Relationship Between Pulmonary Hypertension Before Kidney Transplantation and Early Graft Dysfunction

Khadijeh Abasi,[1] Zahra Lotfi,[2] Mahnaz Ahmadi,[3] Hasan Mehrad Majd,[4] Boshra Hasanzamani[2]

[1]Mashhad University of Medical Sciences, Mashhad, Iran
[2]Kidney Transplantation Complications Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
[3]Cardiology Department, Imam Reza Hospital, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[4]Clinical Research Unit, Mashhad University of Medical Sciences, Mashhad, Iran

Keywords. pulmonary hypertension, delayed graft function, kidney transplantation, chronic kidney disease

Introduction. Pulmonary hypertension (PHTN) is a common complication in patients with chronic kidney disease. Delayed Graft Function (DGF), on the other hand; is an essential complication after kidney transplantation. These two complications increase morbidity and mortality in patients. The effect of PHTN on cardiovascular and graft blood supply, as well as the same mechanisms underlying PTHN and DGF; led us to investigate the relationship between them.
Methods. In this retrospective cohort study, 306 patients aged 18 years or older who underwent kidney transplantation at our center over a 4-year were enrolled. PTHN was diagnosed by transthoracic echocardiography performed by a cardiologist. DGF refers to the cases where the patient needs dialysis in the first week after kidney transplantation or if serum creatinine is ≥ 3 mg/dL on the 5th day after surgery.
Results. The prevalence of PHTN was 43 (14.1%), and the prevalence of DGF was 80 (26.1%). PHTN was not correlated with age, sex, duration of dialysis, type of dialysis, and cause of renal failure. But DGF was associated with the duration and type of dialysis. DGF was found to be higher in patients undergoing hemodialysis ($P < .05$), and patients with a higher mean duration of dialysis were also more likely to have DGF ($P < .05$). Also, we concluded that there was a significant relationship between PHTN and DGF ($P < .05$), meaning that patients with PTHN before transplantation were more likely to develop DFG.
Conclusion. This study found that pre-transplant PTHN is an independent predictor of DGF in renal transplant patients.

IJKD 2020;14:399-404
www.ijkd.org

Original Paper

INTRODUCTION

Pulmonary hypertension (PHTN) is a common complication in patients with chronic renal failure,[1,2] which increases morbidity and mortality in this group of patients.[3,4] The prevalence of PHTN in hemodialysis patients is reported to be 40 to 50%.[5,6] The exact pathogenesis of PHTN in chronic renal failure patients is unclear, but factors have been implicated in this complication. Factors such as oxidative stress and endothelial dysfunction are among them.[7] A pulmonary artery pressure greater than or equal to 25 determined by right heart catheterization is considered as hypertensive pulmonary.[8]

Delayed graft function is one of the major complications after kidney transplantation and has been shown in some studies to decrease graft survival.[9-11] There is also some evidence that DGF increases the likelihood of acute graft rejection.[12,13] The prevalence of DGF has been reported in different

studies ranging from 23 to 34%.[14,15]

One theory is that the factors that increase pulmonary pressure also cause DGF.[16,17] Factors such as changes in hemodynamic status and vasoactive factors cause PHTN as well as decreased blood flow to the transplanted kidney. Given that hypertension pulmonary can affect cardiac output and blood supply to the kidney, as well as the existence of similar mechanisms for these two conditions, we designed the study to examine the relationship between the presence of hypertension pulmonary disease before transplantation and DGF.

MATERIALS AND METHODS

In this retrospective cohort, all patients undergoing kidney transplantation attending Montaseriyeh Hospital (Mashhad, Iran) and aged18 years or older were enrolled. The study period was four years long (from March 2016 to March 2019). Patients with graft loss due to technical problems of surgery, renal vascular thrombosis, or microangiopathic thrombotic purpura were excluded. Finally, 306 patients were included in the study. Patients' data including age, sex, type of dialysis, duration of dialysis, cause of renal failure, and type of kidney transplant (cadaveric or living) were extracted from the patients' records.

Trans-thoracic echocardiography was performed by a cardiologist using a single device. Pulmonary artery pressure based on pulmonary arterial systolic pressure (PASP) ≥ 35 mmHgwas considered as PHTN.[18-20]

DGF refers to cases where the patient needs dialysis in the first week after kidney transplantation or if serum creatinine is ≥ 3 mg/dL on the 5th day after surgery.[15,21]

All patients were treated with a calcineurin inhibitor (tacrolimus or cyclosporine) and an antimetabolite (mycophenolate mofetil or mycophenolate sodium) plus prednisolone. The primary outcome of this study was to investigate the possible association between PHTN and DGF in renal transplant patients.

Statistical Analysis

After entering the data into SPSS-22 software, statistical analysis was used to describe the data. Chi-square test was used to investigate the relationship between qualitative variables and fissure- Exact test was performed for qualitative variables with a frequency less than 2. The 95% confidence level was considered. $P < .05$ was found to be significant. The results of the data collection were presented as descriptive and analytical statistics as follows: Descriptive statistics included mean and standard deviation for quantitative and frequency variables and percentage of frequency and tables for qualitative variables. Chi-square test was used to compare the relationship of PHTN with qualitative variables such as gender and type of dialysis and correlation with DGF. Exact test was used to examine the relationship between DGF and gender.

All patients undergoing renal transplantation were enrolled in the Montaseryeh Hospital from 2016 to 2019, with a total of 306 patients enrolled.

RESULTS

According to the inclusion criteria, 306 patients were enrolled in the study. The mean age of patients was 37.07 ± 10.9. The duration of dialysis before transplantation of all patients was 28.43 ± 16.93 months. Other demographic information is listed in Table 1.

It was found that 31 (12.9%) of the patients undergoing Cadaver transplantation and 12 (18.5%) of the living transplants had PHTN. There was

Table 1. Baseline Characteristics of the Patients

Patient Characteristics	
Sex, n (%)	
Female	136 (44.4)
Male	170 (55.6)
Age (mean ± SD), y	37.07 ± 10.9
Type of Dialysis, n (%)	
Hemodialysis	269 (87.9)
Peritoneal Dialysis	23 (7.5)
No Dialysis	14 (4.6)
PHTN, n (%)	43 (14.1)
DGF, n (%)	80 (26.1)
Cause of ESRD, n (%)	
Diabetes Mellitus	32 (10.5)
Hypertension	65 (21.2)
Vesico-ureteral reflux	14 (4.6)
ADPKD	15 (4.9)
Glomerulonephritis	49 (16)
Unknown	115 (37.6)
Others	16 (5.2)
Donor , n (%)	
Living	65 (21.2)
Cadaver	241 (78.8)
Dialysis Duration (mean ± SD) , mo	28.43 ± 16.93

no statistical difference between the two groups ($P > .05$).

Patients were divided into two groups according to their pulmonary artery pressure [group one PASP ≥ 35 (patients with PHTN) and group two PASP < 35 (no PH)]. Patients' characteristics were not significantly different between the two groups (Table 2).

Patients were divided into two groups according to the presence or absence of DGF (group one patients with DGF and group two patients without DGF). Table 3 shows the patients' characteristics in these two groups. The only difference between the two groups was the type of dialysis and the duration of it. It was found that the probability of DGF was higher in patients undergoing

Table 2. Characteristics of the Subjects Studied, According to PASP

Variables	PASP < 35 mmHg	PASP ≥ 35 mmHg	*P*
PASP, n (%)	263 (85.9)	43 (14.1)	
Sex			
Female	117 (86)	19 (14)	> .05
Male	146 (85.9)	24 (14.1)	
Age (mean ± SD), y	37.33 ± 10.92	35.26 ± 10.3	> .05
Type of Dialysis, n (%)			
Hemodialysis	230 (85.5)	39 (14.5)	
Peritoneal Dialysis	21 (91.3)	2 (8.7)	> .05
No Dialysis	12 (85.7)	2 (14.3)	
Cause of ESRD, n (%)			
Diabetes Mellitus	29 (11.1)	3 (7)	
Hypertension	57 (21.8)	8 (18.6)	
Vesico-Ureteral Reflux	13 (5)	1 (2.3)	
ADPKD	14 (5.3)	1 (2.3)	> .05
Glomerulonephritis	39 (14.9)	10 (23.3)	
Unknown	96 (36.6)	18 (41.9)	
Others	14 (5.3)	2 (4.7)	
Dialysis Duration (mean ± SD), mo	28.24 ± 16.97	28.37 ± 14.07	> .05
Type of Transplant			
Living	58 (81.5)	12 (18.5)	> .05
Cadaver	209 (87.1)	31 (12.9)	

Table 3. Baseline Characteristics of the Subjects Studied, According to DGF

Variables	DGF		*P*
	No, n (%)	Yes, n (%)	
	228 (73.9)	80 (26.1)	
Sex			
Female	105 (77.2)	31 (22.8)	> .05
Male	121 (71.2)	49 (28.8)	
Age (mean ± SD), y	36.62 ± 10.76	38.39 ± 11.26	> .05
Type of Dialysis, n (%)			
Hemodialysis	193 (71.7)	76 (28.3)	
Peritoneal Dialysis	19 (82.6)	4 (17.4)	< .05
No Dialysis	14 (100)	0 (0)	
Cause of ESRD, n (%)			
Diabetes Mellitus	22 (9.7)	10 (12.5)	
Hypertension	44 (19.5)	21 (26.3)	
Vesico-Ureteral Reflux	14 (6.2)	0 (0)	
ADPKD	11 (4.9)	4 (5)	> .05
Glomerulonephritis	34 (15)	15 (18.8)	
Unknown	89 (39.4)	26 (32.5)	
Others	12 (5.3)	4 (5)	
Dialysis Duration (mean ± SD), mo	26.75 ± 16.87	33.3 ± 16.32	< .05

Table 4. Relationship Between PH and DGF

Variables	DGF		*P*
	No, n (%)	Yes, n (%)	
PHTN			
No, n (%)	200 (76)	63 (24)	< .05
Yes, n (%)	26 (60.5)	17 (39.5)	

hemodialysis ($P < .05$), and patients with higher mean dialysis' duration were also more likely to have DGF ($P < .05$). In this study, the relationship between the type of transplantation and DGF was also evaluated. Regarding the qualitative nature of both variables, chi-square test was used again. 69 patients (28.6%) of deceased donor transplantation, and 11 patients (16.9%) of living donor transplant patients had primary renal transplant dysfunction. Given that $P > .05$, the relationship between these two variables is close to significant and is expected to reach $P < .05$ if the sample size was increased. The prevalence of PH in patients was 43 (14.1%) and DGF 80 (26.1%). Finally, the relationship between PH and DGF were investigated (Table 4).

In the study population, 17 (39.5%) of those with PHTN had DGF, and 63 (24%) of those with no PHTN had DGF. It was found that there was a significant relationship between PHTN before kidney transplantation and DGF ($P < .05$).

DISCUSSION

The study suggested that patients with PHTN before kidney transplantation were more likely to have DGF. In ESRD patients, various causes such as endothelial dysfunction, arterio-venous fistula, and hypertension may cause pulmonary hypertension. Endothelial dysfunction results in disruption of the balance

between vasodilator substances such as nitric oxide and vasoconstrictor substances such as endothelin-1 and the presence of AVF increases cardiac output and increases pulmonary pressure. Cardiac complications of hypertension, such as left ventricular hypertrophy, exacerbate the increase in pulmonary artery pressure.

Changes caused by increased pulmonary pressure in hemodynamics and vasoactive substances increase the likelihood of primary graft dysfunction. One of the causes of DGF is ischemic-reperfusion injury. Increased vasoconstrictor material such as endothelin increases the likelihood of this injury. As mentioned, the amount of vasoconstrictor material is high in PH. Therefore, PH patients are more likely

to develop ischemic-reperfusion injury and, therefore DGF. The results of this study are similar to some of the previous studies.[22,23] But some studies have found that PH is not associated with DGF.[24] The prevalence of PHTN in our study was 14.1%, which was less prevalent than other studies in our study population.[5,6,25,26,29] The prevalence of DGF in the present study was 26.1%. In other studies, the incidence varied between 23 and 34 percent.[12,27] The study found that there was no relationship between PHTN, sex, age, duration of dialysis, type of dialysis, and the cause of renal failure. On the other hand, DGF was not correlated with sex, age, and cause of renal failure; but dialysis duration and type before kidney transplantation were associated with DGF. DGF was found to be higher in hemodialysis patients than in patients undergoing peritoneal dialysis, and patients with longer dialysis duration were more likely to develop DGF.

In this study, we examined the association between PHTN before kidney transplantation with DGF, but the association between PHTN and DGF with long-term graft survival was not investigated. Possible mechanisms of PHTN in patients with renal failure are multi-factorial. In patients with chronic renal failure, especially in end stage renal disease (ESRD); the balance between vasoconstrictor and vasodilator factors is disturbed. The level of endothelin-1and vasodilator factors decrease. On the other hand, the presence of hypertension and left ventricular hypertrophy in these patients increases pulmonary vein pressure and pulmonary artery pressure. Uremic toxins and factors such as chronic inflammation, arterial–venous fistula, and contact with dialysis membranes cause endothelial dysfunction.[7] Disturbance in the hemodynamic status and changes in the balance of vaso-active factors cause PHTN and DGF. It has been found that patients with DGF have impaired renal micro-perfusion.[16] The presence of PHTN appears to decrease cardiac output, which in return increases the impairment of transplanted kidney micro-perfusion and increases the risk of DGF.[23]

It has been suggested that endothelin-1 increases ischemia-reperfusion injury in the transplanted kidney and increases the likelihood of DGF.[28]

Therefore, the presence of PHTN may indicate elevated serum endothelin-1 levels, which is one of the factors that increase the probability of DGF. As demonstrated in this study, the presence of PHTN increases the likelihood of DGF.

One of the strengths of this study is the high sample size compared to similar studies. On the other hand, other studies on cadaveric kidney carriers have been performed; but in our study, cadaver and living donors with appropriate sample sizes were selected (cadaver 241 and living 65).

One limitation of this study is that the diagnosis of PHTN was through trans-thoracic echocardiography. While accurate diagnosis of PHTN is by right heart catheterization. However, as this method is invasive, it may not be possible in patients undergoing kidney transplantation. When PHTN is detected by cardiac catheterization, a pressure of ≥ 25 mmHg is considered as PHTN. In this study and other studies that measured pulmonary pressure through trans-thoracic echocardiography, Pulmonary artery pressure ≥ 35 mmHg was considered PHTN. Even in the presence of factors such as volume overload, which changes the pulmonary artery pressure, this pressure also indicates the presence of PHTN.

Other limitations of this study were the lack of long-term follow-up and evaluation of the effect of PHTN on the long-term survival of patients. Therefore, it is recommended to conduct another research to evaluate the long-term survival of patients. Another limitation of this study was that the severity of pulmonary hypertension was not measured. It is suggested that another study is performed to determine the relationship between the severity of pulmonary hypertension and DGF. It is also suggested that another study is conducted to investigate the effect of kidney transplantation on PHTN. According to the results of this study, early detection of ESRD patients with PHTN and an attempt to resolve underlying causes reduces the probability of DGF.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the financial support by Mashhad University of Medical Sciences (Research Project No. P9883 as a MD student dissertation). We would also like to thank the Clinical Research Development Unit, Ghaem Hospital, for their assistance in this manuscript.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Selvaraj S, Shah SJ, Ommerborn MJ, et al. Pulmonary hypertension is associated with a higher risk of heart failure hospitalization and mortality in patients with chronic kidney disease: The Jackson Heart Study. Circ Heart Fail. 2017; 10(6): e003940.
2. Agarwal R. Prevalence, determinants and prognosis of pulmonary hypertension among hemodialysis patients. Nephrol Dial Transplant. 2012; 27(10): 3908–14.
3. Ramasubbu K, Deswal A, Herdejurgen C, et al. A prospective echocardiographic evaluation of pulmonary hypertension in chronic hemodialysis patients in the United States: prevalence and clinical significance. Int J Gen Med. 2010; 3:279–86.
4. Navaneethan SD, Roy J, Tao K, et al. Prevalence, predictors, and outcomes of pulmonary hypertension in CKD. J Am Soc Nephrol. 2016; 27(3): 877–86.
5. Yigla M, Nakhoul F, SabagA.et al. Pulmonary hypertension in patients with end-stage renal disease. Chest. 2003; 123: 1577–82.
6. Abassi Z, Nakhoul F, Khankin E, Reisner S, Yigla M. Pulmonary hypertension in chronic dialysis patients with arteriovenous fistula: pathogenesis and therapeutic prospective. Curr Opin Nephrol Hypertens. 2006; 15:353–60.
7. Thenappan T.Pulmonary hypertension in chronic kidney disease: a hemodynamic characterization. Pulm Circ. 2017; 7:567–8.
8. Hoeper MM, Bogaard HJ, Condliffe R, et al. Definitions and diagnosis of pulmonary hypertension. J Am Coll Cardiol. 2013; 62:42–50.
9. Nicholson ML, Wheatley TJ, Horsburgh T, et al. The relative influence of delayed graft function and acute rejection on renal transplant survival. Transpl Int. 1996; 9:415-9.
10. Ojo AO, Wolfe RA, Held PJ, et al. Delayed graft function: risk factors and implications for renal allograft survival. Transplantation. 1997; 63:968-74.
11. Humar A, Johnson EM, Payne WD, et al. Effect of initial slow graft function on renal allograft rejection and survival. Clin Transplant. 1997; 11:623-7.
12. Troppmann C, Gillingham KJ, Benedetti E, et al. Delayed graft function, acute rejection, and outcome after cadaver renal transplantation. Transplantation. 1995; 59:962-8.
13. Troppmann C, Gillingham KJ, Gruessner RW, et al. Delayed graft function in the absence of acute rejection has no longterm impact. Transplantation. 1996; 61:1331-7.
14. Lehtonen SR, Isoniemi HM, Salmela KT, et al. Long-term graft outcome is not necessarily affected by delayed onset of graft function and early acute rejection. Transplantation. 1997; 64(1):103-7.
15. Hayati F, Beladi Mousavi SS, Mousavi Movahed SM, et al. Pulmonary hypertension among patients undergoing hemodialysis. J Ren Inj Prev. 2017; 6:122-6.

16. Angelescu M, Kraus T, Wiesel M, et al. Assessment of renal graft function by perioperativemonitoring of cortical microcirculation in kidney transplantation. Transplantation. 2003; 75:1190–6.
17. Brezis M, Heyman S, Dinour D, et al. Role of nitric oxide in renal medullary oxygenation. Studies in isolated and intact rat kidneys. J Clin Invest. 1991; 88:390–5.
18. Nakhoul F, Yigla M, Gilman R, et al. The pathogenesis of pulmonary hypertension in haemodialysis patients via arterio-venous access. Nephrol Dial Transplant. 2005; 20:1686–92.
19. Yigla M, Abassi Z, Reisner S, et al. Pulmonary hypertension in hemodialysis patients: an unrecognized threat. Semin Dial. 2006; 19:353–7.
20. Yigla M, Keidar Z, Safadi I, et al. Pulmonary calcification in hemodialysis patients: correlation with pulmonary artery pressure values. Kidney Int. 2004; 66:806–10.
21. Yock P, Popp R. Noninvasive estimation of right ventricular systolic pressure by Doppler ultrasound in patients with tricuspid regurgitation. Circulation. 1984; 70:657– 62.
22. Issa N, Krowka M, Griffin M, et al. Pulmonary hypertension is associated with reduced patient survival after kidney transplantation. Transplantation. 2008; 86:1384– 8.
23. Zlotnick DM, Axelrod DA, Chobanian MC, et al. Non-invasive detection of pulmonary hypertension prior to renal transplantation is a predictor of increased risk for early graft dysfunction. Nephrol Dial Transplant. 2010; 25:3090–6.
24. Goyal VK, Solanki SL, Baj B. Pulmonary hypertension and post-operative outcome in renal transplant: A retrospective analysis of 170 patients. Indian J Anaesth. 2018; 62:131-5.
25. Bozbas SS, Akcay S, Altin C, et al. Pulmonary hypertension in patients with end-stage renal disease undergoing renal transplantation. Transplant Proc. 2009; 41:2753–6.
26. Havlucu Y, Kursat S, Ekmekci C, et al. Pulmonary hypertension in patients with chronic renal failure. Respiration.2007; 74: 503–10.
27. Pfaff W, Howard R, Patton P, et al. Delayed graft function after renal transplantation.Transplantation. 1998; 65(2):219-23.
28. Schilling M, Holzinger F, Friess H, et al. Pathogenesis of delayed kidney graft function: role of endothelin-1, thromboxane B2, and leukotriene B4. Transplant Proc.1996; 28:304–5.
29. Miri M, Hejazi S, Maghsoudlou F, Ahmadi M. Prevalence of Pulmonary Hypertension in End-stage Renal Disease Patients Undergoing Hemodialysis and Peritoneal Dialysis at a Referral Center in Mashhad, Iran, From 2015 to 2016. IJKD. 2018; 12:364-8.

Correspondence to:
Boshra Hasanzamani, MD
Kidney Transplantation Complications Research Center,
Mashhad University of Medical Sciences, Mashhad, Iran
E-mail: hasanzamanib@mums.ac.ir

Received March 2020
Revised May 2020
Accepted July 2020