# The Association of Kidney Function Monitoring Adherence and Estimated Glomerular Filtration Rate Changes Among Patients At-Risk for Chronic Kidney Disease

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## ABSTRACT

***Background:*** *Kidney Disease: Improving Global Outcome in 2012 has provided recommendations to prevent CKD progression by monitoring kidney function periodically according to the CKD stage and the clinician's adherence to these guidelines is important. This is the first study on the relationship between adherence to monitoring renal function and changes in estimated glomerular filtration rate (eGFR) in patients at risk for CKD in Indonesia.* ***Methods:*** *This study was a comparative observational study with a cross-sectional approach. Research subjects were electronic medical record data from the Hasan Sadikin General Hospital information system (SIRS) data collected with the SQL Server Report Builder and "HCLAB" applications on patients at risk for CKD at the Hasan Sadikin General Hospital's Outpatient Clinic from January 2018 to March 2020. The patients' data were taken by the total sampling technique and then processed with the Chi-Square test.* ***Results:*** *From 376 subjects, the results showed that poor adherence in renal function monitoring would increase the risk of decreasing eGFR by 1.51 times compared to good monitoring adherence (PR 1.51 95% CI (1.172 - 1.935); p-value 0.007). The eGFR changes were significant (p-value 0.002) with mean 10.84 ml/min/1.73m$^2$ (95% CI: 4.17 – 17.50).* ***Conclusion:*** *The study demonstrated that poor renal function monitoring adherence had an association with a decrease in eGFR in a group of patients at risk for CKD.*

***Keywords:*** *Frequent monitoring, CKD Progression, eGFR.*

## INTRODUCTION

Chronic kidney disease (CKD) presents a global public health problem with an increasing prevalence and incidence, poor prognosis, and high cost. Based on the Global Burden of Disease report, CKD is the 27th leading cause of death globally and increased to the 12th in 2017. CKD treatment ranks as the fourth most expensive cost of the National Health Insurance after heart disease in Indonesia.[1-3]

Early detection of CKD and frequent monitoring of kidney function in a patient with diseases at risk of CKD complications are vital. Early detection means assessing renal function based on laboratory tests when the underlying disease is diagnosed for the first time, usually asymptomatic. At the same time, frequent monitoring is scheduled to assess the progress

of the complications which is CKD. Those are essential because the first onset of CKD is difficult to assess. Therefore, concurrent management of both underlying disease and complications (CKD) is an important step to reduce the risk of cardiovascular disease, progression of kidney disease, and death.[4]

In 2012, *Kidney Disease: Improving Global Outcome* recommends frequent monitoring of renal function for patients at risk according to CKD stage.[2] This is following The National Institute for Health and Care Excellence (NICE) guideline that stated early detection of CKD should be implemented for patients with diabetes, hypertension, history of acute renal impairment, cardiovascular disease, renal structural abnormalities, multisystem diseases (such as systemic lupus erythematosus), and patients with nephrotoxic drugs (such as lithium, cyclosporin, and NSAIDs).[4-6]

On the contrary, some guidelines based on expert opinions such as the United States Preventive Service Task Force (USPSTF) and the American College of Physicians (ACP) do not recommend assessing renal function in asymptomatic patients. To date, there are no randomized clinical trial (RCT) study that examines the role of early detection of kidney injury with patient's clinical outcome. Both USPSTF and ACP stated that early detection of kidney damage has potential adverse effects, including discomfort during blood collection, psychological effects related to CKD stigma, drug side effects from treatment with an uncertain diagnosis, and financial impacts. [7, 8] There is no data on the clinician's adherence to monitor the population at risk of CKD in Indonesia. Since there is a discrepancy in the recommendation to monitor the population of risk of CKD, this study aims to determine the association between monitoring adherence and changes in estimated glomerular filtration (eGFR) in the population at risk.

## METHODS

This study was a comparative observational study with a cross-sectional approach. We retrospectively analyzed outcomes of at-risk CKD patients who underwent early detection and monitoring between March 2018 and March 2020, at one tertiary-care outpatient clinic government hospital.

### Ethics

The institutional ethics committee of Hasan Sadikin Hospital approved the ethical clearance for this study (LB.02.01/X.6.5/001/2021). Patients' data from medical records were de-identified and analyzed anonymously.

### Inclusion and Exclusion Criteria

We retrospectively extracted and examined patient data from the Hasan Sadikin General Hospital information system (SIRS). Data were collected with the SQL Server Report Builder and "HCLAB" applications on patients at risk for CKD at the Hasan Sadikin General Hospital's Outpatient Clinic from January 2018 to March 2020.

We chose patients at risk for CKD covering congestive heart failure patients in the cardiology clinic, hypertension patients in the nephrology clinic, spondyloarthropathy patients who routinely used non-steroidal anti-inflammatory drugs, systemic lupus erythematosus (SLE) patients in the rheumatology clinic, diabetes patients in the endocrinology clinic, and cancer patients who underwent platinum-based chemotherapy in the oncology clinic. Information on age, sex, CKD risk factors, baseline eGFR, and proteinuria were recorded. Demographic data were collected at the time of study enrollment. We then recorded eGFR at the first encounter with a doctor in our clinic (early detection) and 1 year later (monitoring) to see the changes and counted the number of creatinine examination that was performed within one year to assess the adherence to KDIGO 2012 monitoring recommendation. We used CKD classification based on GFR category and albuminuria category according to KDIGO 2012 (**Table 1**).

The inclusion criteria required at-risk patient aged >18 years who had creatinine results at the first encounter with the doctor in our clinic and one year later. We excluded patients who had previously undergone hemodialysis and patients with the possibility of acute kidney injuries such as infection and acute heart failure.

**Table 1.** Recommended eGFR Monitoring Frequency for At-Risk Patients Based on KDIGO 2012

| | | Albuminuria Category | | |
|---|---|---|---|---|
| | | **A1 (<30 mg/g)** | **A2 (30–300 mg/g)** | **A3 (>300 mg/g)** |
| eGFR category (ml/min/1.73m2) | G1 ³90 | 1 time/year | 1 time/year | 2 times/year |
| | G2 60-89 | 1 time/year | 1 time/year | 2 times/year |
| | G3a 45-59 | 1 time/year | 2 times/year | 3 times/year |
| | G3b 30-44 | 2 times/year | 3 times/year | 3 times/year |
| | G4 15-29 | 3 times/year | 3 times/year | ³4 times/year |
| | G5 <15 | 4 times/year | ³4 times/year | 4 times/year |

The outcome of the study was CKD progression, shown by changes in estimated glomerular filtration rate (eGFR).

### Statistical Analysis

The doctor's adherence to monitoring eGFR was categorized into adherent and non-adherent groups. Baseline characteristics were described across these groups. Estimated GFR changes were categorized into normal and decreased. The comparison of eGFR between patients in the adherent and the non-adherent group was performed using dependent t-test or Wilcoxon Signed Rank test, alternatively. Bivariate analysis between monitoring adherence and eGFR changes was performed using the Chi-square test and reported as prevalence risk (PR) with its 95% confidence interval. Statistical significance was set at ≤0.05 with a two-tailed hypothesis. Statistical analyses were performed with Statistical Product and Service Solution (SPSS) version 22.0 for Windows.

## RESULTS

There were 522 subjects with underlying diseases having a risk for CKD. A total of 376 subjects met the inclusion criteria. The remaining were excluded from the study due to incomplete data. (**Figure 1**)

### Baseline Characteristics

Patients in the adherent group had a risk factor of SLE (21.9%), hypertension (20.7%), and DM type 2 (20.1%). In the non-adherent group, most patients had a risk factor of congestive heart failure (34.9%) and nasopharyngeal carcinoma (23.3%). The subjects' characteristics based on adherence monitoring are shown in **Table 2**.

Overall, 64.1% of subjects were not tested

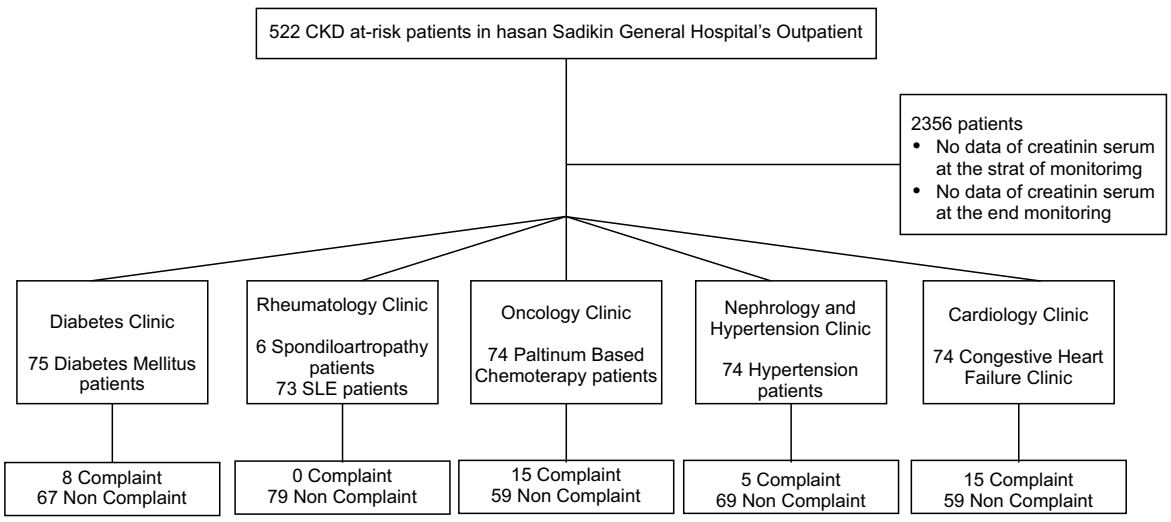


**Figure 1**. Study Sample Selection

**Tabel 2.** Baseline Characteristics

| Baseline Characteristics | Total n=376 | Monitoring Adherence | | p value |
|---|---|---|---|---|
| | | Adherent n=333 | Non-adherent n=43 | |
| **Creatinine Monitoring Frequency per year g** | 5 (1 – 17) | 5 (1 – 17) | 1 (1 – 2) | <0.001[a]* |
| **Proteinuria Monitoring Frequency per year [g]** | 1 (0 – 16) | 1 (0 – 16) | 0 (0 – 3) | <0.001[a]* |
| **Age (years)[g]** | 61 (18 – 86) | 62 (18 – 86) | 58 (18 – 84) | 0.184[a] |
| **Sex, n (%)** | | | | |
| Male | 146 (38.8) | 127 (38.1) | 19 (44.2) | 0.444[b] |
| Female | 230 (61.2) | 206 (61.9) | 24 (55.8) | |
| **Risk Factor, n (%)** | | | | |
| Diabetes Mellitus | 75 (19.9) | 67 (20.1) | 8 (18.6) | **<0.001[b]*** |
| Congestive Heart Failure | 74 (19.7) | 59 (17.7) | 15 (34.9) | |
| Cervical Cancer | 13 (3.5) | 11 (3.3) | 2 (4.7) | |
| Bladder Cancer | 15 (4) | 13 (3.9) | 2 (4.7) | |
| Lung Cancer | 13 (3.5) | 12 (3.6) | 1 (2.3) | |
| Nasopharyngeal Cancer | 33 (8.8) | 23 (6.9) | 10 (23.3) | |
| Hypertension | 74 (19.7) | 69 (20.7) | 5 (11.6) | |
| Spondyloarthropaties | 6 (1.6) | 6 (1.8) | 0 (0) | |
| Systemic Lupus Erythematous | 73 (19.4) | 73 (21.9) | 0 (0) | |
| **Baseline Proteinuria, n (%)** | | | | |
| Negative | 101 (26.9) | 101 (30.3) | 0 (0) | **<0.001[b]*** |
| 1+ | 12 (3.2) | 12 (3.6) | 0 (0) | |
| 2+ | 11 (2.9) | 11 (3.3) | 0 (0) | |
| 3+ | 5 (1.3) | 5 (1.5) | 0 (0) | |
| 4+ | 6 (1.6) | 5 (1.5) | 1 (2.3) | |
| Not Examined | 241 (64.1) | 199 (59.8) | 42 (97.7) | |
| **Albuminuria Stages, n (%)** | | | | |
| A1 | 101 (26.9) | 101 (30.3) | 0 (0) | **<0.001[b]*** |
| A2 | 12 (3.2) | 12 (3.6) | 0 (0) | |
| A3 | 263 (69.9) | 220 (66.1) | 43 (100) | |
| **Stadium** | | | | |
| G1 | 118 (31.4) | 94 (28.2) | 24 (55.8) | |
| G2 | 136 (36.2) | 125 (37.5) | 11 (25.6) | |
| G3a | 69 (18.4) | 63 (18.9) | 6 (14.0) | |
| G3b | 38 (10.1) | 37 (11.1) | 1 (2.3) | |
| G4 | 12 (3.1) | 11 (3.3) | 1 (2.3) | |
| G5 | 3 (0.8) | 3 (0.9) | 0 (0.0) | |

[g]Median (Min-Max), [a]Mann Whitney, [b]Chi Square, *significant p<0,05

for proteinuria at their first admission. At the start of monitoring, most of the patients had stage G2 (36.2%), followed by stage G1 (31.4%), G3a (18.4%), G3b (10.1%), G4 (3.1%), and G5 (0.8%). In the non-adherent group, most patients had stage G1 (55.8%) followed by G2 (25.6%), G3a (14.0%), G3b (2.3%), G4 (2.3%) and G5 (0%) while in the adherent group, most patients were at stage G2 (37.5%), G1 (28.2%), G3a (18.9%), G3b (11.1%), G4 (3.3%) and G5 (0.9%). The median (range) of follow-up in the adherent group was 5 (1-17) times per year, while in the non-adherent group was 1 (1-2) times per year.

The adherent group had a mean ± SD eGFR of 72.02±27.04 ml/min/1.73m$^2$ at the start and 72.84±29.32 ml/min/1.73m$^2$ at the end of monitoring. The eGFR changes was not significant (p>0.05) with mean 0.08 ml/min/1.73m$^2$ (95% CI 1.54 to 1.70ml/min/1.73m$^2$ (**Figure 2**). The association between monitoring adherence with renal function and eGFR changes is shown in **Table 3**. Non-adherent monitoring had a higher decreased eGFR (65.1%) than the adherent group (43.2%). Non-adherent monitoring significantly decreased the eGFR than the adherent group (p<0.05).

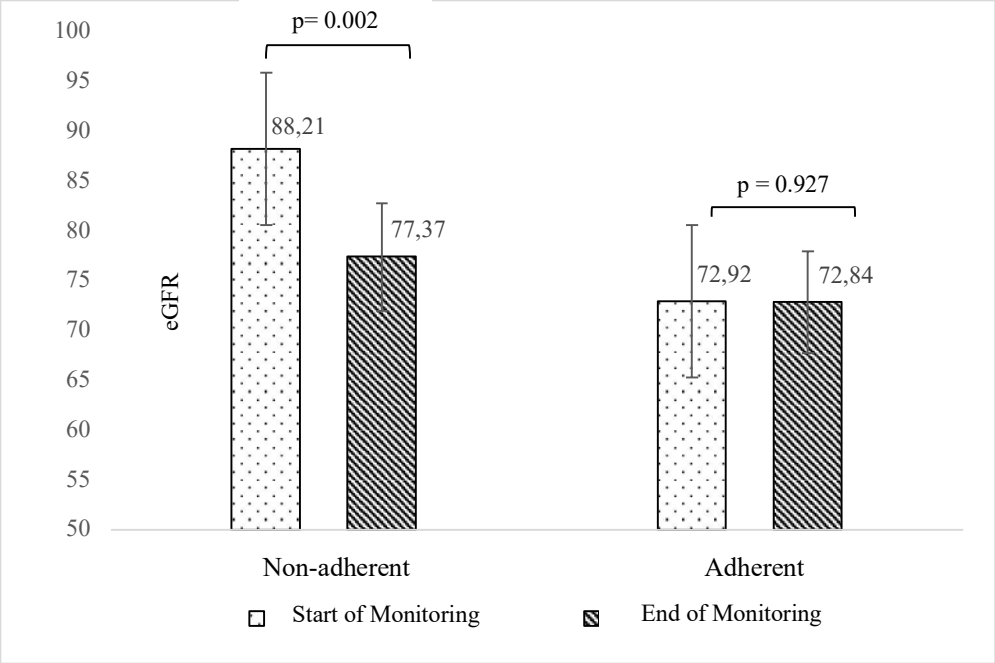


**Figure 2.** Comparison of renal function in one year monitoring

**Table 3.** Association of monitoring adherence and estimated glomerular filtration rate changes

| Monitoring Adherence | n | eGFR changes | | p-Value*) | PR (CI 95%) |
|---|---|---|---|---|---|
| | | Decrease | Constant/Increase | | |
| Non-Adherent | 43 | 28 (65.1) | 15 (34.9) | 0.007 | 1.51 (1.17 – 1.93) |
| Adherent | 333 | 144 (43.2) | 189 (56.8) | | |

*) Chi-square; PR (prevalence ratio) (CI 95%)

## DISCUSSION

This study was a comparative observational study with a cross-sectional method that identifies the association between monitoring adherence with renal function and eGFR changes. To the authors' best knowledge, this is the first investigation conducted in Indonesia. The International Society of Nephrology and The International Federations of Kidney Foundations, on World Kidney Day 2020, has the theme "Kidney health for everyone everywhere from prevention to detection and equitable access to care". The theme emphasizes that CKD and progression to end-stage renal disease (ESRD) can be prevented with proper access to early detection (primary prevention), frequent monitoring (secondary prevention), and simultaneous management (tertiary prevention). [9]

Kidney disease has an enormous economic burden. High-income countries allocate more than 2-3% of the annual health care budget to treat kidney failure. Based on the United States Renal Data System Report in 2019, all CKD patients require an increase in the need for care as the disease progresses, especially if the patient has reached end-stage renal disease requiring renal replacement therapy. [10,11] Our study showed that at the start of monitoring, most patients were at stage G2 (36.2%), followed by stage G1 (31.4%), G3a (18.4%), G3b (10.1%), G4 (3.1%), and G5 (0.8%). This is in accordance with USRDS 2019 data and the meta-analysis conducted by Hill et al. in 2016 that found CKD stages 1-3 are more common than stages 4-5. Therefore, the management of CKD should focus on preventing progression, not on kidney replacement.[11,12]

Many countries have implemented national policies and strategies for non-communicable diseases. However, specific policies directed at education and awareness of kidney disease with early detection, frequent monitoring,

management, and treatment of CKD are still inadequate. Until now, the management of patients with kidney disease is still not optimal. Many patients were presented with kidney failure when first referred to a nephrologist.[13] Lack of knowledge about CKD prevention is reflected in the number of proteinuria assessments as the first screening test. Our study showed that only 35.9% of patients had proteinuria examination at first admission at the outpatient clinic. The NKF-KDOQI, NICE 2008, KDIGO 2012, and CARI 2013 guidelines recommend proteinuria as one of the basics for early detection and monitoring of CKD progression. Proteinuria serves as the most common etiologic marker of CKD (DM, hypertension, and glomerular disease) and in kidney transplant recipients.[4, 14]

In our study, the non-adherent monitoring increased the risk of decreased eGFR compared to adherent monitoring with a prevalence ratio of 1.51 (95% CI 1.172 to 1.935, p=0.007). These results have very significant clinical implications. A study conducted by Matsushita et al. in 2009 found that the group that had a higher decrease in eGFR per year, had an increased incidence of acute coronary syndrome events and mortality. Our study also strengthens the KDIGO 2012 guideline recommendations stating that more frequent monitoring of renal function is needed as renal injury progress. The KDIGO 2012 recommendations were based on one of the main studies, namely the Prevention of Renal and Vascular End-stage Disease (PREVEND). The PREVEND study found that the rate of decrease in eGFR in the proteinuria and hypertension group was faster than in the other groups, indicating the importance of eGFR and proteinuria assessment to determine the number of monitoring frequencies. In addition, our study shows an association between monitoring adherence with renal function and CKD progression. Therefore, our results strengthen the confidence of KDIGO 2012 recommendations serving the basis for determining the minimum amount of renal function monitoring in at-risk patients.

Our study provides epidemiological evidence to reduce the level of trust in other guidelines such as USPSTF 2012 and ACP 2013. These guidelines do not recommend frequent monitoring of the CKD population, especially in asymptomatic patients stages 1 – 3. These recommendations are made only based on expert opinion because no studies have assessed the accuracy, precision, specificity, or sensitivity of frequent monitoring to detect eGFR changes. Both USPSTF and ACP hesitate that the benefit of early detection and frequent monitoring is greater than the harm of adverse event. [7, 8] Our study has shown that frequent monitoring is essential to reduce CKD progression.

However, some limitations should be noted. Most of the patients (64.1%) had no baseline proteinuria data. Baseline proteinuria data in the adherent group reached 59.8%, while in the non-adherent groups, almost all patients were not assessed (97.7%). This follows a study conducted by Plantinga et al. in 2010 revealing awareness of damage detection and frequent monitoring of kidney function both at the patient and doctor level is very low.[15,16] To overcome this limitation, we determined the A3 grade if proteinuria was not checked with the worst assumption so that it could describe the milder A1 or A2 condition.

This study did not include the variables of management changes made, whether appropriate or not since the data were retrospectively taken. There is the potential for selection bias. This bias mainly lies in temporal ambiguity. We cannot conclude that exposure is a risk factor for a particular disease. This may be because one patient may have more than one risk factor. Therefore, we assessed risk factors based on data from the main polyclinic where their underlying disease was controlled. Further research is needed with more accurate information regarding the timing and occurrence of the underlying disease and sensitivity analysis is required.

## CONCLUSION

Renal function monitoring adherence is associated with changes in eGFR in a group of patients at risk for CKD. Patients with poor adherence monitoring were likely to develop decreased eGFR by 1.51 times compared to the adherent monitoring group.

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