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ORIGINAL ARTICLE

Clinical implication of renal dysfunction during the clinical course in patients with paroxysmal nocturnal hemoglobinuria: a longitudinal analysis

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Abstract

Although renal dysfunction at the time of diagnosis of paroxysmal nocturnal hemoglobinuria (PNH) is a risk factor for mortality, subsequent renal events can occur. The objective of this study was to identify clinical implication of renal dysfunction occurring during the disease course in PNH patients. One hundred one patients with a granulocyte clone size of > 10% were enrolled. Renal events were observed in 55 (54.5%) patients during a median follow-up of 94.2 months. Median time to first renal event from diagnosis of PNH was 79.3 months. Thromboembolism (TE) event and recurrent TE events were observed in 25 (24.8%) and 8 (7.9%) patients, respectively. The rate of recurrent TE was significantly higher in patients with renal events ≥ 2 compared with that in patients with renal event ≤ 1 (18.8% vs. 2.9%; $P = 0.012$). The rate of recurrent TE was significantly higher in patients with chronic kidney disease (CKD) + acute kidney disease (AKD) compared with the rest of the patients (27.3% vs. 5.6%; $P = 0.040$). CKD+AKD was the only independent risk factor for OS in multivariate analysis (hazard ratio 7.95, 95% CI 1.24–51.15, $P = 0.029$). Therefore, close monitoring of renal events in PNH patients during the entire clinical course is essential.

Keywords Paroxysmal nocturnal hemoglobinuria · Renal dysfunction · Thromboembolism · Mortality

Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare acquired hematologic disease characterized by sustained and sometimes life-threatening hemolytic anemia due to chronic uncontrolled complement activation [1, 2]. Thromboembolism (TE), pulmonary hypertension, smooth muscle spasm, and renal dysfunction can be developed in PNH patients due to chronic uncontrolled complement activation [1, 3]. Among them, TE is considered one of the life-threatening complications. According to previous Korean Registry data, 18% of patients experienced TE during the disease course. TE was associated with increased risk for mortality [4, 5]. Renal dysfunction also contributed to 8–18% of total PNH-related deaths [3]. It was considered a risk factor for mortality in Korean Registry data [5].

Renal dysfunction can be developed in PNH patients because of increased cell-free plasma hemoglobin and depleted nitric oxide (NO) during intravascular hemolysis. Vasoconstriction due to NO depletion and intravascular TE can alter renal blood flow and directly affect glomerular

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filtration rate (GFR) [6]. Hemosiderin deposition in renal proximal tubular cells can also decrease renal function [7]. Hemosiderin deposition in the kidney can be detected by renal biopsy or renal magnetic resonance imaging (MRI). Loss of cortical signal intensity on both T1- and T2-weighted images is correlated with diffuse hemosiderin deposition within proximal tubular cells [7–9]. Therefore, PNH-related renal dysfunction can be detected by renal biopsy or renal MRI.

Considering pathophysiology of renal dysfunction in PNH, renal events can continuously occur during the entire disease period. However, previous studies only evaluated the prognostic role of baseline renal dysfunction. According to international phase 2 and 3 trial for eculizumab, 27% of patients had major clinical kidney events and 20.5% of patients showed estimated GFR < 60 mL/min/1.73 m^2 (chronic kidney disease (CKD) stage ≥ 3) at the time of diagnosis of PNH [10]. According to the Korean Registry data, 16.6% of patients showed impaired renal function (acute renal failure (ARF) and/or CKD stage ≥ 3) at the time of diagnosis of PNH and the incidence of TE was significantly higher in patients with renal insufficiency (38% vs. 18%) [4]. Because of very few studies about renal dysfunction during the entire disease course, only baseline renal dysfunction has been conceptually considered a prognostic factor in PNH.

As the incidence and prognostic role of renal dysfunction might be underestimated, clinical characteristics and dynamics of renal dysfunction during natural disease course should be longitudinally evaluated. Therefore, the objective of this study was to identify clinical implication of renal dysfunction occurring during the entire disease course in PNH patients.

Methods

Patients and study design

This multicenter retrospective study was conducted in five institutions from the Aplastic Anemia Working Party of the Korean Society of Hematology. One hundred and three PNH patients with granulocyte PNH clone size of more than 10% were enrolled in this study. Serum lactate dehydrogenase (LDH) was ≥ 1.5 × the upper limit of normal (ULN) during the disease course. To avoid the influence of eculizumab on renal function, we captured clinical data until starting eculizumab for patients who received eculizumab for treatment. Renal dysfunction such as acute kidney disease (AKD) or CKD was defined based on the criteria of Kidney Disease: Improving Global Outcomes (KDIGO) [11]. The definition of AKD was acute kidney injury or a decreased estimated GFR of less than 60 mL/min/1.73 m^2 for less than 3 months, or a decreased estimated GFR of ≥ 35%, or increased serum creatinine by > 50% for less than 3 months. The definition of CKD was a decreased estimated GFR of less than 60 mL/min/1.73 m^2 for at least 3 months. According to these criteria, we calculated the number of renal event (AKD or CKD) during the follow-up period to compare patients who experienced no or one renal event (renal event ≤ 1 time) to patients with recurrent renal events (renal event ≥ 2 times). Among patients with recurrent renal events, those who experienced both CKD and AKD were categorized to CKD+AKD group. Two patients were excluded from this analysis because they had a history of renal dysfunction related to cyclosporine as immunosuppressive therapy.

We collected their baseline clinical characteristics, including associated bone marrow disorder (BMD) such as aplastic anemia or myelodysplastic syndrome and baseline renal function (serum creatinine and estimated GFR). In addition, we collected their clinical information including serum LDH at the time of each renal event and history of co-morbidities such as diabetes and hypertension. All cumulative events of TE were collected. This study was conducted in accordance with the Declaration of Helsinki. It was reviewed and approved by the Institutional Review Board (IRB) of participating hospitals. Informed consent was exempted by the IRB due to its retrospective nature.

Statistical analysis

Continuous variables were compared using Mann-Whitney U test while categorical variables were compared using $\chi 2$ test or Fisher's exact test. Cumulative incidences of the first renal event and TE were estimated using Kaplan-Meier methods. Overall survival (OS) rate was analyzed using the Kaplan-Meier method and survival curves of each group were compared using the log-rank test. Univariate analysis for factors that affected the development of recurrent TE or OS was performed using a logistic regression method. Results of multivariate analysis were presented as hazard ratio (HR) and 95% confidence interval (CI). A P value of < 0.05 was defined as statistically significant. The Pearson correlation test was used to measure the degree of the relationship between changes of estimated GFR and LDH fold from the baseline to the onset of renal event. All statistical calculations were performed with SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

A total of 101 patients from five institutions in Korea were analyzed in this study. Baseline clinical characteristics including renal events and TE events are summarized in Table 1. At diagnosis, median granulocyte PNH clone size was 63.4% and median serum LDH was 5.7-fold × ULN. Median serum creatinine was 0.8 mg/dL (range, 0.5–16.2 mg/dL) and median

Table 1 Patient's characteristics according to the number of renal event

Characteristics	Total	Renal event ≤ 1 ($n = 69$)	Renal event ≥ 2 ($n = 32$)	*P* value
Age, median (range)	36 (6–85)	35 (6–85)	40 (20–77)	0.197
Sex, male, *n* (%)	59 (58.4)	39 (56.5)	20 (62.5)	0.571
Preceding BMD, *n* (%)				
Aplastic anemia	38 (40.3)	24 (38.7)	14 (43.8)	0.663
Myelodysplastic syndrome	4 (4.3)	1 (1.6)	3 (9.4)	0.113
Baseline parameters, median (range)				
Hemoglobin (g/dL)	9.2 (1.4–13.8)	9.2 (3.5–13.8)	9.2 (1.4–13.3)	0.822
WBC ($\times 10^9$/L)	3.8 (1.6–11.7)	4.2 (1.6–11.7)	3.4 (2.1–8.1)	0.045
PLT ($\times 10^9$/L)	119.5 (7.0–640.0)	103.5 (7.0–640.0)	133.5 (19.0–257.0)	0.267
Granulocyte clone size	63.4 (10.7–99.7)	74.7 (14.0–99.7)	50.3 (10.7–99.1)	0.057
LDH fold (× ULN)	5.7 (0.9–15.4)	5.6 (1.1–11.8)	5.7 (0.9–15.4)	0.656
Serum creatinine (mg/dL)	0.8 (0.5–16.2)	0.8 (0.5–16.2)	1.0 (0.5–6.8)	0.044
eGFR (mL/min/1.73 m^2)	87.2 (3.2–172.1)	89.2 (3.2–172.1)	81.3 (9.3–116.9)	0.033
eGFR < 60 mL/min/1.73 m^2 (%)	19.7%	10.1%	21.9%	0.130
Renal event during disease course, *n* (%)	55 (54.5)	23 (33.3)	32 (100)	< 0.001
TE during disease course, *n* (%)	25 (24.8)	15 (21.7)	10 (31.3)	0.303
Recurrent TE during disease course, *n* (%)	8 (7.9)	2 (2.9)	6 (18.8)	0.012

BMD bone marrow disorder, *WBC* white blood cell count, *PLT* platelet count, *LDH* lactate dehydrogenase, *ULN* upper limit of normal, *eGFR* estimated glomerular filtration rate, *TE* thromboembolism

estimated GFR was 87.2 mL/min/1.73 m^2 (range, 3.2–172.1 mL/min/1.73 m^2). An estimated GFR < 60 mL/min/1.73 m^2 was observed in 19.7% of patients at the time of diagnosis. During a median follow-up time of 7.7 years (94.2 months; range, 2.8–424.9 months) from diagnosis, renal event such as AKD or CKD was observed in 55 (54.5%) patients. The median time to the first renal event of the 101 enrolled patients was 6.6 years (Fig. 1). Among 55 patients who experienced a renal event, the median time to the first renal event was 2.3 years (range, 0–28.1 years), the median time to the first AKD episode was 2.7 years (range, 0–28.1 years), and the median time to the diagnosis of CKD was 2.6 years (range, 0–18.6 years). TE event and recurrent TE events were observed in 25 (24.8%) and 8 (7.9%) patients, respectively. Among these 55 patients with renal event, seven patients had a history of immunosuppressive therapy with cyclosporine. However, none of these patients with renal event received an immunosuppressive therapy at the time of renal event.

Among a total of 101 patients, 44.5% ($n = 46$) had no renal event, 22.8% ($n = 23$) had one renal event, and 31.7% ($n = 32$) experienced two or more renal events during the disease course. Among the 23 patients who had one renal event, 20 experienced AKD and three patients had CKD. Thirty-two patients experienced recurrent renal events, including recurrent AKD in 21 patients (the recurrent AKD group) and CKD+AKD in 11 patients (the CKD+AKD group). Among the 14 patients with CKD, nine patients had a history of diabetes, hypertension, or both (diabetes, $n = 3$; hypertension, $n = 4$; both, $n = 2$) at the time of first renal event. Among the 11 patients with CKD+AKD, 5 patients experienced combined episodes of AKD event on CKD. During a median follow-up period of 94.2 months, six patients died. The cause of death was TE in 2 patients, infections such as sepsis in 2 patients, and causes non-related to PNH in 2 patients.

Seven patients out of the 14 patients with baseline renal dysfunction (estimated GFR < 60 mL/min/1.73 m^2) experienced subsequent renal events. They were categorized to the recurrent AKD group ($n = 4$) or the CKD+AKD group ($n = 3$). The other seven patients with baseline renal dysfunction had no further experience of renal event (5 patients with AKD and 2 patients with CKD). Among the 14 patients with baseline renal dysfunction, TE and recurrent TE were developed in 5 (35.7%) and 3 (12.4%) patients, respectively. Among the 57 patients without renal dysfunction, TE and recurrent TE were reported in 12 (21.1%) and 2 (3.5%) patients, respectively.

TE and OS according to the number of renal event

Comparing patients with no or one renal event ($n = 69$, renal event ≤ 1 time) with patients with recurrent renal events ($n = 32$, renal events ≥ 2 times), the rate of TE was not statistically significant between patients with renal events ≥ 2 times (10/32, 31.3%) and those with renal event ≤ 1 time (15/69, 21.7%) ($P = 0.303$). However, the rate of recurrent TE was statistically higher in patients with renal events ≥ 2 times (6/32, 18.8%)

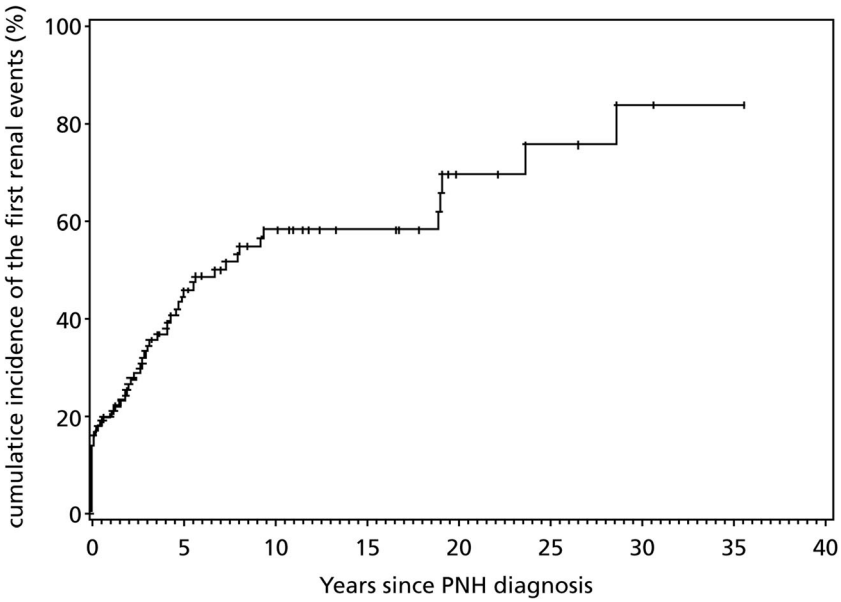


Fig. 1 Cumulative incidence of the first renal event

compared with those with renal event ≤ 1 time (2/69, 2.9%) ($P = 0.012$, Table 1). Those patients with renal events ≥ 2 times showed a trend toward inferior OS compared with those with renal event ≤ 1 time (86.4% vs. 96.0% at 10 years; $P = 0.124$) (Fig. 2a).

Outcomes of patients of the CKD+AKD group ($n = 11$) were compared with those of the rest of the patients ($n = 90$, patients with renal event ≤ 1 time + the recurrent AKD group). Results are shown in Table 2. The rate of TE tended to be higher in patients of the CKD+AKD group compared with that in the rest of the patients (5/11, 45.5% vs. 20/90, 22.2%, $P = 0.134$). However, the rate of recurrent TE was significantly higher in the CKD+AKD group (3/11, 27.3%) than that in the rest of the patients (5/90, 5.6%) ($P = 0.040$, Table 2). In addition, OS was significantly lower in patients with CKD+AKD than that in the rest of the patients (75.0% vs. 95.8% at 10 years; $P = 0.011$) (Fig. 2b).

Risk factors for TE and OS

To identify risk factors for developing TE, recurrent TE, and OS, a logistic regression method was used in this analysis. There was no significant risk factor for TE in this study. Estimated GFR at diagnosis < 60 mL/min/1.73 m^2 (HR, 1.86; 95% CI, 0.56–6.19; $P = 0.311$), recurrent renal events (HR, 1.64; 95% CI, 0.64–4.20; $P = 0.305$), or CKD+AKD (HR, 2.92; 95% CI, 0.81–10.56; $P = 0.103$) was not a significant risk factor for TE. According to univariate analysis, estimated GFR at diagnosis < 60 mL/min/1.73 m^2 (HR, 4.47; 95% CI, 0.94–21.36; $P = 0.060$), recurrent renal events (HR;

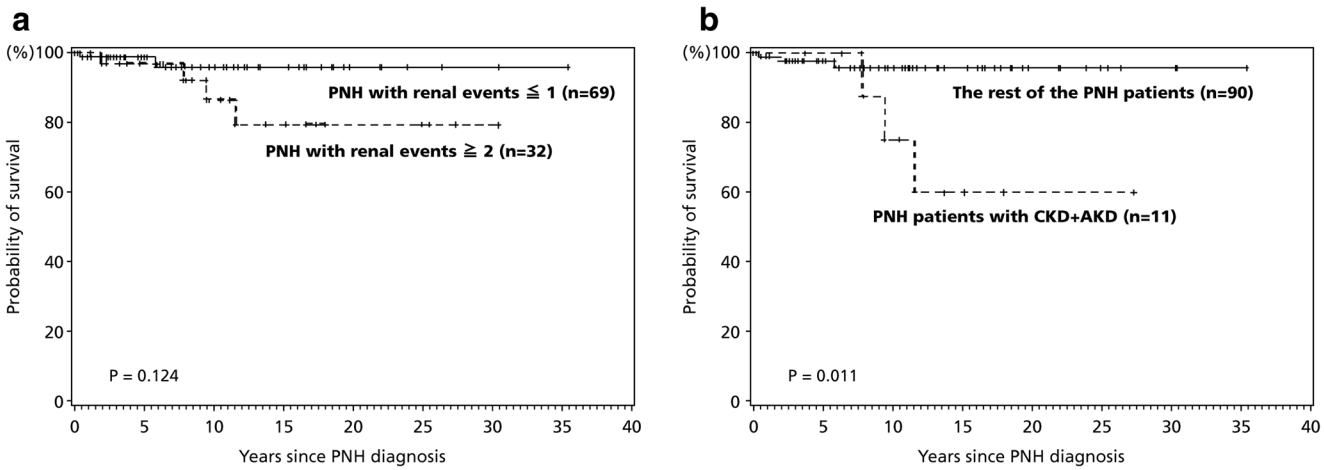


Fig. 2 Probability of survival according to the number of renal event. (**a**) Patients with renal event ≤ 1 vs. patients with renal events ≥ 2. (**b**) Patients with CKD+AKD vs. the rest of the PNH patients

Table 2 Patient's characteristics according to the presence CKD+AKD

Characteristics	CKD+AKD ($n = 11$)	The rest of the patients ($n = 90$)	P value
Age, median (range)	50 (32–77)	35 (6–85)	0.003
Sex, male, *n* (%)	8 (72.7)	51 (56.7)	0.353
Preceding BMD, *n* (%)			
Aplastic anemia	4 (36.4)	34 (41.0)	1.000
Myelodysplastic syndrome	1 (9.1)	3 (3.6)	0.397
Baseline parameters, median (range)			
Hemoglobin (g/dL)	7.7 (1.4–13.3)	9.3 (3.5–13.8)	0.363
WBC ($\times 10^9$/L)	3.3 (2.7–6.3)	4.0 (1.6–11.7)	0.296
PLT ($\times 10^9$/L)	172.0 (19.0–246.0)	105.0 (7.0–640.0)	0.304
Granulocyte clone size	45.0 (10.7–99.1)	66.1 (10.8–99.7)	0.129
LDH fold ($\times$ ULN)	4.3 (0.9–15.4)	6.0 (1.1–11.8)	0.650
Serum creatinine (mg/dL)	1.1 (0.5–2.4)	0.8 (0.5–16.2)	0.135
eGFR (mL/min/1.73 m^2)	68.8 (20.3–116.9)	87.7 (3.2–172.1)	0.133
eGFR < 60 mL/min/1.73 m^2	3 (27.3)	11 (12.2)	0.178
TE during disease course, *n* (%)	5 (45.5)	20 (22.2)	0.134
Recurrent TE during disease course, *n* (%)	3 (27.3)	5 (5.6)	0.040

CKD chronic kidney disease, *AKD* acute kidney disease, *BMD* bone marrow disorder, *WBC* white blood cell count, *PLT* platelet count, *LDH* lactate dehydrogenase, *ULN* upper limit of normal, *eGFR* estimated glomerular filtration rate, *TE* thromboembolism

7.73; 95% CI, 1.47–40.79; $P = 0.016$), and CKD+AKD (HR, 6.38; 95% CI, 1.28–31.72; $P = 0.024$) were risk factors for recurrent TE. Because recurrent renal events and CKD+AKD showed a significant (chi-square test, $P < 0.001$) correlation, multivariate analyses with each risk factor were performed separately. Results of the multivariate analysis showed that recurrent renal events (HR, 6.74; 95% CI, 1.25–36.44; $P = 0.027$) and CKD+AKD (HR, 5.41; 95% CI, 1.03–28.46; $P = 0.046$) were statistically significant risk factors for developing recurrent TE (Table 3).

According to univariate analysis, CKD+AKD (HR, 6.38; 95% CI, 1.28–31.72; $P = 0.008$) and recurrent TEs (HR, 7.73; 95% CI, 1.47–40.7; $P = 0.038$) were significant risk factors for OS. However, estimated GFR at diagnosis < 60 mL/min/1.73 m^2 (HR, 1.26; 95% CI. 0.14–11.68; $P = 0.838$), renal event (HR, 4.50; 95% CI, 0.51–39.99; $P = 0.177$), or TE (HR, 1.57; 95% C, 0.27–9.11; $P = 0.618$) was not a significant risk factor for OS. Multivariate logistic regression analysis demonstrated that only CKD+AKD (HR, 7.95; 95% CI, 1.24–51.15; $P = 0.029$) was independently associated with the risk of mortality (Table 4, Fig. 2b).

Correlations between changes of estimated GFR and LDH fold from baseline to onset of renal event

The Pearson correlation test was used to measure the degree of relationship between changes of estimated GFR and LDH fold from the baseline to the onset of the first renal event. Changes of LDH from the baseline to the onset of the first renal event were negatively correlated with changes of estimated GFR from baseline to onset of the first renal event (Pearson correlation coefficient $r = -0.58$, $P = 0.022$ in patients with one renal event and $r = -0.75$, $P = 0.0002$ in patients with renal events ≥ 2 times) (Fig. 3).

Discussion

Our study provides several valuable findings regarding renal dysfunction in PNH patients. Although the incidence of renal dysfunction at the time of diagnosis of PNH was known to be about 20%, about half of PNH patients experienced various types of renal events during the disease course in this study. Our results showed that both recurrent renal events and CKD+AKD were independent risk factors for recurrent TE events in PNH patients, and CKD+AKD was an independent risk factor for mortality. Therefore, renal function in PNH patients should be regularly monitored during the entire disease course and appropriate management should be considered for patients with renal dysfunction, especially for those with recurrent renal events.

Although previous retrospective studies for PNH patients included the prognostic role of renal dysfunction, these analyses focused on the baseline renal function [4, 10]. Among 14 patients with baseline renal dysfunction in the present study, 50% ($n = 7$) of patients experienced repeated renal events after the initial renal event and TE was developed in 5 (35.7%) patients. Therefore, it is important to assess renal function at

Table 3 Univariate and multivariate analysis of risk factors for recurrent TE

Variables	Univariate	Multivariate		
	P value	*P* value	HR	95% CI
Age ≥ 40 years	0.677			
Bone marrow disorder	0.428			
Granulocyte clone size at diagnosis ≥ 50%	0.350			
LDH fold at diagnosis ≥ 5 (× ULN)	0.666			
eGFR at diagnosis < 60 mL/min/1.73 m^2	0.060	0.153	3.33	0.64–17.35
Renal event	0.953			
Recurrent renal events ≥ 2 times	0.016	0.027	6.74	1.25–36.44
CKD+AKD	0.024	0.046	5.41	1.03–28.46

TE thromboembolism, *LDH* lactate dehydrogenase, *ULN* upper limit of normal, *eGFR* estimated glomerular filtration rate, *CKD* chronic kidney disease, *AKD* acute kidney disease, *HR* hazard ratio, *CI* confidence interval

the time of diagnosis of PNH. A baseline renal dysfunction should be considered a poor prognostic factor. Indeed, as PNH patients suffered from ongoing intravascular hemolysis, they were continuously at risk of subsequent renal events during the disease course. In this study, renal events were observed in 55 (54.5%) PNH patients during median follow-up duration of 94.2 months. The incidence of renal events observed in this study was comparable with 45% observed in the study from the Spanish PNH Registry [12]. Higher rates of renal events were observed in these two studies (Spanish PNH Registry and the current study) compared with those in previous retrospective studies focusing on baseline renal dysfunction, particularly regarding the occurrence of CKD stage 3–5 which was reported in 20.5% of patients in a previous retrospective study [10]. Therefore, it might be more important to evaluate the prognostic role of renal dysfunction during the disease course.

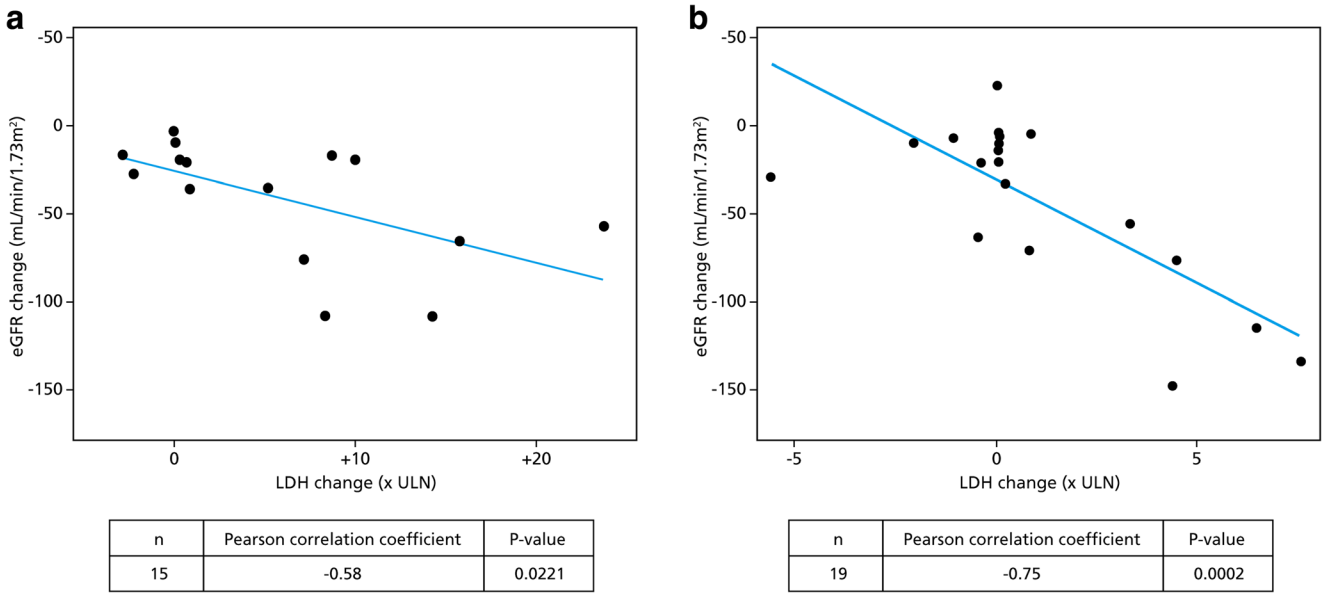
The median time to the first ARF and CRF episode from the Spanish Registry data was 6.5 years and 14.5 years, respectively [12]. The median time to the diagnosis of first renal event in this study was 6.6 years after the diagnosis of PNH. Therefore, the prognostic role of renal event during the disease course should be evaluated in PNH patients with long-term follow-up. The median follow-up duration was 7.7 years in this study. Moreover, we excluded two patients who had a history of renal dysfunction related to immunosuppressive therapy such as cyclosporine in this study. In addition, we analyzed the data until starting eculizumab for patients who were receiving treatment with eculizumab. Therefore, our cohort would be an appropriate population to analyze the prognostic role of PNH-related renal dysfunction during the disease course.

According to a previous retrospective study from the Korean National PNH Registry, elevated hemolysis (LDH ≥ 1.5 × ULN) at diagnosis was suggested as an associated risk factor for TE. Combinations of LDH ≥ 1.5 × ULN with clinical symptoms such as abdominal pain, chest pain, dyspnea, and hemoglobinuria were associated with greater risk for TE

Table 4 Univariate and multivariate analysis of risk factors for mortality

Variables	Univariate	Multivariate		
	P value	*P* value	HR	95% CI
Age ≥ 40 years	0.084			
Bone marrow disorder	0.957			
Granulocyte clone size at diagnosis ≥ 50%	0.948			
LDH fold at diagnosis ≥ 5 (× ULN)	0.855			
eGFR at diagnosis < 60 mL/min/1.73 m^2	0.838			
Renal event	0.177			
Recurrent renal events ≥ 2 times	0.080			
CKD+AKD	0.008	0.029	7.95	1.24–51.15
TE	0.618			
Recurrent TE	0.038	0.196	4.02	0.49–33.01

LDH lactate dehydrogenase, *ULN* upper limit of normal, *eGFR* estimated glomerular filtration rate, *CKD* chronic kidney disease, *AKD* acute kidney disease, *TE* thromboembolism, *HR* hazard ratio, *CI* confidence interval



n	Pearson correlation coefficient	P-value
15	-0.58	0.0221

n	Pearson correlation coefficient	P-value
19	-0.75	0.0002

Fig. 3 Correlations between changes of estimated GFR (eGFR) and LDH fold from the baseline to the onset of the first renal event in patients with 1 renal event (**a**) and in patients with renal events ≥ 2 (**b**)

than LDH ≥ 1.5 × ULN or clinical symptoms alone [4]. However, the criterion of LDH ≥ 1.5 × ULN at diagnosis is insufficient to predict the risk of TE in classic PNH patients because most classic PNH patients with hemolytic features are usually accompanied by serum LDH ≥ 1.5 × ULN at diagnosis. In addition, symptoms related to PNH would be subjective, not objective. Therefore, it is necessary to explore more objective clinical parameters for predicting TE in PNH patients. Although we did not find appropriate risk factors for TE in this study, we were able to find risk factors for recurrent TE in this study. Recurrent renal events during disease course and CKD+AKD were statistical significant risk factors for developing recurrent TE. Therefore, it is essential for physicians to recognize newly developing renal event during the disease course and decide appropriate treatment for PNH patients.

The Korean National PNH Registry data suggested factors associated with increased mortality in PNH patients. PNH patients with TE, renal impairment, or PNH-cytopenia have higher mortality rate compared with age- and sex-matched general population [5]. Although that study reported that 16.9% of patients had renal impairment defined as a history of ARF or CKD stage ≥ 3 (estimated GFR < 60 mL/min/1.73 m^2) at the baseline, renal dysfunction was not evaluated longitudinally during the entire disease course. Therefore, clinical implication of both baseline renal dysfunction and subsequent renal dysfunction should be re-validated. Although patients with recurrent renal events showed a trend toward inferior OS compared with those with renal event ≤ 1 time, the OS rate of patients with CKD+AKD was significantly inferior compared with that of the rest of the patients in this study (75.0% vs. 95.8% at 10 years, $P = 0.011$). Therefore, the important risk factor affecting OS would not be a baseline renal dysfunction at diagnosis, but recurrent renal events, especially in those with CKD+AKD during the clinical course.

Eculizumab is a humanized monoclonal antibody that inhibits terminal complement cascade. It can significantly reduce intravascular hemolysis and thrombotic events [13, 14]. Eculizumab treatment can improve intravascular environments of PNH patients such as increased cell-free plasma hemoglobin and NO depletion. LDH level is rapidly and consistently reduced following the initiation of eculizumab therapy [14, 15]. In this study, we demonstrated that changes of LDH from baseline to the onset of the first renal event were negatively correlated with changes of the estimated GFR (Fig. 3). These findings suggest that increased intravascular hemolysis (higher level of LDH) compared with that at the baseline was closely associated with renal dysfunction (markedly decreased estimated GFR). In other words, correlations between increased renal dysfunction in patients with PNH and increased intravascular hemolysis were clearly observed in this study. Improvement in renal function with eculizumab was more commonly seen in patients with baseline CKD stages 1–2, although such improvement was also observed in patients with CKD stages 3–4 [10, 16, 17]. Therefore, eculizumab therapy must be initiated as soon as possible in PNH patients with renal dysfunction during follow-up period. Monitoring of renal function is essential not only for identifying high-risk patients, but also for making an appropriate decision for PNH management.

In this study, we defined renal dysfunction according to the criteria of KDIGO. Therefore, we were unable to evaluate early event of damaged renal proximal tubular cells

such as proteinuria in this study. In addition, we enrolled patients who had a history of diabetes or hypertension, although two patients with a history of renal dysfunction related to immunosuppressive therapy were excluded. We could not exactly analyze the impact of concurrent diabetes or hypertension on renal dysfunction in this study due to very small number of patients with a history of diabetes or hypertension and no available data for renal biopsy. Among the nine CKD patients who had history of diabetes and/or hypertension, six patients experienced additional AKD events during the disease course. Therefore, the impact of diabetes or hypertension on renal dysfunction in this study might be considered minimal. Nevertheless, our results are sufficient to emphasize the prognostic role of renal dysfunction, especially recurrent renal events, because we analyzed longitudinal renal events during the disease course in PNH patients with sufficient long-term follow-up period.

In conclusion, our results showed that renal function in PNH patients should be regularly monitored during the entire disease period because subsequent renal events after the diagnosis of PNH could frequently develop. Eculizumab therapy should be considered in PNH patients with renal dysfunction during the disease course. Moreover, PNH patients who experienced repeated renal events, especially CKD+AKD, should be treated with eculizumab as soon as possible.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical compliance All the authors stated that the study have been approved by the appropriate institutional review board and have been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Since this is a retrospective study, formal informed consent is not required.

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