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LITERATURE REVIEW: IDENTIFICATION OF TYPES OF BIOMARKERS FOR THE DETECTION OF ACUTE KIDNEY DISEASE AND CHRONIC KIDNEY DISEASE

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Abstract

Kidney disease is one of the global public health problems having high mortality rates. Patients suffering from kidney disease have the risk of experiencing losses in the form of mental health and financial state. Further identification of kidney disease biomarkers needs to be conducted to accelerate diagnostic activities so that the treatment can be carried out more quickly. This study is a literature review which was conducted to explore types of biomarkers that can be used to detect acute kidney disease and chronic kidney disease. The literature search was conducted in September 2021. The research sources were taken from several databases, namely Science Direct, ProQuest, PubMed, and Google Scholar. There were 49,115 articles found in Science Direct database, 161,983 articles found in ProQuest, 9,749 articles found PubMed, and 45,850 articles found in Google Scholar. Out of the entire database, only 21 articles met the inclusion criteria. The variables in this study were biomarkers, acute kidney disease, and chronic kidney disease. This literature review shows that the examination of biomarkers for acute kidney disease and chronic kidney disease can be done by taking urine and blood samples of the patient. There are 10 types of biomarkers that can be used to detect acute kidney disease and 41 types of biomarkers that can be used to detect chronic kidney disease. Acute kidney disease and chronic kidney disease can be diagnosed by examining the biomarkers present in the patient's body. The examination of biomarkers can reduce delays in the treatment of acute kidney disease and chronic kidney disease.
Keyword: Biomarkers, acute kidney disease, chronic kidney disease

INTRODUCTION

Kidney disease is a global public health problem having more than 750 million cases occurring worldwide (Crews *et al.*, 2019). In general, kidney diseases are divided into two, which are acute kidney disease and chronic kidney disease. Acute kidney disease is characterized by an increase in serum creatinine levels in the body, while chronic kidney disease is characterized by a decrease in the glomerular filtration rate to <60mL/min for more than 3 months (Ostermann, Bellomo, *et al.*, 2020). In 2017, deaths from chronic kidney disease reached 1-2 million cases worldwide with the highest number of cases reported in people coming from developing countries (Bikbov *et al.*, 2020).

The high cost of treating kidney disease can have a negative economic impact on the sufferers. In Indonesia, kidney disease treatment occupies the second largest source of expenditure for BPJS health claims (Infodatin Kementerian Kesehatan Republik Indonesia, 2017). Another negative impact that can be experienced by patients with kidney disease is the decreased quality of life. Patients with kidney disease in general will experience a decrease in their physical ability to carry out

activities, so this will also influence their work and interpersonal skills, triggering depression (Dąbrowska-Bender *et al.*, 2018).

The determination of the diagnosis of acute kidney disease and chronic kidney disease needs to be done as early as possible to minimize the losses which can be experienced by the patients. Since long ago, the determination in the diagnosis of kidney disease has been identified through the results of the examination of biomarkers in the form of serum creatine and urine output, but both have weaknesses in the form of slow changes and low sensitivity and specificity, resulting in the delay in diagnosis and treatment of kidney disease, which further leads to an advanced stage of kidney disease (Ostermann, Zarbock, *et al.*, 2020). Based on this, it is essential to conduct further studies to identify other types of biomarkers which have higher specificity and sensitivity to help detect kidney disease earlier.

RESEARCH METHODS

This literature review was conducted to explore biomarkers in patients with acute kidney disease and chronic kidney disease. The literature search was carried out in September 2021. The researcher searched for data sources using several databases, namely Google Scholar, Science Direct, ProQuest, and PubMed by connecting the terms of the main topic, namely the biomarker "AND" acute kidney injury "AND" chronic kidney injury. There was a limitation in the search for related journals carried out by the researcher in that the search was based on the year of publication of the literature, namely between 2016-2021 to find valid and updated data sources.

Inclusion criteria which were included in the selection of this literature review study included the relation between journals to biomarkers of acute kidney disease and chronic kidney disease, and complete journal texts which are available in English or Indonesian. The exclusion criteria included in the selection of this literature review study were literature review articles. The variables in this study were biomarkers of acute kidney disease and chronic kidney disease.

Data Extraction.

Data Selection and Data Analysis: the journals were selected by the researcher independently. The Science Direct, ProQuest, and PubMed databases were searched using the same keywords, "Biomarkers", "Acute Kidney Injury", and "Chronic Kidney Injury". Meanwhile, the Google Scholar database was searched using the keywords "Biomarkers", "Acute Kidney Injury", and "Chronic Kidney Injury". During data synthesis, 266,697 articles were obtained through searches in databases of Google Scholar, Science Direct, ProQuest, and PubMed. 248,496 articles were later removed after reviewing the year of publication, namely 2016-2021. 18,084 articles were removed by reviewing the title, and 43 articles were removed by reviewing the abstract. 36 studies were found to be relevant because the articles discuss biomarkers in acute kidney disease and chronic kidney disease. During the full-text analysis of 36 studies, another 15 articles were excluded because the data did not meet the inclusion criteria. This systematic review ultimately selected 21 relevant studies which met the inclusion criteria of the study.

Table 1. PICOS criteria for inclusion and exclusion of studies.

Parameter	Inclusion criteria	Exclusion criteria
Patients	Patients with acute kidney disease and chronic kidney disease	Not patients with acute kidney disease and chronic kidney disease
Intervention	Acute kidney disease and chronic kidney disease	
Comparator	Types of biomarkers to help detect kidney disease early	
Outcomes	Types of biomarkers have higher specificity and sensitivity to help detect kidney disease early	
Study Design	Experimental research; with or without control group	Observational studies, literature studies, meta-analysis, comments, short communication, editorial letters, and non-English and Bahasa articles.

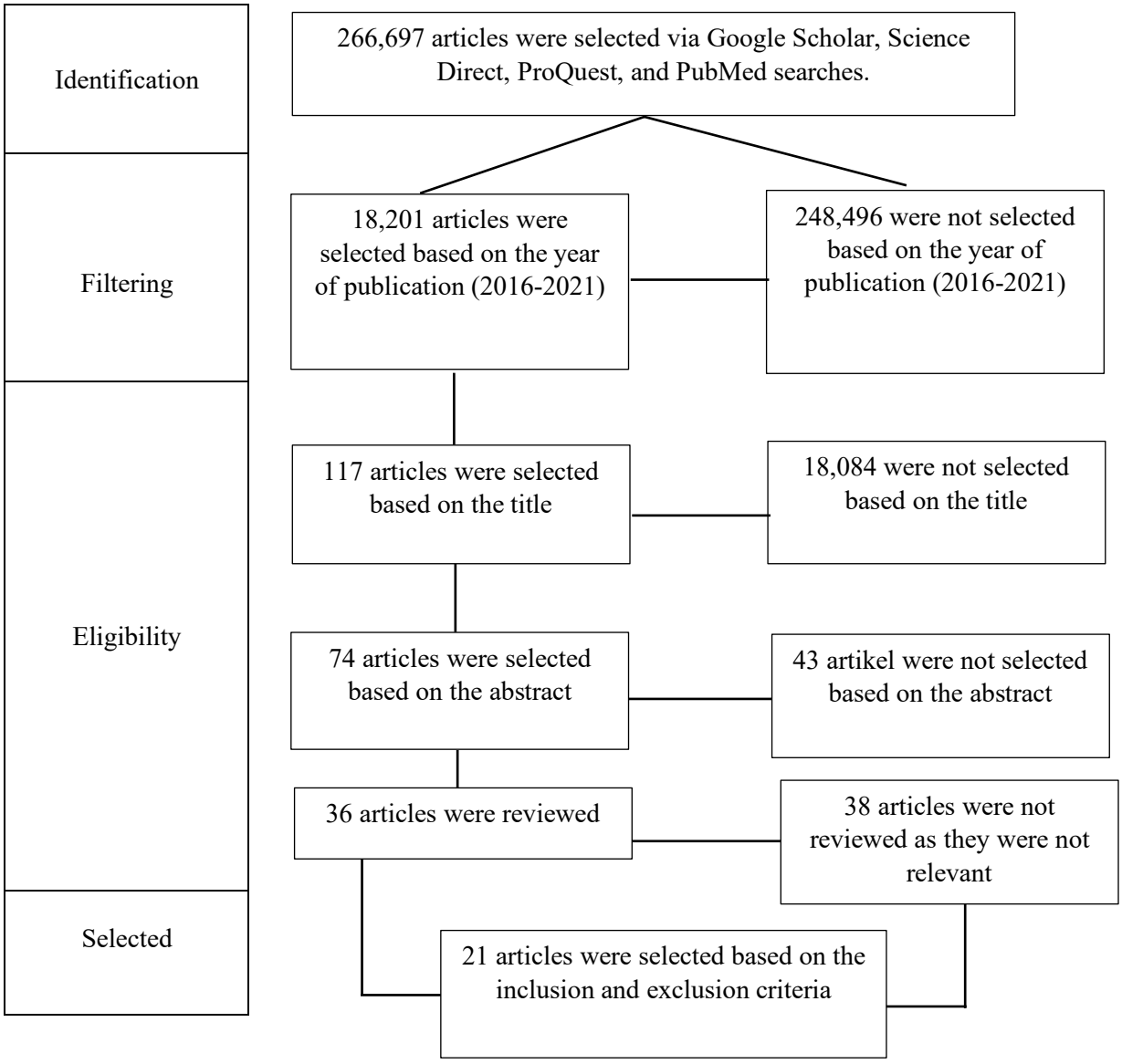

Figure 1. PRISMA Flowchart for Research Literature Review

Figure 1 describes the process of selecting articles according to the guidelines of the Preferred Reporting Literature Reviews and Meta-analysis (PRISMA). The initial search yielded a total of 266,697 articles showing high relevance to the topic under review. After duplicating the articles and filtering the year of publication, title and abstract, 36 articles entered the next stage, namely full-text review and eligibility according to the inclusion and exclusion criteria previously determined by the researcher. The 21 research articles that met the requirements were later reviewed for quality and were synthesized in this final literature review report.

RESULT AND DISCUSSION

Tabel 1 mendeskripsikan ciri responden The results of this literature review show that there are several types of biomarkers which can be used as an indicator in determining the diagnosis of acute kidney disease and chronic kidney disease. In patients with acute kidney disease, there are a number of changes that occur in the patients' body, which include an increase in the levels of Interleukin 18 and Interleukin 24 in the patients' urine (Parikh *et al.*, 2016; Faisal, 2019; Tabata *et al.*, 2020). Urinary Kidney Injury Molecule-1 (uKIM-1) and serum creatinine are types of biomarkers that are commonly used to detect changes in the body, which serve as markers of kidney function

abnormalities as early symptoms of acute kidney disease experienced by both neonatal and adult groups (Jin *et al.*, 2017; Permatasari *et al.*, 2018; ElSadek *et al.*, 2020). NGAL is able to detect early stage of acute kidney disease (Parikh *et al.*, 2016; Park *et al.*, 2019).

NAG (N-Acetyl-β-D-Glucosaminidase) biomarker in urine is also able to detect early symptoms of acute kidney disease by 7,4805 times more accurately (Zulkifli *et al.*, 2018). Cystatin C could also be used as a biomarker to detect acute kidney disease because it has a specificity value of 61% with a positive predictive value of 57.50% (Permatasari *et al.*, 2018). Other biomarkers that can be used are increased levels of miR-452, serum γ-glutamyl transferase to alanine aminotransferase ratios (GGT/ALT), proenkephalin A 119-159 and serum procalcitonin in the body (Parikh *et al.*, 2016; Zhou *et al.*, 2017; Hollinger *et al.*, 2018; Park *et al.*, 2019; Liu *et al.*, 2020).

Table 2. Synthesis of Research Results Related to Biomarkers in Patients with Acute Kidney Disease

No	Author (s)	Title	Characteristic			Result (s)
			Subject	Method	Instruments	
1	Faisal, (2019)	Interleukin 18 (IL-18) Urine as Early Detection of Acute Kidney Disorders in Sepsis Patients	Patient	Prospective	Secondary data	Elevated urinary IL-18 levels can be used as a biomarker for early detection of acute renal impairment. Urinary IL-18 at 6 hours after sepsis had a sensitivity of 77.78% and a specificity of 82.60%, while urinary IL-18 at 48 hours after sepsis had a sensitivity of 70.37% and a specificity of 69.56%.
2	ElSadek *et al.*, (2020)	Kidney Injury Molecule-1/Creatine as A Urinary Biomarker of Acute Kidney Injury in Critically Ill Neonates	Patient	Case-control prospective	Medical check up	uKIM-1 and uKIM1/creatinine are early biomarkers for diagnosing neonatal acute kidney disease before creatinine levels rise.
3	Tabata *et al.*, (2020)	Interleukin-24 is a Novel Diagnostic Biomarker for The Severity of Acute Kidney Injury	Mice	Cross sectional	Medical check up	Serum IL-24 was detected earlier than creatinine levels and urinary IL-24 was detected concurrently with increased neutrophil gelatinase levels. Urinary and serum IL-24 levels will increase with time ischemia.
4	Zulkifli *et al.*, (2018)	Sensitivity and Specific of Urine N-Acetyl-β-D-Glucosaminidase as an Early Biormarker for	Patient	Retrospective	Medical check up	Urinary NAG has a cut-off of 7.98 Ng/mL points, sensitivity of 68.57% and specificity of 77.42%, with an odds ratio of 7.4805 (95% CI 2.4808 - 22.5562), so

No	Author (s)	Title	Characteristic			Result (s)
			Subject	Method	Instruments	
		Acute Kidney Injury				that urine NAG is capable of diagnosing disease. acute kidney by 7.4805 times greater.
5	Permatasari *et al.*, (2018)	Serum Cystatin C and Creatinine in Diagnosing Acute Kidney Disorders in Critically Sick Children	Patient	Diagnostic Test	Medical check up	The mean levels of cystatin C and serum creatinine will increase in patients with acute renal impairment. The cut off point for cystatin C was 0.56 mg/L, sensitivity 85%, specificity 61%, positive predictive value 57.50% and negative predictive value 13.33%. While the cut off point for creatinine is 0.95 mg/dL, sensitivity is 52%, specificity is 100%, positive predictive value is 100% and negative predictive value is 23.21%.
6	Liu *et al.*, (2020)	Discovery and Validation of miR-452 as an Effective Biomarker for Acute Kidney Injury in Sepsis	Patient and Mice	Cohort	Medical check up	Serum and urine miR-452 increased earlier in septic mice before renal dysfunction or tissue damage was detected. Septic patients with acute kidney disease had significantly higher serum and urine miR-452 levels than patients without acute kidney disease. The results of logistic regression analysis showed a 72.48-fold increase in the risk of acute kidney disease for each 1-fold increase in urinary miR-452 in the patient.
7	Parikh *et al.* (2016)	Application of New Acute Kidney Injury Biomarkers in Human Randomized Controlled Trials	Patient	Prospective cohort	Secondary data	Interleukin-18 and NGAL are biomarkers that can be used as consideration for the initial diagnosis of acute kidney disease, thereby potentially increasing the proportion of patients who will develop acute kidney disease and

No	Author (s)	Title	Characteristic			Result (s)
			Subject	Method	Instruments	
						reducing the cost of further investigations.
8	Hollinger *et al.* (2018)	Proenkephalin A 119 – 159 (Penkid) is an Early Biomarker of Septic Acute Kidney Injury : The Kidney in Sepsis and Septic Shock (Kid-SSS) Study	Patient	Cohort	Medical check up	Proenkephalin A 119-159 (Penkid) and serum creatinine are commonly used biomarkers to detect acute renal failure. An increase in penkid was detected earlier than an increase in serum creatinine
9	Park *et al.* (2019)	Urinary Neutrophil Gelatinase-associated Lipocalin as a Biomarker of Acute Kidney Injury in Sepsis Patients in The Emergency Department	Patient	Retrospecti ve	Medical check up	Serum procalcitonin concentrations and urinary NGAL were found to be significantly higher in patients diagnosed with acute kidney disease (PGA) than in non-PGA.
10	Zhou *et al.* (2017)	A New Plasma Biomarker Enhance the Clinical Prediction of Postoperative Acute Kidney Injury in Patients with Hepatocellular Carcinoma	Patient	Prospective	Medical check up	Serum -glutamyl transferase to alanine aminotransferase ratios (GGT/ALT) were shown to have higher concentrations in patients with acute kidney disease than in non-acute kidney disease.
11	Jin *et al.* (2017)	Urinary Kidney Injury Molecule-1 as an Early Diagnostic Biomarker of Obstructive Acute Kidney Injury and Development of a Rapid Detection Method	Mice	Prospective	Medical check up	There is a positive correlation between increased levels of u-KIM1 with an increase in acute obstructive kidney disease. u-KIM1 is a biomarker that has been shown to be more sensitive in determining acute obstructive kidney disease when compared to vimentin and α-SMA.

Chronic kidney disease can also be detected by examining biomarkers. Citrulline (CIT), sysmmetric dimethylarginine (SDMA), S-adenosylmethionine (SAM), Hgb, CP, ORM, Frt, CIT, CNN, SDMA, nC4, SAM, CIS4DEC, S1P, BIL, UNCR, plasma CREA, YKL-40, ACR, 2M, 1M, and uromodulin are biomarkers that can be used for early detection of the risk of stage 1 chronic kidney disease (Benito *et al.*,

2018; (Benito *et al.*, 2019; Castro-Sesquen *et al.*, 2020; Zhang *et al.*, 2020 ;Ko *et al.*, 2021).

Table 3. Synthesis of Research Results Related to Biomarkers in Patients with Chronic Kidney Disease

No	Author (s)	Title	Characteristic			Result (s)
			Subject	Method	Instruments	
1	Akin, Ozmen and Yilmaz, (2017) (Akin, Ozmen and Yilmaz, 2017)	Hyaluronic Acid as a New Biomarker to Differentiate Acute Kidney Injury from Chronic Kidney Disease	Patient	Prospective	Medical check up	The concentration of hyaluronic acid in the group with chronic kidney disease (146.1 ± 119.3 ng/mL) was higher than in the group with acute kidney disease (68.9 ± 69.1 ng/mL). There is a correlation between serum hyaluronic acid and serum albumin levels in the group of patients with chronic kidney disease with a sensitivity level of 82% and a specificity of 67%.
2	Zhang *et al.*, (2020) (Zhang *et al.*, 2020)	Kidney Damage Biomarkers and Incident CKD During Blood Pressure Reduction: A Case-Control Study within SPRINT	Patient	Case-control	Medical check up	There was a significant increase in the concentration of YKL-40, ACR, 2M, 1M, and uromodulin levels in patients with chronic kidney disease.
3	Jiang *et al.*, (2021) (Jiang *et al.*, 2021)	Novel Predictive Biomarkers for Acute Injury Superimposed on Chronic Kidney Disease	Mice	Cohort	Medical check up	The increasing severity of kidney disease from acute to chronic is characterized by an increase in serum creatinine, NGAL, RHBDL2 and SDC-1 protein mRNA, TIMP-2 protein and a decrease in IGFBP7 protein. The large increase in IGFBP-7 protein levels in the body indicates an increase in the severity of chronic kidney disease.
4	Benito *et al.* (2018), (Benito *et al.*, 2018)	Plasma Biomarker Discovery for Early Chronic Kidney Disease Diagnosis based on Chemometric Approaches using LC-QTOF Targeted Metabolomics Data	Patient	Cohort	Medical check up	Citrulline (CIT), symmetric dimethylarginine (SDMA) and S-adenosylmethionine (SAM) is a combination biomarker that can support the diagnosis of early-stage chronic kidney disease which has an accuracy of 18% better than using only serum creatinine measurement.
5	Ascher *et al.*, (2021)	Urine Biomarkers of	Patient	Cohort	Medical check up	EGF, A1M and albumin are urinary biomarkers that can

No	Author (s)	Title	Characteristic			Result (s)
			Subject	Method	Instruments	
	(Ascher *et al.*, 2021)	Kidney Tubule Health and Incident CKD Stage 3 in Women Living with HIV: A Repeated Measures Study				provide early information about the risk of chronic kidney disease in a group of women living with HIV infection.
6	Schmidt *et al.*, (2021) (Schmidt *et al.*, 2021)	Cadherin-11, Sparc-related Modular Calcium Binding Protein-2, and Pigment Epithelium Derived Factor are Promising Non-invasive Biomarkers of Kidney Fibrosis	Patient	Prospective	Medical check up	In patients with chronic kidney disease, the biomarkers SMOC2, PEDF, and DH11 can be used to predict progression of disease severity to renal fibrosis.
7	Castro-Sesquen *et al.*, (2020) (Castro-Sesquen *et al.*, 2020)	Use of Multiple Urinary Biomarkers for Early Detection of Chronic Kidney Disease in Sickle Cell Anemia Patients	Patient	Cohort	Medical check up	The use of a combination of biomarkers in the form of Hgb, CP, ORM and Frt resulted in specificity and AUC values of 82.6% and 78.3-82.7% or similar to the complete combination of biomarkers in determining stage 1 chronic kidney disease.
8	Benito *et al.*, (2019) (Benito *et al.*, 2019)	LC-QQQ-MS Routine Analysis Method for New Biomarker Quantification in Plasma Aimed at Early Chronic Kidney Disease Diagnosis	Patient	Case-control	Medical check up	CIT, CNN, SDMA, nC4, SAM, CIS4DEC, S1P, and BIL can significantly be used as biomarkers to detect early stage chronic kidney disease. CIT, CNN, SDMA, nC4, SAM, CIS4DEC, and S1P will show an increase in concentration levels in patients with chronic kidney disease compared to the control group, whereas the concentration of BIL levels will decrease in patients with chronic kidney disease.
9	Ko *et al.*, (2021) (Ko *et al.*, 2021)	Cystatin C and Neutrophil Gelatinase-Associated Lipocalin as Early Biomarkers for Chronic Kidney Disease in Dogs	Dog	Case-control	Medical check up	Dogs diagnosed with early stage chronic kidney disease had significantly increased concentrations of SDMA, CysC, and UNCR while plasma CREA decreased.

No	Author (s)	Title	Characteristic			Result (s)
			Subject	Method	Instruments	
10	Shcheloch kov *et al.*, (2019) (Shcheloc hkov *et al.*, 2019)	Chronic Kidney Disease in Propionic Acidemia	Patient	Cross section al	Medical check up	Cystatin C, plasma uric acid, 25-OH-vitamin D, 1,25-OH-vitamin D, PTH, plasma osmolality, are biomarkers that can be used to detect complications of chronic kidney disease in patients with propionic acidemia.

Chronic kidney disease can occur as a result of the accumulation of other comorbidities. Biomarkers which can be used to detect chronic kidney disease as a complication of other diseases such as Propionic acidemia and HIV are Cystatin C, plasma uric acid, 25-OH-vitamin D, 1,25-OH-vitamin D, PTH, plasma osmolality, EGF, A1M and albumin (Shchelochkov *et al.*, 2019 ;Ascher *et al.*, 2021). Meanwhile, chronic kidney disease occuring as a form of accumulation of severity due to untreated acute kidney disease can be detected by increasing levels of hyaluronic acid, serum creatinine, NGAL, RHBDL2, SDC-1 protein mRNA, and TIMP-2 protein (Akin, Ozmen and Yilmaz, 2017; Jiang *et al.*, 2021). A higher stage of chronic kidney disease will cause fibrosis of kidney which can be characterized by changes in biomarkers in the form of increased levels of SMOC2, PEDF, and DH11 (Schmidt *et al.*, 2021).

Based on 21 articles that have been found, there are various types of biomarkers that can be used as indicators in determining the diagnosis of acute kidney disease and chronic kidney disease. 11 of the 21 articles discuss 10 types of biomarkers that can be used for the detection of acute kidney disease. Biomarkers can be detected through the patient's urine and blood as an indication of changes caused by decreased kidney function (Simsek, Tugcu and Tasci, 2013).

Serum creatinine is a biomarker that can be used to detect the presence of early-stage acute kidney disease through blood samples. Serum creatinine has been widely used for the detection of acute kidney disease, but some weaknesses are often found in its measurement as it has a weak sensitivity to changes in the glomerular filtration rate in a quantity that is less than 50%, resulting in a relatively late diagnosis and treatment of acute kidney disease (Cho, 2020).

Serum γ-glutamyl transferase to alanine aminotransferase ratios (GGT/ALT) and serum procalcitonin are biomarkers for acute kidney disease that can be tested through blood samples. Based on research which was conducted on patients with kidney disease in Korea, it was found that serum GGT/ALT is a more suitable biomarker for detection of kidney disease at an advanced stage (Lee *et al.*, 2020).

Interleukin 18, Interleukin 24, NGAL, uKIM-1, and N-Acetyl-β-D-Glucosaminidase are biomarkers which can be obtained through urine samples. MiR-452, proenkephalin A 119-159, and uKIM-1 are biomarkers with the highest sensitivity and specificity for early detection of acute kidney disease through urine samples (Li *et al.*, 2020 ; Geng *et al.*, 2021). The other 10 articles discuss 41 types of biomarkers commonly used to detect chronic kidney disease. In chronic kidney disease, there are five stages or severity of kidney damage which can be determined by different biomarkers (Gaitonde, Cook and Rivera, 2017). Five out of 10 articles discuss the biomarkers which are used to detect stage 1 of chronic kidney disease where there are 21 types of biomarkers that can be regrouped based on the sampling method. CIT, CNN, SDMA, nC4, SAM, CIS4DEC, S1P, BIL, UNCR, and plasma CREA are biomarkers that can be detected through blood samples. SDMA has a higher level of reliability to indicate a decrease in the glomerular filtration rate in chronic kidney disease (Nabity, 2018).

Biomarkers for the diagnosis of early-stage chronic kidney disease that can be detected through urine are YKL-40, ACR, 2M, 1M, uromodulin, Hgb, CP, ORM, and Frt. Based on another cohort study, the biomarker YKL-40 has a higher significance level than Hgb for detecting early-stage chronic kidney disease (Keskin *et al.*, 2019). Hyaluronic acid, serum creatinine, NGAL, RHBDL2, SDC-1 protein mRNA, TIMP-2 protein, SMOC2, PEDF, and

DH11 are biomarkers which aid in the diagnosis of advanced chronic kidney disease. The TIMP-2 protein has an important role in the detection of kidney disease (Chindarkar *et al.*, 2016; Srisawat and Kellum, 2020).

Chronic kidney disease can occur as a result of complications in the main disease suffered Ekrikpo *et al.*, (2018), which can be detected through examination of biomarkers in the form of Cystatin C, plasma uric acid, 25-OH-vitamin D, 1,25-OH-vitamin D, PTH, plasma osmolality, EGF, A1M and albumin. This is in line with other studies which state that there is a change in the concentration of cystatin c, plasma uric acid, and vitamin D in the body of a person suffering from chronic kidney disease (Tapper *et al.*, 2021).

CONCLUSION AND SUGGESTION

Acute kidney disease and chronic kidney disease can be diagnosed earlier if they are tested using appropriate biomarkers. 10 types of biomarkers can be used to diagnose acute kidney disease, and 41 types of biomarkers can be used to diagnose chronic kidney disease.

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