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Feasibility of inspiratory muscle training as a rehabilitation program for chronic kidney disease patients in a developing country

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Abstract. – OBJECTIVE: Hemodialysis (HD) twice a week is a Renal Replacement Therapy (RRT) option other than kidney transplantation in developing countries, such as Indonesia, due to its cost, limited facilities, and national social-health policy. The effectiveness of inspiratory muscle training (IMT) as a rehabilitation program for chronic kidney disease (CKD) patients undergoing HD twice a week remains unclear. This study aims to evaluate the effect of IMT on kidney function, the immune system, and quality of life (QOL) of CKD patients undergoing HD twice a week.

PATIENTS AND METHODS: A randomized controlled trial (RCT) study was conducted at Regional Province Hospital of West Java, involving thirty-two CKD patients receiving HD twice a week. All participants underwent 12 weeks of IMT, administered three days a week at a 50% Maximal Inspiratory Pressure (MIP) in the intervention group (n=16), and at a 10% MIP in the control group (n=16). Urea level, creatinine level, Interlukine-6 (IL-6) level, and QoL score were measured before and after intervention.

RESULTS: The MIP increased after IMT rehabilitation in both groups (p=0.0001). Urea, IL-6, and creatinine levels decreased after IMT rehabilitation in intervention groups, although the differences were not significant. Significant improvements were observed in the intervention group's QoL score after IMT rehabilitation (p=0.001).

CONCLUSIONS: IMT rehabilitation improved the MIP and QoL scores in CKD patients. Although not statistically significant, there were decreases in urea, creatinine, and IL-6 levels after the IMT rehabilitation. This trial was registered at ClinicalTrial.gov with the identifier number: NCT05241652.

Key Words:
Chronic kidney disease, Rehabilitation, Quality of life.

Introduction

Chronic kidney disease (CKD) is a major global health issue that is increasing in prevalence, paralleling the rise in mortality and morbidity, thereby exacerbating the impact of CKD. According to the 2017 Global Burden of Disease (GBD) report, 35.8 million years of healthy life are lost due to CKD-related premature death and disability[1]. It is characterized by changes in the kidney structure and functions for more than three months and is grouped into several stages, including end-stage renal disease (ESRD) requiring renal replacement therapy (RRT)[2].

Hemodialysis (HD) is one of the RRT options other than kidney transplantation[2]. Renal transplant services are currently recommended in preference to other therapies due to improved quality of life (QoL). However, the availability of kidney donors is a challenge, as is the need for additional health facilities that provide kidney donor services. There are currently only ten hospitals that can perform kidney transplantation in Indonesia. The Indonesian Social Health Insurance Administration Body or Badan Penyelenggara Jaminan Sosial Kesehatan (BPJS) provides a wide range of kidney failure health services, including transplantation and HD twice a week for each patient[3].

The uremic syndrome is a complication of CKD that causes myopathy and muscle mass loss in 75% of patients on HD, leading to decreased respiratory and peripheral muscle strength and cardiorespiratory endurance, which impacts daily activities and causes patients to exhaust quickly, thereby decreasing QoL[4-6]. Chronic HD can enhance inflammation, with levels of pro-inflammatory cytokines, Interlukine-6 (IL-6), and tumor

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necrosis factor-alpha (TNF-α) increasing in patients with CKD. The elevated levels of these chronic inflammatory mediators have been associated with numerous disorders, including muscle atrophy, malnutrition, chronic infections, and atherosclerosis, which are the main causes of morbidity and mortality[7].

Regular moderate-intensity exercise may improve some aspects of the immune system and have anti-inflammatory benefits[8]. Aerobic exercise, extremity muscle strength exercises, and inspiratory muscle training (IMT) have been reported to improve kidney function and QoL in CKD patients receiving HD three times a week[8]. Stretching resources to maximize outcome benefits is critical, and twice-weekly HD sessions are an improved and cost-effective clinical practice in Indonesia[9-11]. Additionally, observational studies[12,13] of twice-weekly HD in Taiwan and China have shown a possible benefit of slower renal function decline and good nutritional status in recent years. However, the effect of IMT on kidney function and QoL in CKD patients receiving HD twice a week remains unclear[4-6].

This study evaluated the impact of IMT rehabilitation on improving inflammatory cytokine IL-6, kidney function, and QoL in end-stage CKD patients receiving HD twice a week.

Patients and Methods

Study Design

A randomized controlled trial compared the impact of IMT rehabilitation on improving inflammatory cytokine IL-6, kidney function, and QoL in the controlled and intervention group of end-stage CKD patients receiving HD twice a week. The study was approved by The Profession and Research Ethics Committee of the Medical Committee of Padjadjaran University Faculty of Medicine (ethical clearance number: 1158/UN6.KEP/EC/2019) and was registered at ClinicalTrial.gov (NCT05241652). Furthermore, the study was conducted following the Declaration of Helsinki. All participants provided written informed consent.

Participants and Inclusion/Exclusion Criteria

Participants diagnosed with end-stage CKD who received HD twice a week for more than three months in Regional Province Hospital of West Java, were selected by consecutive sampling. The inclusion criteria were: age 45-54 years, can perform respiratory muscle training (RMT) procedures, have a maximal inspiratory pressure (MIP) <70% of the predicted measurement results using the MicroRPM respiratory pressure meter (RPM) tool (Lewiston, ME, United States), hemoglobin level ≥8 g/dL, ability to understand oral and written instructions, cooperative and willing to participate in the research, and able to do exercises after signing an informed consent form. The RMT used was inspiratory muscle training (IMT). The exclusion criteria were: patients with obstructive lung disease, pleural effusion, cardiomegaly, heart failure, coronary heart disease, history of pneumothorax, history of thoracic or abdominal surgery in the last six months, disturbances related to eardrum damage, have received inspiratory and expiratory muscle training in the past six months, and blood pressure >180/110 mmHg or <80/60 mmHg. Thirty-two subjects were randomly divided into two groups: control (n=16) and intervention (n=16) (Figure 1).

Procedure and Outcome Measures

Urea, creatinine, and IL-6 (before HD) levels were measured, and an interview using the Indonesian version of the Kidney Disease Quality of Life Instrument Short Form (KDQoL-SF) was conducted before and after the IMT rehabilitation[14].

The intervention group was assigned an IMT rehabilitation that included inspiratory muscle strengthening rehabilitation thrice a week for 12 weeks at a 50% MIP intensity, five sets per time, ten breathing repetitions per set, for an estimated duration of 20 minutes each using Philip Respironic Threshold IMT equipment (Tangmere, Chichester, UK). The control group received the same intervention, except for the intensity of MIP, which was 10%.

Serum urea and creatinine levels were used to measure kidney function. IL-6 levels were used to measure immune function. The IMT rehabilitation included specific exercises to improve ventilation through coordination, endurance, and respiratory strength of the inspiratory muscles. MIP was measured using MicroRPM (Lewiston, ME, USA) before inspiratory muscle strengthening rehabilitation.

The KDQoL-SF v1.3 questionnaire was used to measure the QoL. This questionnaire consists of a physical component summary (PCS), a mental component summary (MCS), and a kidney disease component summary (KDCS).

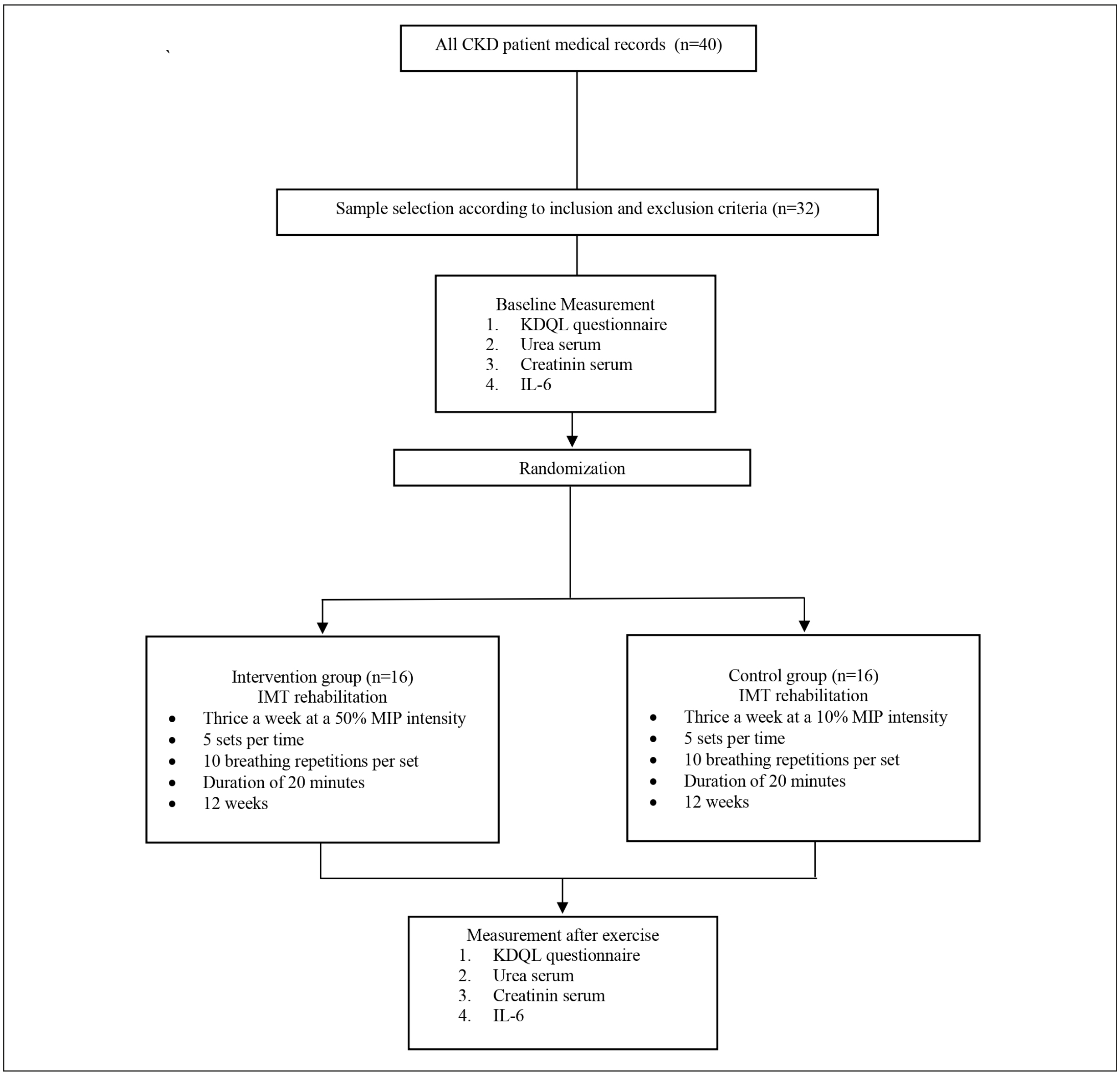

Figure 1. Flow diagram of patients throughout the study.

Statistical Analysis

The Shapiro-Wilk test was used to determine the normality of the variables. Normally distributed data were compared using unpaired *t*-tests and the Mann-Whitney test was used for non-normally distributed data. Categorical data were compared using Fisher's test. A paired *t*-test was used to compare mean differences before and after intervention for normally distributed data, and the Wilcoxon's test was used for non-normally distributed data. The data were analyzed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA) for Windows with a *p*-value <0.05 considered statistically significant.

Results

Thirty-two patients met the inclusion criteria and were divided into two groups of sixteen subjects each. The patients' clinical and demographic characteristics are presented in Table I, and there is no significant difference between the two groups indicating data homogeneity.

There was no significant difference in the MIP and IL-6 levels between the two groups (Table II). However, there was a significant difference in the MIP before and after the IMT rehabilitation, with the MIP increasing by 52.13 cmH_2O (p<0.001) and 50.75 cmH_2O (p<0.001) in the intervention

Table I. Subjects' characteristics.

Variable	Intervention group (n=16)	Control group (n=16)	*p*-value
Age (years)			**0.864***
Mean±SD	45.13±8.17	45.69±10.14	
Median	46.00	44.00	
Range (min-max)	31.00-59.00	30.00-59.00	
Sex			**0.433****
Male	6 (37.5%)	3 (18.8%)	
Female	10 (62.5%)	13 (81.3%)	
Weight (kg)			**0.089***
Mean±SD	57.91±10.62	51.95±8.41	
Median	55.25	50.50	
Range (min-max)	41.50-77.50	41.00-69.00	
Height (m)			**0.797***
Mean±SD	1.56±0.07	1.55±0.09	
Median	1.56	1.55	
Range (min-max)	1.48-1.70	1.43-1.80	
BMI (kg/m^2)			**0.068***
Mean±SD	23.71±4.02	21.46±2.55	
Median	22.53	20.79	
Range (min-max)	18.20-34.44	16.98-26.95	
HD duration (month)			**0.102*****
Mean±SD	40.94±17.15	32.00±20.19	
Median	48.00	24.50	
Range (min-max)	9.00-67.00	9.00-87.00	
BSA (m^2) – Mosteller			**0.136 ***
Mean±SD	1.58±0.16	1.49±0.15	
Median	1.55	1.47	
Range (min-max)	1.32-1.88	1.28-1.76	
Hemoglobin (mg/dl)			**0.451***
Mean±SD	10.43±1.16	10.14±0.96	
Median	10.40	10.10	
Range (min-max)	8.40-12.20	8.50-11.40	
MIP (cmH_2O)			**0.911***
Mean±SD	34.06±21.47	34.75±11.86	
Median	27.50	34.50	
Range (min-max)	9.00-75.00	17.00-56.00	

$p<0.05$ indicating statistical significance. *Unpaired *t*-test, **Fisher's test, ***Mann-Whitney Test. SD: Standard Deviation, BMI: Body Mass Index, BSA: Body Surface Area, HD: hemodialysis, MIP: Maximal Inspiratory Pressure.

and control groups, respectively, after the IMT rehabilitation. The effects of IMT rehabilitation on kidney function are presented in Table II, showing no significant difference in urea levels between the groups before and after the IMT rehabilitation. There was a decrease in urea levels before and after the IMT rehabilitation in the intervention group ($p>0.05$). Meanwhile, there was an increase in urea levels in the control group before and after the IMT rehabilitation ($p>0.05$). There was no significant difference in creatinine levels in the two groups before and after the IMT rehabilitation (Table II).

The effects of IMT rehabilitation on QoL parameters are presented in Table III, showing no significant difference between the intervention and control groups in PCS, MCS, and KDCS before the IMT rehabilitation. However, the groups showed a significant difference in PCS, MCS, and KDCS after the IMT rehabilitation. The intervention group's PCS, MCS, and KDCS scores were higher than the control group after the IMT rehabilitation ($p<0.001$).

Discussion

Age is associated with estimated glomerular filtration rate (eGFR), affecting urea and creatinine levels. The age of the subjects ranged between 30 to 59 years. According to Hemmelgarn et al[15], the eGFR of elderly CKD patients will decline by 0.8 to 2.7 mL/1.73m^2 every year. Age is related to the QoL. Manavalan et al[16] stated that age >50 years was associated with a low PCS value. Similarly,

Table II. Effect of the IMT as a rehabilitation program on MIP, immune function, and kidney function parameters.

Variable	Intervention group (n=16)	Control group (n=16)	*p*-value
MIP (cmH_2O)			
Before	34.06±21.47	34.75±11.86	**0.911***
After	86.19±26.89	85.50±28.72	**0.945***
***p*-value**	**0.0001********	**0.0001********	
IL-6 (pg/ml)			
Before	6.77±11.44	11.24±14.76	**0.423*****
After	3.72±2.32	6.18±7.09	**0.752*****
***p*-value**	**0.215*********	**0.070*********	
Urea levels (mg/dl)			
Before	157.56±25.42	152.94±36.22	**0.679***
After	147.00±24.73	157.38±35.89	**0.349***
***p*-value**	**0.169********	**0.429********	
Creatinine levels (mg/dl)			
Before	14.44±2.44	13.11±2.10	**0.112***
After	13.79±2.37	12.89±2.07	**0.269***
***p*-value**	**0.058********	**0.378********	

$p<0.05$ indicate statistical significance. *Unpaired *t*-test, ***Mann-Whitney Test, ****Paired *t*-test, *****Wilcoxon test. MIP: Maximal Inspiratory Pressure, IL-6: Interleukin-6.

Table III. Effects of the IMT as a rehabilitation program on quality-of-life parameters.

Variable	Intervention group (n=16)	Control group (n=16)	*p*-value
PCS (mean±SD)			
Before	40.09±4.92	40.87±7.39	**0.743***
After	51.86±7.61	43.06±6.88	**0.001*****
***p*-value**	**0.0001*********	**0.063********	
MCS (mean±SD)			
Before	50.13±8.81	44.18±8.68	**0.064***
After	53.10±6.69	44.88±7.68	**0.005***
***p*-value**	**0.115********	**0.752********	
KDCS (mean±SD)			
Before	72.32±8.33	69.60±9.58	**0.445*****
After	80.69±6.41	71.34±11.06	**0.007***
***p*-value**	**0.001********	**0.469*********	

$p<0.05$ indicates statistical significance. *Unpaired *t*-test, ***Mann-Whitney Test, ****Paired *t*-test, *****Wilcoxon test. PCS: Physical Component Summary, MCS: Mental Component Summary, KDCS: Kidney Disease Component Summary.

the study by AL-Jumaih et al[17] also reported that patients aged >40 had a lower PCS value.

Our study subjects comprised primarily women, accounting for 71.9 % of all subjects. Carrero et al[18] and Fenton et al[19] reported that men tend to have higher GFR than women. The decrease in GFR in men is not very significant with age, but estrogen decreases with increasing age in women, which can disrupt kidney structure. Nisha et al[20] reported higher urea and creatinine levels in male HD patients compared to their female counterparts. Creatinine is synthesized in skeletal muscle, so its levels are determined by muscle mass. Since men have more muscle mass than women, their creatinine levels are higher.

IMT rehabilitation improved MIP in the present study, with no significant differences between groups, indicating a similar increase in MIP after the IMT rehabilitation in both the intervention and control groups. Similar effects were observed in previous studies[4,6,21]. However, Da Silva et al[22] found no significant effect of IMT rehabilitation on MIP, but the intensity and duration in their study differed from the current study, with the IMT rehabilitation performed for eight weeks with a duration of 15 and 30 minutes in the first and latter four weeks, respectively. The respiratory muscles respond to exercise in the same way that the skeletal muscles do and adapt to changes in their structure, which improves muscle performance. Simultaneous IMT can engage the expiratory muscles during continuous exercise. The histological test showed an increase in type I muscle fibers and decreased type II fibers after respiratory muscle training. Type I fibers are slow to contract and weak but are highly durable, whereas type II fibers are fast-contracting but not as durable. The strength of the MIP is correlated to the thickness of the diaphragm muscle[23].

The chronic inflammatory state in CKD is caused by a complex dysfunction that affects both the innate and adaptive immune systems. The progressive renal injury affects metabolite elimination through endotoxin exposure and decreased excretion due to changes in renal filtration, resulting in local and systemic activation of pro-inflammatory cytokines[24]. Elevated plasma IL-6 levels are prevalent in CKD patients and increase renal injury and complications, including chronic vascular disease (CVD)[25,26]. Exercise causes a variety of immunological responses, including the production of interleukins. There is some evidence that exercise is correlated with a reduction in systemic inflammation[27]. In our study, there was a decrease in IL-6 levels after IMT rehabilitation in both groups, albeit insignificant. A similar effect was observed in the studies of Lavratti et al[28] and Kapilevich et al[29] who reported that prolonged exercise and regular exercise decrease baseline IL-6 levels.

A study by Viana et al[8] showed that plasma IL-6 levels tended to decline, whereas plasma IL-10 levels increased, resulting in a significantly lower IL-6 to IL-10 ratio in the circulation after six months of regular exercise (home-based walking exercise program) in CKD patients. In contrast, our study used IMT as an exercise mode with a 12-week duration with the decrease in IL-6 associated with the mode, intensity, and duration of physical exercise and other characteristics such as age and fitness levels of the study participants[11,30].

Many other studies[31,32] have also reported that an increase in IL-6 levels caused by acute exercise causes an anti-inflammatory response by inhibiting the activation of pro-inflammatory TNF-α and by promoting the release of other predominantly anti-inflammatory immunological molecules. Viana et al[8] observed an increase in plasma IL-6 levels after acute exercise in the form of a 30-minute walk on a motorized treadmill with a 1% gradient at a pace that elicited a rating of perceived effort (RPE) in the 12-14 range.

Progressive kidney disease is characterized by increased creatinine and urea levels, so the assessment of their serum levels helps to assess GFR and kidney function[20]. Our study shows that a 12-week IMT rehabilitation can reduce urea and creatinine levels, albeit not statistically significant. However, the mean creatinine levels decreased in both groups after the IMT rehabilitation despite the intervention group showing a more significant reduction than the control group.

Pellizzaro et al[4] previously reported that administering IMT exercise with three sets, 15 repetitions, 50% MIP intradialytic for ten weeks in CKD patients receiving HD thrice a week provided a more significant reduction in urea and creatinine levels compared to knee extensor muscles strengthening exercises. Our study used exercise intensity identical to that of Pellizzaro et al[4], but the duration increased to 12 weeks. Although not statistically significant, our study found a decrease in urea and creatinine levels after exercise. Previous studies[33,34] showed that patients with a residual renal function who underwent twice-a-week HD had lower HD adequacy than those with thrice-a-week HD. Hwang et al[34] also reported that the urea levels of patients undergoing HD twice a week were higher than those undergoing HD thrice a week.

Twice-a-week HD frequency affects remaining kidney function, HD adequacy, and urea and creatinine excretion. Additional exercise in CKD patients is assumed to optimize HD outcome, although the treatment still plays a significant role as RRT for excretory function. In the present study, the subjects only underwent HD twice a week compared to Pellizzaro et al[4] thrice-a-week frequency. Thus, it might have played a role in the insignificant reduction of urea and creatinine levels.

The mechanism through which IMT rehabilitation improves HD efficiency remains controversial. Intradialytic exercise can improve muscle blood flow and capillary surface area, increasing molecular availability and enabling solute transport to the intravascular compartment, increasing dialysis effectiveness[4,35]. IMT rehabilitation can improve lung capacity, make breathing better, and allow more oxygen into the bloodstream36. Optimal oxygenation is predicted to help improve endothelial function, maintain remaining kidney function, and delay the progression of kidney disease.

IMT rehabilitation can improve endothelial function and oxidative stress, which affect kidney disease progression. Renal tubules have many mitochondria, making them particularly vulnerable to oxidative stress[37]. Endothelium and glycocalyx play critical roles in atherosclerotic processes, including those in the renal tubules. Although the underlying mechanism through which IMT rehabilitation improves endothelial function is unknown, IMT rehabilitation can induce a decrease in sympathoadrenal activation and a decrease in adrenaline and noradrenaline circulation, thereby preventing endothelial and glycocalyx injury. According to Campos et al[38], performing intradialytic IMT can significantly reduce syndecan-1 and endothelin-1, both biomarkers of endothelial and glycocalyx disorders, although the reduction in oxidative stress was not significant. Since various factors affect kidney disease, increasing exercise duration may only inhibit some of them, and the damage may still progress and interfere with kidney function.

The clinical manifestations of CKD and unexpected psychosocial consequences increase stress levels and impact the patient's QoL[39]. According to De Medeiros et al40, IMT can improve patients' QoL with end-stage renal disease. QoL in this study was assessed using the KDQoL-SF v1.3 questionnaire, which consisted of three components: PCS, MCS, and KDCS.

Previous studies[39,40] on CKD patients discussed the effect of exercise on PCS and MCS, stating that combining aerobic exercise and strengthening extremity muscles in CKD patients could improve the QoL measured in the PCS, MCS, and KDCS components. Pellizzaro et al[4] reported that eight weeks of IMT could improve the QoL in pain (PCS sub-component), energy/fatigue (MCS sub-component), disease symptoms, and sleep quality (KDCS sub-component) but not significantly in total PCS, MCS, and KDCS components.

In the literature, it was reported that a considerable amount of time is needed for the exercise to exhibit its effects on QoL. Thus, we set a longer duration for our IMT rehabilitation compared to the study of Pellizzaro et al[4] to significantly improve all QoL components. Our study showed a significant increase after 12 weeks of IMT rehabilitation in the sub-component scores and the overall PCS and KDCS scores.

The PCS is affected by functional capacity. The ability to walk, cardiopulmonary capacity, muscle strength, endurance, coordination, and balance are very influential for daily activities in patients with chronic diseases such as CKD[38]. Increasing the PCS score is essential because this physical component can be used to predict dialysis patient survival. A previous study[17] stated that the increased KDCS score in dialysis patients was related to an increased PCS score. In our study, the mean PCS score increased by 11.77 points (20%) after exercise in the intervention group (p<0.001), while in the control group, it only increased by 2.19 points (5%) (p>0.05).

IMT rehabilitation can increase MIP and improve functional performance. De Medeiros et al[40] reported a mean increase in MIP of 23 cmH_2O after receiving IMT in CKD patients[4]. The current study also observed similar findings in terms of mean MIP, where we observed a significant increase of 52.13 cmH_2O (p<0.001) and 50.75 cmH_2O (p<0.001) in the intervention and the control group, respectively, after IMT rehabilitation. Increased inspiratory muscle strength can improve lung capacity so that less energy is used for deeper breathing and more oxygen enters the bloodstream. IMT rehabilitation for at least six weeks significantly reduces the oxygen needed by the respiratory muscles so that more oxygen is available to other muscles. In other words, oxygenation for both respiratory muscles and extremity muscles will be better and will improve functional performance[35,41].

The MCS is affected by emotion, social function, energy, and fatigue. The MCS score in both groups in our study was higher than the PCS score, similar to Manavalan et al[16] who reported an indication of psychological adaptation to chronic disease. The MCS score in our study showed an increase in the items related to energy and fatigue. IMT rehabilitation increased MIP by increasing respiratory muscle strength[41]. Da Silva et al[22] stated that IMT exercises in CKD patients could reduce the Borg scale of shortness of breath in a 6-minute walk test. An increase in IMT can increase energy, thus reducing fatigue during activities[11].

No study has assessed the QoL in CKD patients receiving HD twice a week with IMT exercises. Our study showed that IMT rehabilitation significantly improved the QoL as measured using the PCS and KDCS components of the KDQoL-SF v1.3 questionnaire in CKD patients undergoing HD twice a week.

This study has some limitations as it did not examine other factors affecting urea levels, such as muscle mass, HD adequacy, inflammatory factors, and oxidative stress.

Conclusions

IMT rehabilitation can improve QoL as measured using the PCS and KDCS components of the KDQoL-SF v1.3 questionnaire and increase MIP, thereby improving lung capacity in terminal-stage

CKD patients undergoing HD twice a week. There was also a reduction in urea, creatinine, and IL-6 after IMT in terminal-stage CKD patients undergoing HD twice a week, albeit not significant.

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Authors' Contributions

Irma Ruslina Defi: conceptualization, data curation, investigation, validation, supervision, writing (original draft), reviewing, and editing. Megi Virgiabanon Otafirda: conceptualization, data curation, investigation, writing (original draft), reviewing, and editing. Novitri Novitri: data curation, investigating, reviewing, and editing. Ami Rachmi: data curation, reviewing, and editing.

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Conflicts of Interest

The authors declare no conflict of interest.

Ethics Approval

Ethical clearance was provided by the Ethical Research Committee of Hasan Sadikin General Hospital (Number: 1158/UN6.KEP/EC/2019). This study was registered at Clinical Trials.gov with the reference number: NCT05241652.

Informed Consent

Informed consent was obtained from all subjects involved in the study.

Data Availability

The data used to support the findings of this study have been included in this article.

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