The Correlation between Disease Stage and Pulmonary Edema Assessed with Chest X-Ray in Chronic Kidney Disease Patients

Background: Pulmonary edema is one of the most common complications in patients with chronic kidney disease (CKD). Chest radiography is the most practical method for assessing pulmonary edema. This study aimed to identify the relationship between chronic kidney disease and pulmonary edema assessed with chest X-ray.

Material and methods: A cross sectional study was conducted in inward patients at Dr. Moewardi Hospital Surakarta Indonesia from May 2017 to May 2018. Patients who were diagnosed with CKD and performed chest X-ray were eligible to this study and consecutively recruited as study subject. The data were analyzed using the simple logistic regression with p value <0.05.

Results: There were 120 patients who participated in this study, consisted of 90 patients with end-stage of CKD or end-stage renal disease (ESRD) and 30 CKD patients without ESRD. End-stage renal disease (ESRD) was significantly associated with pulmonary edema incidence (OR=6.77; 95% CI=1.37- 33.51; p=0.02).

Conclusion: ESRD is closely related to pulmonary edema. Early diagnosis and prompt treatment are the key points in avoiding further disease progression in patients with CKD.

Keywords: Chronic kidney disease ▪ Pulmonary edema ▪ Chest X-ray

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Introduction

The number of people with chronic kidney disease (CKD) has increased progressively in all over the world, especially in developing countries [1]. CKD has a high prevalence of 13.4% globally, and accounts for a large economic burden on the health care system in various parts of the world [2]. The national prevalence of CKD in Indonesia is 0.2%, however based on data from Social Security Agency or Badan Penyelenggara Jaminan Sosial (BPJS) of Indonesia, treatment cost for kidney disease ranks the second highest after heart disease [3].

The prevalence of CKD patients increases with the increasing prevalence of CKD risk factors, such as diabetes, hypertension, and obesity. CKD is a progressive disease and has various complications. Respiratory system abnormality, particularly pulmonary edema is one of the most common complications in CKD patients [4,5] Respiratory symptoms, however, are often underestimated or ignored in clinical practice [6]. Dyspnea associated with pulmonary edema is often assessed in hemodialysis patients to determine whether dialysis is required [7].

To assess extravascular fluid in the lungs, several techniques can be used, such as auscultation, chest X-ray, pulmonary ultrasonography, and thermodynamic trans-pulmonal. Chest X-ray has been used to diagnose and to assess the progression of pulmonary edema for a long time because it is the most practical and useful method [8,9]. The advantage of chest X-ray is that this modality is available in many health care facilities, non-invasive, easy, and relatively inexpensive [8]. Until now, studies investigating the relation between chronic kidney disease to pulmonary edema assessed with chest X-ray are still very limited. Therefore, the researchers conducted the study on the relation between chronic kidney failure and pulmonary edema seen on chest X-ray.

Material and methods

■ Study design and population

A cross sectional study was conducted in patients at Dr. Moewardi Hospital, Surakarta who had been diagnosed with CKD, had undergone chest X-ray, and had completed medical record data. The exclusion criteria are patients with comorbidities which can cause pulmonary edema, such as: lung infection/ pneumonia, pulmonary tuberculosis, malignancy, corrosive gas inhalation, gastric aspiration, blunt chest trauma, pancreatitis, etc.

■ Study data

The medical records of CKD patients registered between May 2017 and May 2018, referring to the concept of fixed-exposure sampling, Pulmonary edema was determined based on a patient's chest X-ray. Other characteristics which were observed include age, gender, underlying diseases such as hypertension, diabetes mellitus, and obstruction and reflux uropathy, as well as various laboratory tests such as hemoglobin, urea, creatinine and eGFR.

Statistical analysis

Pulmonary edema was determined based on a patient's chest X-ray interpretation by two assessors which will be reliability or consistency tested between the two according to the Cohen Kappa agreement test. Categorical variables are described with numbers of frequencies and percentages, while numerical variables are described as mean and standard deviations. Statistical test for categorical variables is by chi square test, while for numerical variable is by independent samples t test. The relation between CKD and the characteristics of other patients with pulmonary edema was analyzed by multivariate logistic regression model. All statistical analyses were performed at the 5% significance level. Statistical analysis was performed by using SPSS Windows v.16 software.

Ethical consideration

This study was reviewed and approved by the ethics committee of Faculty of Medicine Universitas Sebelas Maret with the decision no. 187/UN27.6/KEPK/2018.

Results

The mean age of patients observed was 50.28 years (SD = 15.48 years), comprising of 73 men (60.8%) and 47 women (39.2%). Underlying disease in the form of hypertension was found in 77 patients (64.2%), diabetes mellitus was present in 24 patients (20.0%), and obstruction and reflux uropathy in 10 patients (8.3%). The description of the characteristics of the full study subjects can be seen in Table 1.

Of the 120 study subjects, pulmonary edema was found in 77 patients (64.2%). There were significant differences in the incidence of pulmonary edema between ESRD and non ESRD patients (76.7% vs. 26.7%). ESRD was also significantly related to several characteristics, including younger age, hypertension, higher creatinine levels, and lower eGFR levels. Bivariate analysis of pulmonary edema incidence based on CKD stage and various characteristics are presented in Table 2.

Table 1. Description of research samples.

Variable	N (%)	mean ± SD
Age (years-old)		50.28 ± 15.48
Gender		
Men	73 (60.8)	
Women	47 (39.2)	
Hypertension		
Yes	77 (64.2)	
No	43 (35.8)	
Diabetes mellitus		
Yes	24 (20.0)	
No	96 (80.0)	
Obstruction and reflux uropathy		
Yes	10 (8.3)	
No	110 (91.7)	
Hb (g/dl)		8.93 ± 1.95
Ureum (mg/dl)		166.83 ± 80.22
Creatinine (mg/dl)		9.34 ± 5.37
eGFR (ml/min/1,73m^2)		8.73 ± 10.99
CKD		
ESRD	90 (75.0)	
Non ESRD	30 (25.0)	
Pulmonary Edema		
Yes	77 (64.2)	
No	43 (35.8)	

The incidence of pulmonary edema was significantly associated with age, hypertension, creatinine levels, eGFR levels, obstruction, and reflux uropathy and hemoglobin levels. The results of multivariate analysis using logistic regression models is shown in Table 3. It was found that ESRD was significantly associated with the incidence of pulmonary edema (OR = 6.77; 95% CI = 1.37 - 33.51). Hypertension is also related to ESRD with (OR = 3.52; 95% CI = 1.20-10.39) Table 3.

Table 2. Differences in the incidence of pulmonary edema based on CKD's stage and differences in sample characteristics based on CKD and pulmonary edema.

Variable	CKD			Pulmonary Edema		
	ESRD	Non ESRD	P	Yes	No	P
	(n = 90)	(n = 30)		(n = 77)	(n = 43)	
Pulmonary Edema						
Yes	69 (76.7)	8 (26.7)	<0.001			
No	21 (23.3)	22 (73.3)				
Age (years-old)	48.62 ± 14.83	55.23 ± 16.56	0.042	47.68 ± 14.90	54.93 ± 15.59	0.013
Gender						
Men	53 (58.9)	20 (66.7)	0.45	46 (59.7)	27 (62.8)	0.743
Women	37 (41.1)	10 (33.3)		31 (40.3)	16 (37.2)	
Hypertension						
Yes	69 (76.7)	8 (26.7)	<0.001	61 (79.2)	16 (37.2)	<0.001
No	21 (23.3)	22 (73.3)		16 (20.8)	27 (62.8)	
Diabetes mellitus						
Yes	19 (21.1)	5 (16.7)	0.598	17 (22.1)	7 (16.3)	0.446
No	71 (78.9)	25 (83.3)		60 (77.9)	36 (83.7)	
Obstruction and reflux uropathy						
Yes						
No	6 (6.7)	4 (13.3)	0.253	4 (5.2)	6 (14.0)	0.096
	84 (93.3)	26 (86.7)		73 (94.8)	37 (86.0)	
Hb (g/dl)	8.77 ± 1.88	9.62 ± 2.12	0.071	8.69 ± 1.70	9.39 ± 2.30	0.075
Ureum (mg/dl)	168.4 ± 79.5	160.9 ± 84.3	0.691	161.0 ± 77.5	177.2 ± 84.8	0.309
Creatinine (mg/dl)	10.19 ± 5.16	6.11 ± 5.02	0.001	10.10 ± 5.42	8.00 ± 5.06	0.047
eGFR (ml/min/1,73m²)						
	6.10 ± 3.23	18.78 ± 20.73	0.008	6.68 ± 4.32	12.38 ± 16.91	0.042

Table 3. Multivariate analysis of the relationship between ESRD and variables related to lung edema.

Variable	P	OR	95% CI	
			Lower	Upper
ESRD (yes)	0.019	6.773	1.369	33.511
Hypertension (yes)	0.022	3.523	1.195	10.387
Obstruction and reflux uropathy (yes)	0.688	0.71	0.1	3.788
Age (years-old)	0.087	0.97	0.937	1.004
Hb (g/dl)	0.333	0.876	0.67	1.145
Creatinine (mg/dl)	0.722	1.02	0.917	1.134
eGFR (ml/min/1,73m²)	0.884	0.995	0.931	1.063

Discussion

Chronic kidney disease, which can progress to end-stage renal disease (ESRD) is a global health problem which is associated with increased morbidity, mortality, and reduced quality of life. This condition could lead into excess of fluid along with an increase in pulmonary capillary permeability, resulted in pulmonary edema and pleural effusion, which ultimately reducing pulmonary function [6].

To assist the diagnosis and evaluation of pulmonary edema, chest x-ray plays as the most practical and useful method, which is widely available in health care facilities, non-invasive, portable, and relatively inexpensive [8,9]. In present study, evaluation by chest X-ray in patients with CKD obtained incidence of pulmonary edema by 64.2%. As glomerular filtration rate falls, pulmonary edema and respiratory muscle dysfunction become more common due to fluid retention and metabolic alterations [10]. An increase in the patient's respiratory rate triggers pulmonary hyperventilation so that more oxygen enters the alveoli. The entry of oxygen into the alveoli is followed by a diffusion process. The more oxygen is added, the more diffusion occurs between O2 and CO2. This condition has an impact on increasing carbon in the blood so that it triggers changes in the metabolic state towards acidosis.

Pulmonary edema occurs because of fluid displacement from the vascular to the interstitial space or to the alveoli which exceeds the amount of fluid returned to the blood vessels and lymph vessels. In normal circumstances, the exchange of fluids, colloids, or dissolved materials from the blood vessels to the interstitial space follows the principles of Starling's Law. Based on Starling's Law, the rate of transudation from the blood vessels to the interstitial space is the difference between the intravascular and the interstitial hydrostatic and osmotic pressures. Starling pressure imbalance results in increased pulmonary venous pressure. Pulmonary edema occurs when the pulmonary capillary pressure increases beyond the colloid plasma osmotic pressure which ranges from 28 mmHg. This increase in pressure occurs due to the failure of the left ventricle to perform systemic ejection. It is then resulting in fluid retention which increases the amount of pressure on the organ behind the left ventricle.

The heart, lungs and kidneys are organs that are interrelated in their function. The three of them can influence each other, both as a cause and as a result. Pulmonary edema caused by kidney failure occurs due to reduced renal mass resulting in structural and functional hypertrophy of the nephrons. The process of these changes is mediated by vasoactive molecules and growth factors. This condition causes hyperfiltration followed by an increase in capillary pressure and glomerular blood flow. The hyperfiltration that occurs in the glomerolus causes large molecules such as albumin to pass through the filtration until their levels decrease in the blood vessels. This decrease in albumin levels causes the release of fluid binders in the vascular, causing extravasation of fluid from intravascular to extravascular, causing edema.

Increased activity of the intrarenal renin-angiotensin-aldosterone axis also contributes to the incidence of hyperfiltration. Ultimately, hyperfiltration causes more areas of the nephron to experience sclerosis, resulting in failure of renal function to maintain osmotic pressure and intravascular oncotic pressure throughout the body, including in the intrapulmonary vascular area. Reduced pulmonary function in patients with renal failure with pulmonary edema causes shortness of breath that does not decrease with rest. Cellular oxygen demand increases so that the heart will increase cardiac output which causes the heart rate higher.

Our study corroborates previous finding of ESRD and hypertension as related to pulmonary edema. Pulmonary edema can also be partly related to heart function and is one of the indications of heart failure [11,12]. The pathophysiology of pulmonary edema in patients with CKD is related to changes in body fluid volume. Excess fluid is common in ESRD patients who need hemodialysis [6,7,13]. The value of glomerular filtration rate (GFR) decreases progressively in CKD patients and the kidneys cannot maintain salt and fluid balance. Inadequacy of elimination of fluid in kidney disease results in excess fluid throughout the body.13 Excess fluid affects the preload-afterload factor which can lead to left ventricular hypertrophy (left ventricular hypertrophy; LVH) which is a typical feature that there has been involvement of left heart systolic-diastolic function in patients with CKD [7,14] Left heart abnormality causes an increase in pulmonary venous pressure and shifts the power balance between capillaries and lung interstitial. Pulmonary capillary hydrostatic pressure increases because the blood

damages in the lungs and the fluid coming out of the capillaries to the interstitial space increases. At some point the lymphatic system of the lung is unable to compensate for fluid that has extravasation, resulting in cardiogenic pulmonary edema. Interstitial edema initially occurs, and in more severe cases alveolar edema can occur [4,14,15]. It is known that most CKD patients die of cardiovascular disease, not because the progression of kidney disease to end-stage disease itself and heart failure is a complex syndrome and is considered the end point of all cardiovascular disorders [16–18]. Therefore, it is important to evaluate the presence of signs of cardiac dysfunction in CKD patients.

Cardiogenic pulmonary edema is the most common cause of end-stage renal failure patients entering the intensive care unit, amounting to 24% of patients. Cardiogenic pulmonary edema is also a leading cause of death in end-stage CKD patients undergoing dialysis [19,20]. The percentage of deaths due to pulmonary edema in chronic dialysis patients reaches 10% [21]. Fluid intake and excessive use of salt are the most common causes of pulmonary edema in patients who need renal replacement therapy [20,21]. However, until now studies that examine the causes and clinical outcomes of acute pulmonary edema in patients with end-stage CKD are still very limited [20]. Patients with chronic kidney disease will experience failure in regulating blood pressure because the kidneys are the main blood pressure regulators. Blood pressure that tends to be high will increase the workload of the heart and cause damage to the vascular endothelium. In addition, kidney function failure causes a decrease in glomerular filtration rate, urine production tends to be small so that intracellular fluid retention will occur which eventually goes extravasation to the interstitial tissue. If this event occurs in the lungs, pulmonary edema is inevitable.

This study is limited to the chest x-ray in assessing pulmonary edema in patients with chronic kidney disease. Corroboration with other examination modalities was not performed. Future studies are expected to further explore pulmonary edema with radiological multimodalities.

The results of this study provide the evidence of the association of ESRD with the incidence of pulmonary edema. Therefore, it is necessary to do early prevention and regular treatment in patients with CKD to avoid further disease progression. In addition, medical personnel are expected not to ignore respiratory complaints felt by patients and to do chest X-ray to detect the possibility of pulmonary edema in patients with chronic renal failure, especially in patients who have reached the final stage of the disease.

Acknowledgements

The authors would like to acknowledge the entire staff of Radiology Departments of Dr. Moewardi Hospital.

Funding

None

Conflict of interest

The authors declare that they have no conflict of interest.

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