed medical history was obtained from anamnestic data, medical records and self-report. After regular clinical evaluation, all patients were asked to complete SF-36 questionnaire. Furthermore, for each participant a malnutrition-inflammation score (MIS) was calculated.

The MIS has four sections (nutritional history, physical examination, body mass index, and laboratory values) and 10 components. Each component has four levels of severity, from 0 (normal) to 3 (severely abnormal). The sum of all 10 MIS components can range from 0 (normal) to 30 (severely malnourished). A higher score reflects a more severe degree of malnutrition and inflammation in dialysis patients (56).

3.4. Data analysis

Statistical software MedCalc ver. 11.5.1.0 for Windows (MedCalc Software, Ostend, Belgium) was used for data analysis. Data were expressed as means ± standard deviation for continuous variables and as whole numbers and percentage for categorical variables. Kolmogorov-Smirnov test has been used for normality of data distribution.

Chi-square test or student t-test were used to compare baseline population characteristics for men and women. Student t-test was used for comparison of different domains of SF-36 between men and women. Pearson's correlation coefficient was used for assessment of correlation between SF-36 domains and other variables and correlation between MIS and baseline characteristics of study participants. The statistical significance was defined as $P<0.05$.

4. RESULTS

Baseline characteristics measured in hemodialysis patients are presented in Table 1. Differences between men and women were observed in body weight, both before and after the dialysis, but not in BMI value. Furthermore, female patients had a longer duration of chronic kidney disease, when compared to male patients (27.6±19.9 vs. 16.1±16.2 years; P=0.031).

Table 1. Baseline population characteristics

Parameter	Men (N=26)	Women (N=24)	Total (N=50)	P*
Age (years)	69.4±12.7	68.0±12.5	68.7±12.7	0.684
Body weight before dialysis (kg)	82.8±14.8	64.6±13.9	74.1±16.9	<0.001
Body weight after dialysis (kg)	80.6±14.8	62.5±13.7	71.9±16.8	<0.001
Body height (cm)	179.6±7.9	166.1±6.5	173.1±9.9	<0.001
Waist circumference (cm)	102.8±10.1	92.1±13.8	97.7±13.1	0.002
Hip circumference (cm)	107.2±10.8	101.2±11.6	104.3±11.4	0.065
BMI (kg/m^2)	25.6±4.6	22.8±6.0	24.3±5.4	0.070
Duration of chronic kidney disease (years)	16.1±16.2	27.6±19.9	21.6±18.9	0.031
Duration of dialysis treatment (years)	6.4±6.3	9.5±11.4	7.8±9.2	0.236
Arterial hypertension (N, %)	14 (53.8)	9 (37.5)	27 (54.0)	0.251
Smoking (N, %)	4 (15.4)	7 (29.2)	11 (22.0)	0.244

Data presented as mean ± standard deviation or number (percentage) where appropriate

*t-test for independent samples or chi-square test

For majority of the patients included in the present study the most common vascular access route for initiating HD was arterio-venous fistula (Figure 4).

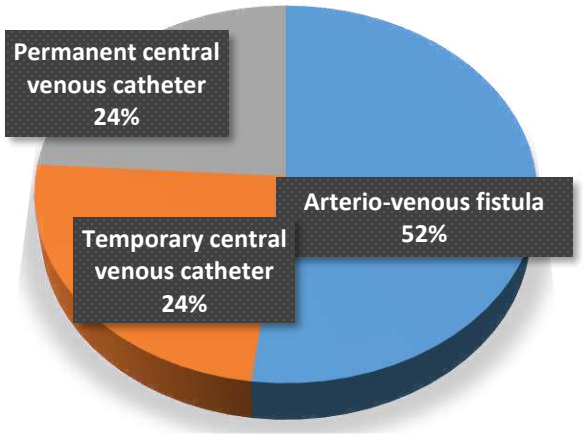

Figure 4. Distribution of patients according to venous approach to hemodialysis

Patients self-assessment of health-related quality of life is presented in Table 2. Females had statistically significantly lower scores than males in the following domains: physical functioning (48.7±35.0 vs. 68.4±26.9; P=0.029), energy/vitality (70.4±20.1 vs. 84.6±12.0; P=0.004), emotional well-being (71.8±18.1 vs. 83.5±10.1; P=0.008), pain (75.5±36.8 vs. 95.7±14.2; P=0.005) and general health perception (37.1±10.4 vs. 44.6±14.9; P=0.042).

Table 2. SF-36 scores between males and females

SF-36 dimensions	Men (N=26)	Women (N=24)	Total (N=50)	P*
Physical functioning	68.4±26.9	48.7±35.0	59.0±32.3	0.029
Role limitations physical	80.7±40.2	66.6±48.1	74.0±44.3	0.269
Role limitations emotional	70.1±25.4	60.6±29.1	65.4±27.5	0.221
Energy/vitality	84.6±12.0	70.4±20.1	77.8±17.7	0.004
Emotional well-being	83.5±10.1	71.8±18.1	77.9±15.6	0.008
Social functioning	78.3±34.0	61.4±37.9	70.2±36.5	0.104
Pain	95.7±14.2	75.5±36.8	84.1±29.8	0.005
General health perception	44.6±14.9	37.1±10.4	41.0±13.4	0.042

Data presented as mean ± standard deviation

*t-test for independent samples

Older age was associated with lower quality of life in 4 of the questionnaire domains: physical functioning (r= -0.334; P=0.017), role limitations both physical (r= -0.298; P=0.035) and emotional (r= -0.361; P=0.010) and social functioning (r= -0.309; P=0.029). Moreover, the duration of the disease only negatively influenced the domain of general health perception (r= -0.283; P=0.047), The amount of time on dialysis negatively affected the domains of energy/vitality (r= -0.326; P=0.020) and emotional well-being (r= -0.282; P=0.047).

Table 3. Correlation of age, duration of chronic kidney disease and duration of dialysis treatment score with SF-36 domains

SF-36 domain	Age (years) *r**(P)	Duration of CKD (years) *r**(P)	Duration of dialysis (years) *r**(P)
Physical functioning	-0.334 (0.017)	-0.082 (0.572)	-0.214 (0.135)
Role limitations physical	-0.361 (0.010)	-0.033 (0.817)	-0.155 (0.281)
Role limitations emotional	-0.298 (0.035)	-0.045 (0.756)	-0.195 (0.174)
Energy/vitality	-0.080 (0.578)	-0.205 (0.154)	-0.326 (0.020)
Emotional well-being	-0.017 (0.907)	-0.193 (0.178)	-0.282 (0.047)
Social functioning	-0.309 (0.029)	-0.129 (0.370)	-0.197 (0.170)
Pain	0.073 (0.616)	-0.203 (0.157)	-0.231 (0.107)
General health perception	-0.252 (0.077)	-0.283 (0.047)	-0.263 (0.065)

CKD – chronic kidney disease

* Pearson's correlation coefficient

There was a statistically significant difference in the MIS score between males and females with females having a higher score than male patients (7.45±4.31 vs. 5.28±3.18; P=0.048) (Figure 5).

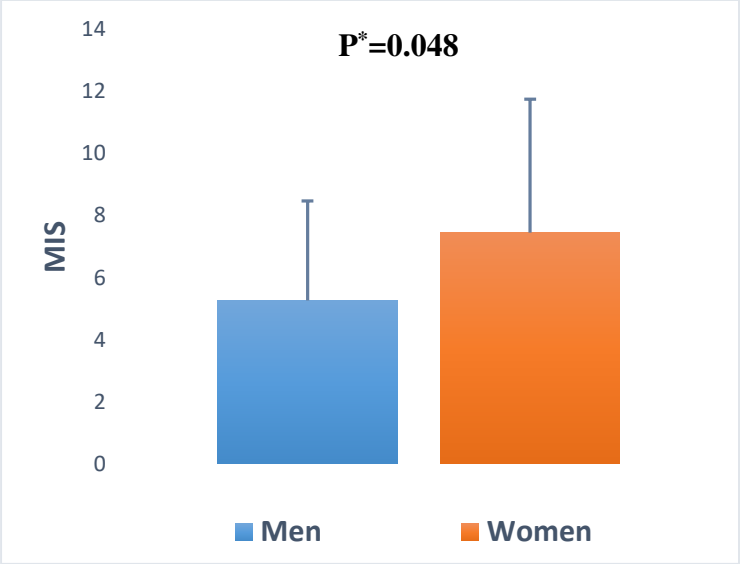

Figure 5. Differences in MIS between men and women

Correlation between MIS and baseline characteristics and SF-36 domains are presented in Tables 4 and 5. There was a statistically significant negative correlation between MIS and all anthropomorphic parameters (Table 4). Moreover, there was statistically significant negative correlation between MIS and all domains of SF-36 questionnaire (Table 5).

Table 4. Correlations between baseline characteristics and MIS score

Parameter	**MIS**	
	r*	**P**
BMI (kg/m^2)	-0.420	0.002
Waist circumference (cm)	-0.331	0.018
Hip circumference (cm)	-0.344	0.014
Age (years)	-0.005	0.972
Duration of chronic kidney disease (years)	0.032	0.822
Duration of dialysis treatment (years)	0.182	0.205

* Pearson's correlation coefficient

Table 5. Correlations between SF-36 domains and MIS

Parametar	MIS	
	r*	P
Physical functioning	-0.582	<0.001
Role limitations physical	-0.318	0.024
Role limitations emotional	-0.318	0.024
Energy/vitality	-0.527	<0.001
Emotional well-being	-0.565	<0.001
Social functioning	-0.480	<0.001
Pain	-0.465	<0.001
General health perception	-0.476	<0.001

* Pearson's correlation coefficient

5. DISCUSSION

In the present study female patients had lower score in all domains of SF-36 questionnaire and it can be stated that they reported lower health related quality of life when compared to men. Our results were in concordance with a 2016 study that also found a negative association between female sex and quality of life (57). Future studies should investigate association of female gender with these specific domains in order to provide patient centered care to female patients. This is however contrary to some previous findings. In study by He *et al.* the men patients experienced more negative emotions when compared to women patients. However, both patient group reported relatively poor quality of sleep and quality of life (58). Another study had several negative predictive factors identified and among these was male gender. However, this particular study was conducted in Saudi Arabia where males play a dominant role in society and for whom illness of any kind could have large changes to the life they have grown accustomed to (59). In contrast to our study and the aforementioned Saudi study, a 2015 Greek study found no statistically significant difference between the quality of life in males and females (60).

It should be acknowledged that males and females included in this study did not differ in duration of dialysis treatment, prevalence of arterial hypertension or any other baseline characteristic, except duration of CKD. However, the duration of the disease did not show a strong correlation with health related quality of life in presented study. Therefore, it can be assumed that poorer quality of life reported in women is not a direct consequence of longer duration of the disease in this patient group.

The difference between females and males was also observed in malnutrition evaluation. Higher MIS observed in female patients reflects a more severe degree of malnutrition and inflammation, compared to male dialysis patient. In recently published research by Rodrigues *et al.* MIS showed the strongest association with hospitalization and mortality risk when compared to other nutritional markers of HD patients (61). Moreover, increased malnutrition could be the cause of low life satisfaction in patients (62). Therefore, the more severe degree of malnutrition in women could have influenced their self-perceived lower quality of life as MIS was highly correlated with HD patients' quality of life in the presented study.

Study by Gencer *et al*. reported positive correlation between the duration of dialysis and MIS (62). However, our study did not have the same finding. An explanation of this difference in results of two studies with similar sample sizes could be the fact that published study involved

younger patients. Future studies are needed to give a definite conclusion of relationship between duration of dialysis and MIS.

Additionally, duration of the dialysis was correlated with domains energy and emotional well-being of SF-36 questionnaire in our study. Previous studies have also found a correlation between decreasing quality of life and amount of time spent on HD. Even though this can be a logical conclusion of many years' patients have been living with a life restricting therapy. However, some studies contradict these findings and indicate no relationship between quality of life and time on HD. This discrepancy could be due to a difference in provided quality of care at different hospitals (59,63).

Health related quality of life of the study participants was strongly correlated with their age in several domains. Similar findings were observed in some previous studies. Elderly experience functional decline within the first 6 months after initiating HD. This risk is even higher in older and frail patients. Loss in functional status in this patients group is driven by decline in instrumental activities of their daily life (64).

Additionally, a small number of patients included in this study reported that they were smokers. However, it has been stated that smoking imposes higher cardiovascular risks for CKD patients on HD, as it is associated with higher levels of serum phosphorus. Furthermore, in study by Li *et al*., which involved 22 230 HD patients, risks for death and hospitalization were elevated for smokers group of HD patients. Moreover, the highest risks were amongst younger HD patients and those patients with diagnose of diabetes. Interestingly, second-hand smoke was not associated with risks. Clinicians should become aware of the risks for HD patients and help their patients with smoking cessation (65,66).

The main limitations of the presented study are small sample size and that it is a single center study. Moreover, the addition of control group of healthy participants would have added a value to the results of this study. Further, several other factors could have influenced patients' quality of life, and were not included in the present study. For instance, impact of the depression and level of education on quality of life in HD patients was observed in previous studies (67,68). Even with the presented limitations our results are consisted with findings of previous studies. Furthermore, this study should rise awareness of health care professionals of quality of life measurements and MIS, since both could influence HD patients' outcomes.

6. CONCLUSION

1. Female patients on hemodialysis reported lower health related quality of life when compared to males.
2. Female patients had higher MIS in comparison to male patients.
3. There was statistically significant negative correlation between MIS and all domains of the SF-36 questionnaire.
4. The amount of time on dialysis negatively affected the domains of energy/vitality and emotional well-being.
5. Duration of the chronic kidney disease only negatively influenced the domain of general health perception.

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8. SUMMARY

Objectives: Living on hemodialysis is a challenge to many patients, impacting various aspects of their lives and ultimately influencing their quality of life. The aim of this was to determine the differences in quality of life between male and female patients on hemodialysis and to evaluate the relationship between quality of life and malnutrition-inflammation score.

Patients and methods: This study included 50 patients in total, 26 males and 24 females. To evaluate health related quality of life the Short Form-36 questionnaire was utilized. This is a multifunctional, non-disease specific 36 question health survey in 8 different domains. In addition to this, the malnutrition-inflammation score (MIS) which included four sections (nutritional history, physical examination, body mass index, and laboratory values) was determined.

Results: Females had statistically significantly lower scores than males in the following domains: physical functioning (48.7±35.0 vs. 68.4±26.9; P=0.029), energy/vitality (70.4±20.1 vs. 84.6±12.0; P=0.004), emotional well-being (71.8±18.1 vs. 83.5±10.1; P=0.008), pain (75.5±36.8 vs. 95.7±14.2; P=0.005) and general health perception (37.1±10.4 vs. 44.6±14.9; P=0.042). Older age was associated with lower quality of life in 4 of the questionnaire domains: physical functioning (r= -0.334; P=0.017), role limitations both physical (r= -0.298; P=0.035) and emotional (r= -0.361; P=0.010) and social functioning (r= -0.309; P=0.029). Moreover, the duration of the chronic kidney disease only negatively influenced the domain of general health perception (r= -0.283; P=0.047). The amount of time on dialysis negatively affected the domains of energy/vitality (r= -0.326; P=0.020) and emotional well-being (r= -0.282; P=0.047). Additionally, there was statistically significant negative correlation between MIS and all domains of SF-36 questionnaire.

Conclusion: We can conclude that female patients on dialysis had lower health related quality of life when compared to men. Furthermore, quality of life inversely correlated with malnutrition-inflammation status.

9. CROATIAN SUMMARY

Naslov: Malnutricijsko-inflamacijski zbir i kvaliteta života u pacijenata na hemodijalizi.

Ciljevi: Život na hemodijalizi izazov je za mnoge pacijente, koji utječe na različite aspekte njihovog života i naposljetku utječe na njihovu kvalitetu života. Cilj ovog istraživanja bio je utvrditi razlike u kvaliteti života između muškaraca i žena koje su na hemodijalizi i utvrditi vezu između kvalitete života i zbira pothranjenosti.

Pacijenti i metode: Ispitivanje je obuhvatilo ukupno 50 pacijenata, 26 muškaraca i 24 žene. Za procjenu zdravstvene kvalitete života korišten je Upitnih zdravstvenog stanja SF-36. Ovo je multifunkcionalni, bolest nespecifični, zdravstveni upitnik s 36 pitanja u 8 različitih domena. Uz to, izračunat je i malnutricijsko-inflamacijski zbir (MIS) koji je uključivao četiri dijela (povijest prehrane, fizički pregled, indeks tjelesne mase i laboratorijske vrijednosti).

Rezultati: Žene su imale statistički značajno niži zbir od muškaraca u sljedećim domenama: fizičko funkcioniranje (48,7±35,0 nasuprot 68,4±26,9; P=0,029), energija/vitalnost (70,4±20,1 nasuprot 84,6±12,0; P=0,004), emocionalno blagostanje (71,8±18,1 nasuprot 83,5±10,1; P=0,008), bol (75,5±36,8 nasuprot 95,7±14,2; P=0,005) i percepcija općeg zdravlja (37,1±10,4 nasuprot 44,6±14,9; P=0,042). Starija dob bila je povezana s nižom kvalitetom života u 4 područja upitnika: fizičko funkcioniranje (r=-0,334; P=0,017), ograničenja zbog fizičkih (r=-0,361; P=0,010) i emocionalnih poteškoća (r=-0,361; P=0,010) i socijalno funkcioniranje (r=-0,309; P= 0,029). Nadalje, trajanje kronične bubrežne bolesti samo je negativno utjecalo na domenu percepcije općeg zdravlja (r=-0.283; P=0.047). Vrijeme provedeno na dijalizi negativno je utjecalo na domenu energija/vitalnost (r= -0,326; P=0,020) i emocionalno blagostanje (r=-0,282; P=0,047). Pronađena je statistički značajna negativna korelacija između MIS zbira i svih domena SF-36 upitnika.

Zaključak: Žene su imale nižu procjenu kvalitete života u usporedbi s muškarcima. Nadalje, kvaliteta života je negativno korelirala sa zbirom pothranjenosti.

10. CURRICULUM VITAE

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