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Correlation betweenQuantitative C-Reactive Protein and Dialysis Duration: A Study of Twice-a-Week Hemodialysis Patients

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Introduction. The correlation between quantitative C-reactive protein (CRP) and dialysis duration in twice-a-week hemodialysis patients has not been examined extensively. This study aimed to examine the relationship between quantitative CRP and dialysis duration in twice-a-week hemodialysis patients.
Methods. It involved cross-sectional observation of 62 hemodialysis patients at H. Adam Malik General Hospital, Medan, Indonesia, between March and October 2019. Interviews, clinical examinations, and a review of medical records were used for data collection. Hematology analyzer was used to measure the Blood Urea Nitrogen (BUN), Hemoglobin, creatinine, and differential leucocyte counts, while colored latex immunofiltration assays (IFAs) was used to analyze the qualitative CRP. The correlation between quantitative CRP and dialysis duration and hemoglobin assessed using the Spearman's correlation test.
Results. The result did not show any correlation between quantitative CRP and dialysis duration (r = 0.091; p = 0.240), but there was a significant inverse correlation between dialysis duration and hemoglobin (r = -0.234; p = 0.033) and a significant inverse correlation between quantitative CRP and hemoglobin (r = -0.144; p = 0.032).
Conclusion. This study revealed that there was no significant correlation between quantitative CRP and dialysis duration, but it was correlated with low hemoglobin twice-a-week in hemodialysis patients. The findings of the report provide the basis for further study.
Keywords: Quantitative CRP, Hemoglobin, dialysis duration, twice-a-week hemodialysis

INTRODUCTION

The risk of morbidity and mortality is higher forChronic hemodialysis (HD) patients than the general population [1,2]. There is a growing perception of inflammation as a new risk factor for morbidity and mortalitydue to increasing interest in the role of inflammation in end-stage renal disease (ESRD), and HD has increased [3].The causes of inflammation in HD patients is associated with multiple factors associated with senescence, toxic uremic milieu, white blood cells countand sometimes the dialysis itself[4,5,6].

Detecting circulating inflammatory disorders in chronic HD patients has been done using various markers such as interleukin-6, C-reactive protein (CRP), and tumor necrosis factor-α [7]. Some studies regard CRP as the most effective forecaster of cardiovascular events[2,8,9].

Hemodialysis is a major renal replacement therapy for ESRD patients. Sufficient dialysis improves health-related quality of life, biochemical outcomes, and increases patient survival of the patient and reduces hospitalization health complications related to the disease [10]. Additionally, adequate therapy reduces morbidity and mortality of the patients [11,12]. Traditionally, patients' dialysis has involved the use of Thrice-weekly HD as standard renal replacement therapy. Twice-weekly HD is the most common method in developing countries and sometimes in developed countries[13,14]. Measuring the adequacy of dialysis is the essentialprinciple for assessing the HD process. The is uncertain in the patients undergoing dialysis twice a week experience uncertainty of target urea reduction ratio (URR),with each treatment expected to achieve URR of ≥65% [15]. This study was conducted based on prior studies of patients undergoing HD twice a week due to the significance of inflammatory factors, specifically the quantitative CRP.

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MATERIALS AND METHODS

Study Population

This study involved a cross-sectional method and was carried out in Medan, Indonesia, between March and October 2019.The study population comprised of all HD patients at H. Adam Malik General Hospital. The researcher obtained approval to research the Health Research Ethics Commission Faculty of Medicine, University of Sumatera Utara. H. Adam Malik General Hospital in Medan, Indonesia no 433/TGL/KEPK FK USU-RSUP HAM/2019. The subjects were issued with written informed consent to participate in this study. Vascular access was performed through functioning arteriovenous (AV) graft.

The selection criteria for research participants involved the patient receiving routine HD and the following requirements: (a) The participants must have undergone regular HD twice a week and have a stable hemodynamic state. (b) The participants must be male and females aged 18 years and above. (c) Must have used drugs related to the primary diseases only with no effects on CRP (d) Used the Fresenius Polysulfone® high-flux dialysersand bicarbonate solution to conduct HD (e) discontinuation of the medicines that affected CRP at least during the drug washout period(f) only nonsmokers Participants were included. (g) The participants includedpatients without diabetic foot, coexisting inflammatory diseases, who had not received blood transfusions three months before the study, and with no infectious diseases except underlying renal disease.

Measurements and Definitions

Interviews, clinical examinations, and a review of medical records were used for data collection. All the laboratory tests were carried in at a single laboratory. Venous blood samples were collected before the HD procedure. Immediately after the completion of HD, the body mass index (BMI) was calculated. DIRUI BCC-3000B hematology analyzer was used to measure the Blood Urea Nitrogen (BUN), Hemoglobin, creatinine, and differential leucocyte counts(Dewei Medical Equipment Co., Ltd.), while colored latex immunofiltration assays (IFAs) was used to analyze the qualitativeCRP data.

The assessment of dialysis adequacy was done using the URR calculated three days and before the next HD session with thefollowing formula: URR (%) = 100 × (1- Ct/Co), BUN before (Co), and BUN after (Ct) HD.URR >65% denotesufficient dialysis.Standard maintenance HD was appliedto all patients.

The formula for calculating BMI include: BMI = weight (kg)/height (m^2).The Asian-Pacific cutoff pointswas categorize BMI into four clusters according including underweight (<18.5 kg/m^2), normal weight (18.5–22.9 kg/m^2), overweight (23–24.9 kg/m^2), and obese (≥25 kg/m^2) [16].

The standard laboratory value referenceswereas follows: hemoglobin (g/dL) (13–18), white blood cells ($10^3/\mu L$) (4–11),basophils (%) (0–1), lymphocytes (%) (20–40), eosinophils (%) (1–3), neutrophils (%) (50–70), monocytes (%) (2–8),creatinine (mg/dL) (0.7–1.3), and quantitative CRP (mg/dL) (<0.7).

The primary objective of this study was to examine the relationshipbetween quantitative CRP and dialysis duration. The secondary objective was to examine the correlation between the dialysis periodand some characteristics in twice-a-week hemodialysis patients.

Statistical Analysis

The IBM Social Sciences Statistical Package (SPSS) was used for statistical calculations (IBM-SPSS Inc., Chicago, IL, USA). The normally distributed data was determined for all the parametersusing the Shapiro–Wilk test. The Normally distributed binary data were presented as mean, and the standard deviation or abnormally distributed data areshown as median (Me) and minimum-maximum, number (n)and percentage (percent) of categorical data. Abnormally distributed data correlations were determined using Spearman's correlation test. $P<0.05$ was considered significant.

RESULTS

Table 1. Characteristics subject.

Characteristics	n=62
Gender: n (%)	
Male	45 (72.60)
Female	17 (27.40)
Age (years): median (range)	54(20–77)
Co-morbidities: n (%)	
Hypertension	27 (43.54)

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Diabetes nephropathy	21 (33.87)
Obstructive uropathy	14 (22.59)
Dialysis vintage (month): median (range)	36.00 (8.00–84.00)
Body mass index: mean±SD	22.64± 4.25
Hemoglobin (g/dL): mean±SD	9.45±1.43
White blood cells (10^3/μL): mean±SD	7.53±2.98
White blood cell differential:	
Neutrophils (%): median (range)	70.70 (33.70–85.90)
Lymphocytes (%): median (range)	16.38 (3.7–27.80)
Monocytes (%): median (range)	8.10(4.30–12.60)
Eosinophil (%): median (range)	3.20 (0.40–39.20)
Basophils (%): median (range)	0.40 (0.00–1.60)
Creatinine (mg/dL): mean±SD	15.50±3.90
Quantitative-CRP (mg/dL): mean±SD	0.58± 0.49
Urea reduction rate (%): mean±SD	69.95±8.99

A total of 62 HD patients participated in the study. Fifty-four years was the median age of the subjects (45 males and 17 females),and36 months was the median dialysis duration.Hypertension patients were 27 (43.54% of the total), andcreatinine, monocytes, Neutrophils, and quantitative CRPwere higher than the laboratory reference value, while thehemoglobin value was lower(Table 1).

Table 2. Relationships between quantitative-CRP and various characteristics.

Characteristics	r	r^2	p-value
Age	0.027	0.001	0.418
Dialysis vintage	0.091	0.008	0.240
Body mass index	0.071	0.005	0.293
Hemoglobin	-0.144	0.021	0.032*
White blood cells	0.332	0.110	0.004*
White blood cell differential: Neutrophils Lymphocytes Monocytes Eosinophil Basophils	0.182 -0.233 0.102 -0.094 -0.114	0.033 0.054 0.010 0.008 0.013	0.078 0.034* 0.215 0.233 0.188
Creatinine	0.053	0.003	0.342
Urea reduction rate	-0.142	0.020	0.136

Spearman correlation test, *p<0.05.

Table 2 shows the correlation between quantitative CRPand various characteristics.There was no substantial correlation between quantitative CRP and all the characteristics;However,there wassignificant correlation observed with white blood cells ($r = 0.332$; $p = 0.004$), hemoglobin ($r = -0.144$; $p = 0.032$), and lymphocytes ($r = -0.233$; $p = 0.034$).

Table 3. Correlation between dialysis vintage and various characteristics.

Characteristics	r	r^2	p-value
Body mass index	-0.027	0.001	0.418
Hemoglobin	-0.234	0.0545	0.033*
White blood cells	-0.108	0.012	0.278

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White blood cell differential: Neutrophils Lymphocytes Monocytes Eosinophil Basophils	 0.047 -0.76 0.128 -0.044 0.016	 0.002 0.577 0.016 0.001 0.000	 0.358 0.279 0.160 0.368 0.452
Creatinine	0.029	0.000	0.412
Urea reduction rate	-0.076	0.006	0.278
Qualitative-CRP	0.091	0.008	0.240

Spearman correlation test, *p<0.05.

Table 3 shows the correlation between dialysis duration and numerous characteristics. There was a significant correlation of dialysis duration with all the characteristics; however, there was a significant inverse correlation with Hemoglobin (r = -0.234; p = 0.033).

DISCUSSION

Previous studies described the linkage of prolonged dialysis duration with higher mortality in HD patients [17–19], which is related to a higher risk of cardiac disease mortality[20,21]. HD has varioussignificant risk factors, such as inflammation [22].Patients with chronic HD have a higher risk of inflammatory reactions to dialysis membranes, fistulas, grafts, and infection sites. The increased levels of inflammatory markers such as CRP serum, is related to these reactions[23].

The study established three significant outcomes: The first finding is that quantitative CRP and dialysis duration have no significant correlation; secondly, quantitative CRP and Hemoglobin have a significant inverse correlation; and thirdly, dialysis duration and Hemoglobin have a significant inverse correlation. These findings show that high quantitative CRPis related to lowHemoglobin in prolonged dialysis duration twice-a-week HD patients.

These results support the evidence that the inflammation process changes the hemoglobin level of converse CRP concentrationswith a linear relationship pattern in HD patients[24–27].

There is a direct correlation between inflammation and glomerular filtration rate in chronic kidney disease (CKD) that culminates in dialysis patients, where extracorporeal factors such as bioincompatible dialysis circuit, dialysate microbiological quality, and water dialysis impurities play crucial role. Currently Genetic and epigenetic effects that lead to inflammatory activation in CKD are under rigorousstudy[3].

Inadequate production of endogenous erythropoietin (EPO), a hormone that influences the differentiation and maturation of red blood cell precursors, is the leading cause of anemia in CKD. Recently, certain causative factors have been identified as an impaired response of the bone marrow toEpo caused by inflammation, decreased iron availability for erythropoiesis, increased hepcidin levels, shortened half-life, uremic toxins, or vitamin deficiencies of red blood cells (vitamin B12 or folic acid), among others [28].

Inflammation in CKD is a significant factor contributing to resistance to anemia and Epo[29]. The inflammatory process alters the hemoglobin level in a converse correlation with the CRP concentration with a linear relationship pattern [26].

Sufficient dialysis can improve the quality of life,reduce mortality, and increase the longevityof patients undergoing HD [30]. URR and urea kinetic modeling (Kt/V) is used to assess the sufficiency of dialysis [31], a URR of approximately 65% (equivalent to a single pool Kt/V of 1.2) is considered sufficient[32].

The other findings of the study showedthat qualitative CRP and URR do not correlate. These findings are related to the findings of Hemayati*et al*. and Yin *et al*. 's research that suggests that adequacy and inflammatory status do not correlate[33,34].

There are limited clinical studies involving inflammation and anemia for twice-weekly HD patients. Aretrospective cohort researchin Shanghai and the findingsestablished that twice-weekly HD patients did not havelowHemoglobin as compared with thrice-weekly HD [35].

Colored latexIFAs were used in the studyto measure quantitative CRP. These assays are easy to use, made of expensive materials or equipment, and do not require highly skilledtechnicians[36].However, they have limitations because they are not sufficient for analyzing high concentrations of analytes. These primary causes of these

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limitations are that IFAs depend on label accumulation to generate detectable signals, cross-reactivity effects, and nonspecific bindings thatmainly occur at a high protein concentration[37]. It is essential to consider statistical power and sample size whenever there are negative findings from the study. This study's statistical power was low, although it was one of the largest studies involving repeated CRP measurements in chronic HD patients. The nonsignificant correlation may have been due to the small sample sizeand significant variations between participants.

In conclusion, high quantitative CRP was not correlated with dialysis duration, but it was associated with lower hemoglobin in twice-weekly hemodialysis patients on prolonged dialysis.

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CONFLICTS OF INTEREST

All the authors declare that there are no conflicts of interest related to this paper.

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