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# A novel complex model of hemodialysis adequacy: predictive value and relationship with malnutrition-inflammation score

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**Abstract**: Target dialysis dose to ensure the best patient outcome is still a matter of debate. Traditional models have a number of limitations and do not comprehensively reflect all factors involved. In this study we present a new complex model of dialysis adequacy, the hemodialysis adequacy score (HAS), and evaluate its prognostic value, as well as its relationship with the malnutrition-inflammation score (MIS). The components of HAS included paradigms of the 6 major factors known to influence the outcome of hemodialysis (HD) patients: the modified Karnofsky index (KI), the Charlson comorbidity index (CCI), Kt/V and URR measures of dialysis dose, body mass index (BMI) and serum albumin level, serum levels of hemoglobin and ferritin, intact parathyroid hormone (iPTH) and calcium-phosphorus solubility product. The score was evaluated in a 24-month prospective study on 147 HD patients. Odds ratio analysis showed that hospitalized patients had twice the chance to have HAS >13 compared to those who were not hospitalized during the study period (OR=2.152, CI 95% (1.0024-4.619). Mortality rate was significantly higher in patients with a HAS >13 at the 12-month follow-up ($\chi 2$=16.416, p <0.0001). Patients with a HAS≤13 had significantly higher survival rate (Kaplan-Meier), while those with a HAS>13 had significantly higher probability of death (log-rank Cox-Mantel=17.920, df=1, p <0.00023). The HAS directly and significantly correlated with the MIS at all measurements (p <0.0001). Results confirmed that the HAS is a useful tool to assess dialysis adequacy with a good prognostic value. The cutoff level for the HAS at 13 points was associated with an unfavorable outcome.

**Key words:** adequacy; hemodialysis; malnutrition-inflammation; model; score

## INTRODUCTION

Introducing hemodialysis (HD) in the treatment of end-stage renal failure has helped preserving the lives of millions of end-stage renal disease patients. From the beginning of the dialysis era, the issue of target dialysis dose to ensure the best patient outcome has been a matter of debate. In the last decades, with advances in technology, adequate dialysis should provide a good general condition and quality of life, low morbidity and mortality rate, and social independence for patients [1]. It is, therefore, of great importance to accurately define and quantify the delivered dialysis dose in a reproducible manner.

Traditionally, the measurement of dialysis dose has relied on urea kinetic modeling, i.e. the estimation of clearance of the small, water-soluble, nitrogenous waste product – urea. The Kt/V ratio is universally used to express fractional urea clearance during a hemodialysis (HD) session, where K is the dialyzer urea clearance (in liters per hour), t is time on dialysis (in hours) and V is the volume of distribution of urea (in liters). A simpler substitute, the urea reduction ratio (URR), which represents the percentage reduction in urea acquired during a single HD session, has also been used. Both these models, however, have a number of limitations. Firstly, they do not take into account residual renal

function, which has a significant impact on patient outcome. Secondly, they ignore the role of ultrafiltration and mass transfer between body compartments, and finally, they only rely on the measurement of urea and ignore larger molecules that have diffusion-limited transport [2]. The HEMO and ADEMEX studies have actually proved that further increases in dialysis dose, as expressed by the Kt/V index, in patients with good clearance of small molecules, has virtually no significant influence on lowering mortality [3,4].

Recent studies have shown that besides the efficiency of the dialysis procedure itself (clearance of small molecules, ultrafiltration rate), dialysis adequacy is influenced by a number of factors dependent on the patient and underlying renal disease – nutritive status, protein catabolism rate, anemia and blood pressure control, inflammation and overall health status [5]. Namely, malnutrition, inflammation and atherosclerosis, the components of malnutrition inflammation complex syndrome (MICS), have been recognized to independently influence HD patients' morbidity and survival [6]. Thus, after achieving the optimal dialysis dose, as defined by the urea kinetic model, other factors, and especially MICS, can have significant influence on the final outcome. This complexity has precluded the design of a universal and simple model of dialysis adequacy.

In this study we hypothesized that combining parameters that have been individually used to assess dialysis adequacy, the level of MICS and patient functional status, would produce a more comprehensive and more reliable model, with better predictive value. With this purpose, a new complex model of dialysis adequacy, the hemodialysis adequacy score (HAS), has been created. The aim of this study was to evaluate reliability of HAS in assessing dialysis adequacy and its prognostic value, as well as its relationship with the malnutrition-inflammation score (MIS), as a measure of MICS.

## MATERIALS AND METHODS

### Patients

The data necessary to evaluate HAS were collected in a prospective study conducted over a period of 24 months, which included patients treated for chronic HD in the Hemodialysis Center in Banja Luka, Republika Srpska. All patients gave their informed consent to participate and the study was performed in accordance with the Helsinki Declaration. Out of 150 patients initially enrolled, 147 completed the study (63 females and 84 males, average age 55.09±12.93 years). The exclusion criteria were time on dialysis less than three months, less than 3 HD sessions per week and previous limb amputation. During the follow-up period, the patients were thoroughly examined and detailed laboratory analyses were performed at baseline and each sixth months. The HAS was determined at baseline and after a 12-month follow-up.

### Hemodialysis adequacy score (HAS)

The components of HAS included paradigms of the 6 major factors known to influence the outcome of HD patients: the modified Karnofsky index (KI) to assess patients' functional status, the Charlson comorbidity index (CCI) to assess comorbidities (without adding points for age), dialysis dose expressed by the Kt/V and URR measured by single-pool technique, nutritional status assessed by the body mass index (BMI) and serum albumin level, anemia control expressed by the serum levels of hemoglobin and ferritin, and calcium and phosphate metabolism assessed by the level of intact parathyroid hormone (iPTH) and calcium-phosphorus solubility product (Ca×P) [7-9]. The number of points assigned to each component varied from 0, representing achievement of the optimal values, to 6, indicating unsatisfactory results and poor outcome. The only exception was the comorbidity assessment, where the number of points could have been higher than 6. The sum of points produced the final value of the HAS as a predictive model. The higher the HAS value, the poorer the prognosis, and *vice versa*.

### Blood samples analyses

Blood samples for laboratory analyses were obtained before and after the first weekly dialysis and analyzed in Biochemical Laboratory for Medical Investigations, Institute for Nuclear Medicine and Biochemical Laboratory at University Clinical Center of the Republic of Srpska. The serum hemoglobin level was determined by the cyanmethemoglobin method on a Cell Dyn 1700, Abbott counter. The serum ferritin level was de-

termined by the microparticle enzyme immunoassay (MEIA) technique on an IMx apparatus (Abbott). The reference values for HD patients were 400-600 ng/mL according to the European Best Practice Guidelines for Hemodialysis [10]. An Alcyon apparatus (Abbott) was used to determine serum urea by the urease-glutamate-dehydrogenase method (reference values in the general population 2.6-6.7 mmol/L for women and 3.2-7.3 mmol/L for men); serum albumin levels by spectrophotometric bromocresol green method (reference range for the general population 32-52 g/L, minimum recommended level for HD patients 40 g/L); total serum calcium (reference range for the general population 2.25-2.7 mmol/L) and phosphorus levels (reference range for the general population 0.84-1.45 mmol/L) by photometry. Serum iPTH was determined on an autogenous counter (CIS, France) by the ELISA-PTH method as described [11].

### Body mass index (BMI) and urea reduction ratio (URR)

The BMI was calculated according to the Quetelet formula [12,13]. The URR was calculated according to the following equation:

$$URR = \frac{Upre - Upost}{Upre} \times 100\%,$$

where $U_{pre}$ is the predialysis urea level and $U_{post}$ is the postdialysis urea level.

Kt/V was calculated according to the Daugirdas formula:

$$Kt/V = -\log\left[{Upost}/{Upre} - 0.008t\right] + \left[4 - 3.5\,{Upost}/{Upre}\right] \times {(Wpre - Wpost)}/{Wpost},$$

where $U_{pre}$ is the predialysis urea level and $U_{post}$ is the postdialysis urea level, $W_{pre}$ is is predialysis body weight and $W_{post}$ is postdialysis body weight.

### Malnutrition-inflammation score (MIS)

The MIS questionnaire comprises 10 components in four sections, including nutritional history, physical examination, BMI and laboratory values (serum albumins and total iron-binding capacity). Each component is given a score between 0 (normal) and 3 (severely malnourished) [14]. The first outcome measure was the rate of hospitalization, evaluated by the number of hospitalizations and length of hospital stay. The second outcome measure was mortality.

### Statistical analysis

The results were statistically analyzed with χ-square test, one-tailed ANOVA (F test), Pearson's correlation, Kaplan-Meier survival analysis and log-rank test using the SPSS 12.0.

## RESULTS

During the two-year follow-up period, 19 (12.96%) patients died (13 men and 6 women), 2 (1.36%) patients continued HD in another center, 1 (0.68% was transferred to peritoneal dialysis and 1 successfully underwent kidney transplant surgery. Thus, 124 (84.35%) patients (68 men and 56 women) successfully completed the whole study. Half of the patients (74; 50.4%) were hospitalized once or more during the study period.

The original HAS questionnaire is presented in Table 1. The elements of the HAS and values of the MIS during the study period are shown in Table 2. The HAS was determined for 117 (79.59%) of the patients at baseline, out of which 44 (37.6%) had a HAS >13. Significantly more men had HAS >13 than women ($\chi 2=3.974$, $p<0.046$). The HAS directly and significantly correlated with the MIS and CCI at all measurements ($p<0.0001$). The HAS, MIS and CCI were significantly inversely correlated with KI during the whole follow-up period ($p<0.0001$). Furthermore, a significant positive correlation was found between the HAS, KI, CCI and MIS ($p <0.0001$) in non-hospitalized patients. The CCI and KI increased over the follow-up period, while the MIS showed a decrease in hospitalized patients. The strength of correlation between the HAS and the other scores increased over the follow-up period (Table 3).

Patients who were hospitalized during the study period had significantly higher levels of HAS at baseline ($F=11.472$, $p <0.0009$), but not at the 12-month follow-up. In patients who were not hospitalized during the study period, the levels of HAS were significantly higher at the 12-month follow-up compared to

**Table 1.** Hemodialysis Adequacy Score (HAS).

| | | | | | |
|---|---|---|---|---|---|
| 1. Functional status – modified Karnofsky Index | | | | | |
| 1.1. | Able to carry on normal activity and work; minor signs of symptoms or disease; no help needed (80-100%) | | | | **0** |
| 1.2. | Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed | 1.2.1. | Cares for self, unable to carry on normal activity ar to do active work (70%) | | **1** |
| | | 1.2.2. | Requires occasional assistance but is able to care for most of his personal needs (60%) | | **2** |
| | | 1.2.3. | Requires considerable assistance and frequent medical care (50%) | | **3** |
| 1.3. | Unable to care for self, requires equivalent of institutional hospital care, diseases may be progressing rapidly | 1.3.1. | Disabled; requires special care and assistance (40%) | | **4** |
| | | 1.3.2. | Severely disabled; hospital admission is indicated although death not imminent (30%) | | **5** |
| | | 1.3.3. | Very sick; hospital admission necessary; active supportive treatment necessary (20%) | | 6 |
| 2. Charlson Comorbidity Index | | | | | |
| 2.1. | Myocardial infarction | | | 1 | |
| 2.2. | Congestive heart failure | | | 1 | |
| 2.3. | Peripheral vascular disease | | | 1 | |
| 2.4. | Cerebrovascular disease (except hemiplegia) | | | 1 | |
| 2.5. | Dementia | | | 1 | |
| 2.6. | Chronic lung disease | | | 1 | |
| 2.7. | Connective tissue disease | | | 1 | |
| 2.8. | Ulcer | | | 1 | |
| 2.9. | Chronic liver disease | | | 1 | |
| 2.10. | Diabetes (no complications) | | | 1 | |
| 2.11. | Diabetes with end organ damage | | | 2 | |
| 2.12. | Hemiplegia | | | 2 | |
| 2.13. | Moderate to severe kidney disease | | | 2 | |
| 2.14. | Malignant tumor | | | 2 | |
| 2.15. | Leukemia | | | 2 | |
| 2.16. | Lymphoma | | | 2 | |
| 2.17. | Moderate or severe liver disease | | | 3 | |
| 2.18. | Metastasis | | | 6 | |
| 2.19. | AIDS | | | 6 | |
| 3. Hemodialysis dose | | | | | |
| 3.1. | Single pool Kt/V(Daugirdas) | | | | |
| | *spKt/V* ≥1.4 | *spKt/V* 1.2-1.3 | *spKt/V* 0.9-1.1 | *spKt/V*≤0.8 | |
| | **0** | **1** | **2** | **3** | |
| 3.2. | Urea Reduction Ratio (URR) | | | | |
| | *URR* ≥75% | *URR* 65-74% | *URR* 60-64% | *URR*≤60% | |
| | **0** | **1** | **2** | **3** | |
| 4. Nutritional status | | | | | |
| 4.1. | Body Mass Index (BMI) | | | | |
| | BMI≥20 $kg/m^2$ | BMI 18-19.99$kg/m^2$ | BMI 16-17.99$kg/m^2$ | BMI<16 $kg/m^2$ | |
| | **0** | **1** | **2** | **3** | |
| 4.2. | Serum Albumins | | | | |
| | Albumins ≥40 *g/l* | Albumins 35-39 *g/l* | Albumins 30-34 *g/l* | Albumins <30 *g/l* | |
| | **0** | **1** | **2** | **3** | |

**Table 1.** continuited

| | | | | |
|---|---|---|---|---|
| 5. Anemia | | | | |
| 5.1. | Hemoglobin (Hgb) | | | |
| | Hgb ≥ 110*g/dl* | Hgb ≥100-109*g/dl* | Hgb 76-99*g/dl* | Hgb≤75*g/dl* |
| | **0** | **1** | **2** | **3** |
| 5.2. | Serum Ferritin (Fer) | | | |
| | Fer 201-500 μ*g/ml* | Fer ≤ 200 μ*g/ml* | Fer 500-999 μ*g/ml* | Fer ≥1000 μ*g/ml* |
| | **0** | **1** | **2** | **3** |
| 6. Bone metabolism | | | | |
| 6.1. | Parathormone (PTH) | | | |
| | PTH 151-299 *pg/ml* | PTH ≤ 150 *pg/ml* | PTH 300-799 *pg/ml* | PTH ≥ 800 *pg/ml* |
| | **0** | **1** | **2** | |
| 6.2. | CaxP product | | | |
| | *CaxP* ≤ 3 mmol$^2$/L$^2$ | *CaxP* 3.1-3.9 mmol$^2$/L$^2$ | *CaxP* 4-4.3 mmol$^2$/L$^2$ | *CaxP* ≥ 4.4 mmol$^2$/L$^2$ |
| | **0** | **1** | **2** | **3** |
| Date: / / | | | SUM | |

**Table 2.** Values of elements of Hemodialysis Adequacy Score and MIS.

| **Variable** | **Baseline** | **6 months** | **12 months** | **18 months** | **24 months** |
|---|---|---|---|---|---|
| | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD |
| KI (%) | 67.2±13.2 | 66.69±11.09 | 68.15±9.71 | 68.19±10.45 | 68.71±9.37 |
| CCI | 4.13±1.45 | 4.89±1.4 | 4.97±1.28 | 5.23±1.38 | 5.59±1.52 |
| URR | 67.04±8.11 | 66.8±9.12 | 66.55±6.66 | 67.04±6.81 | 66.94±6.91 |
| spKt/V | 1.4±0.3 | 1.39±0.32 | 1.36±0.24 | 1.38±0.25 | 1.37±0.25 |
| BMI | 22.14±3.49 | 22.31±3.48 | 22.37±3.35 | 22.513.17± | 22.55±3.21 |
| Albumins (g/L) | 39.88±3.51 | 42.77±3.76 | 41.05±3.38 | 40.82±5.36 | 40.59±2.79 |
| Hemoglobin (g/L) | 101.81±16.07 | 97.47±21.91 | 106.15±29.21 | 100.67±14.37 | 112.09±15.79 |
| Ferritin (ng/mL) | 591.93±367.97 | 614.14±315.27 | 582.14±280.27 | 550.99±266.97 | 580.17±279.24 |
| Ca×$PO_4$ (mmol$^2$/L$^2$) | 3.36±1.09 | 3.58±1.15 | 3.24±0.93 | 3.39±1.01 | 3.37±0.86 |
| iPTH (pg/mL) | 172.9±368.93 | - | 84.01±186.02 | - | - |
| HAS | 13±4.2 | - | 13.02±3.53 | - | |
| MIS | 6.06±4.47 | 6.49±3.76 | 6.32±3.23 | 6±3.38 | 6.03±2.93 |

Legend: KI – Karnofsky Index, CCI – Charlson Comorbidity Index, URR – Urea Reduction Ratio, spKt/V – single-pool Kt/V, iPTH – intact parathyroid hormone, HAS – Hemodialysis Adequacy Score, MIS – Malnutrition Inflammation Score

**Table 3.** Correlations between Malnutrition Inflammation Score, Charlson Comorbidity Index, Karnofsky Index and Hemodialysis Adequacy Index at baseline and after 12 months follow-up.

| **Score** | | **Baseline** | | | | **12 months** | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | **MIS** | **CCI** | **KI** | **HAS** | **MIS** | **CCI** | **KI** | **HAS** |
| MIS | R | 1 | 0.547 | -0.702 | 0.441 | 1 | 0.455 | -0.573 | 0.555 |
| | p | - | 0.000 | 0.000 | 0.000 | - | 0.000 | 0.000 | 0.000 |
| CCI | R | 0.547 | 1 | -0.647 | 0.679 | 0.455 | 1 | -0.591 | 0.679 |
| | p | 0.000 | - | 0.000 | 0.000 | 0.000 | - | 0.000 | 0.000 |
| KI | R | -0.702 | -0.647 | 1 | -0.532 | -0.573 | -0.591 | 1 | -0.597 |
| | p | 0.000 | 0.000 | - | 0.000 | 0.000 | 0.000 | - | 0.000 |
| HAS | R | 0.441 | 0.647 | -0.532 | 1 | 0.555 | 0.679 | -0.597 | 1 |
| | p | 0.000 | 0.000 | 0.000 | - | 0.000 | 0.000 | 0.000 | - |

MIS – Malnutrition Inflammation Score, CCI – Charlson Comorbidity Index, KI – Karnofsky Index, HAS – Hemodialysis Adequacy Score; R – correlation coefficient, p – significance

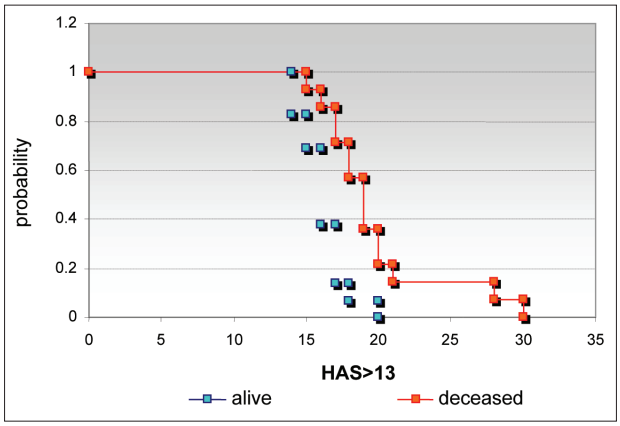


**Fig. 1.** Estimated survival probability at 24 months follow-up based on HAS cutoff at 13 points. Log-Rank (Cox-Mantel=8.5, df=1, p <0.0035).

baseline measurement (p<0.015). Odds ratio analysis showed that hospitalized patients had twice the chance of having a HAS >13 compared to those who were not hospitalized during the study period (OR=2.152, CI 95% (1.0024-4.619).

At the end of the study period, 15 patients were deceased. The mortality rate was insignificantly higher in men than in women. The HAS values at baseline were measured in 12 out of 15 of the deceased patients and 11 of those had a HAS >13. The mortality rate was significantly higher in patients with a HAS >13 at the first 12-month follow-up ($\chi 2$=16.416, p<0.0001). Kaplan-Meier survival analysis showed that patients with a HAS≤13 had a significantly higher survival rate. The survival rate decreased in patients with a higher HAS, and was just 2.1% in subjects with a HAS >18. Patients with a HAS >13 had significantly higher probability of death (log-rank Cox-Mantel=17.920, df=1, p <0.00023) (Fig. 1).

## DISCUSSION

Traditionally used models to assess dialysis adequacy relied on different, single or combined, parameters known to influence the quality of the treatment. Introducing measurements of dialysis dose (the URR and Kt/V indexes) enabled quantification and individualization of treatment, significantly contributing to quality improvement. However, besides good laboratory results, current dialysis treatment should provide the patient with full rehabilitation, a satisfactory nutritional status, stabilized blood pressure, anemia and bone metabolism should be under control, and prevent the development of neuropathy, resulting in low comorbidity rates and longer survival. A contemporary, comprehensive model of dialysis adequacy would include elements previously used to assess the quality of HD treatment, as well as the presence of MICS, and would be predictive of patients' outcome.

Previous research has shown that different parameters, such as anemia, hyperphosphatemia and comorbidities have significant impact on the final outcome in HD patients [15-21]. By optimizing the dialysis treatment, these parameters and the outcome can be improved. Furthermore, optimizing these variables is one of the major prerequisites to prevent MICS, which independently influences outcome in HD patients [22-24].

In this study, we evaluated the predictive value of the HAS as a novel complex model to assess quality and outcome of treatment in HD patients, but also the presence and severity of MICS. The HAS was designed to include several elements previously known to exert significant impact on dialysis adequacy, quality of treatment and development of MICS. The first two scores included in the HAS, the CCI and KI, assessed functional status and comorbidities in HD patients. Other elements of the HAS were chosen as determinants of major clinical features of end-stage renal failure itself and HD treatment, which are independently related to outcome – dialysis dose, nutrition, anemia and calcium-phosphate metabolism [18,19,25,26].

The CCI and KI are known and well-validated models that have been successfully used to evaluate functional status and comorbidities in HD patients [27,28]. Previous studies have shown that comorbidities are among the key predictors of morbidity and mortality rate in dialyzed patients [20,29]. The merit of the CCI and KI in predicting morbidity and mortality in HD patients has been validated in a number of studies [30,31]. In order to avoid the influence of age, no points were added for seniority. Individual CCI values confirmed a high prevalence of comorbidities in our population group. The functional capacity in our study population, as determined by KI, showed significant improvement over the study period, indicating efficient HD treatment in surviving patients.

Dialysis dose as an element of the HAS was determined by referring to the URR and Kt/V indexes, which have traditionally been used as measures of HD adequacy [31]. However, several studies have shown that in patients with good clearance of small molecules, a further increase in dialysis dose has virtually no influence on lowering mortality, thus implying that from thereon other factors may be involved [3,4]. Nonetheless, providing an adequate dialysis dose is mandatory to achieve optimum values of other important parameters of HD quality. All patients in our study group received an optimum dialysis dose, based on the URR and KT/V values.

Protein-energy malnutrition (PEM) is well-known and highly prevalent among HD patients [33]. It is known to decrease functional capacity and quality of life, and increase morbidity and mortality rates in these patients [24,34]. Nutrition status as an element of the HAS has been evaluated with BMI and serum albumin levels in this study. PEM is also associated with chronic inflammation, which independently contributes to malnutrition in HD patients [35]. Because these two conditions often occur concomitantly in HD patients, they have been referred to together as the MICS. MICS is reported to correlate with poor outcome, including a decreased quality of life, refractory anemia and significantly greater rates of hospitalization and mortality [36]. The presence of MICS in our study population was evaluated by the MIS, as a well-established and validated score [14]. The significant correlation between the CCI, KI and MIS suggested a strong relationship between the presence of comorbidities, functional capacity and MICS. The MIS also correlated significantly with the HAS, thus implying an important connection between dialysis quality and the presence and severity of MICS.

Anemia is a major risk factor that contributes to mortality in patients with chronic kidney disease [36]. It is associated with left ventricular hypertrophy and heart failure [17,29,38]. Laboratory surrogates of iron stores, nutritional status and the delivered dose of dialysis are predictive of hemoglobin concentration [40]. Furthermore, anemia is known to be more frequent in HD patients with MICS [37,41]. Our model of dialysis adequacy included hemoglobin and ferritin as indices of anemia and iron stores. Serum ferritin is also a marker of inflammation. Their levels at baseline suggested suboptimal anemia correction in our study population, but a tendency of improvement was noted during the study period.

It is a well-established fact that hyperphosphatemia, hypercalcemia, high calcium-phosphate product and hyperparathyroidism are independent risk factors for mortality in HD patients [18,19]. The disturbed calcium-phosphate metabolism contributes to chronic inflammatory response, progressive cardiovascular calcifications, atherosclerosis and poor anemia correction in end-stage renal disease patients [24,41]. Calcium-phosphate product and iPTH were included in the HAS. During the follow-up period, these parameters showed high variability, resulting in fluctuating bone metabolism activity, which was mirrored by the iPTH levels.

Hemodialysis patients have up to 20 times higher mortality rate than the general population, and thus, their expected survival rate is significantly lower [3,25,42]. We confirmed a significant correlation between survival rate and the level of the HAS. The probability of survival was significantly higher in HD patients with a HAS <13, but was decreased with a further increase in 13 HAS points, implying that the cutoff level for the HAS at 13 points could be associated with an unfavorable outcome.

The complexity of physiological kidney functions and the HD process as a partial substitution of insufficient organs explains the difficulties in defining a universal and comprehensive model to assess the adequacy of dialysis therapy. The HAS, the novel complex model of dialysis adequacy presented and evaluated in this study, appears to be a reliable predictor of dialysis adequacy and outcome in HD patients, and is well associated with the MIS as a measure of MICS.

**Authors' contribution:** Vlastimir Vlatković, Biljana Stojimirović and Jasna Trbojević-Stanković were responsible for the study conception and design and the drafting of the manuscript. Jasna Trbojević-Stanković and Dejan Nešić collected the literature. Vlastimir Vlatković and Biljana Stojimirović made critical revisions to the paper. Jasna Trbojević-Stanković and Dejan Nešić provided statistical expertise.

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