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Editorial

Original Article

Review Article

Case Report

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Editorial

Should All Patients with Nephrotic Syndrome Undergo a Renal Biopsy?

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Nephrotic syndrome (NS) is defined by proteinuria exceeding 3.5 g per 24 hours, hypoalbuminemia, hyperlipidemia, and peripheral edema. Rather than being a distinct disease, NS is a clinical manifestation of underlying renal disease.[1] NS has the potential to cause serious complications, both related to the disease itself and due to the therapy given. Therefore, the NS diagnosis must be accurate to provide more targeted therapy decisions.

In the diagnostic process, renal biopsy serves as an essential component. Standard evaluation of biopsy specimens consists of light microscopy (LM), immunofluorescence (IF), and electron microscopy (EM). At the same time, standard staining includes hematoxylin and eosin (H&E), periodic acid-Schiff (PAS), Masson's trichrome, Jones-methenamine silver, and Congo red staining if amyloidosis is suspected. However, these standard examinations are still challenging to provide optimally in many centers. Fortunately, recent advancements, particularly in the evolution of new antibodies (e.g., PLA2R-ab and Nephrin-Ab), have introduced new opportunities for non-invasive NS diagnostics with promising potential for current and future applications.

The following presents some of the causes of NS and the extent to which a renal biopsy is needed to confirm the underlying disease.

- **Minimal Change Disease (MCD).** MCD accounts for about 10% of NS cases in adults and is primarily idiopathic. The pathological features of MCD are loss of foot processes on EM but normal on LM and no complement or immunoglobulin (Ig) deposits on IF. It is suspected that a systemic process causes the production of glomerular permeability factors, such as autoantibodies, to nephrin. However, MCD has also been linked to secondary factors, including malignancies, infections, and drug use.[1,2]
- **Diagnosis**. Renal biopsy is necessary for diagnosing MCD in adults, as no specific laboratory test is capable of distinguishing MCD from other forms of NS. Following the diagnosis of MCD, the next step is to assess potential secondary causes.[2]

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- **Focal Segmental Glomerulosclerosis (FSGS).** FSGS is a pattern of kidney damage primarily affecting podocytes, which in LM is indicated by sclerosis observed in parts (segmental) of some glomeruli (focal). Depending on the underlying cause, FSGS can be classified into primary, secondary, and genetic forms.[1] The pathogenesis of primary FSGS likely involves circulating factors that cause podocyte dysfunction, typically leading to effacement of the foot processes.
- **Diagnosis.** Renal biopsy is essential for identifying FSGS lesions. Since FSGS represents a histologic pattern rather than a distinct disease, detecting these lesions should prompt an evaluation of the underlying cause. Differentiating primary from secondary FSGS requires assessing the absence or presence of NS, the degree of podocyte foot process effacement (usually diffuse in primary FSGS and segmental in secondary FSGS), and risk factors associated with secondary FSGS. However, these clinical and pathologic characteristics do not suffice for identifying a genetic cause of FSGS. Consequently, genetic testing is advisable in patients whose diagnosis remains unclear after clinicpathologic assessment.[1]

- **IgA nephropathy (IgAN).** IgAN is the most prevalent form of primary glomerulonephritis worldwide but rarely presents with NS. Renal biopsies in some IgAN patients with NS showed inconsistent findings, including mesangial IgA deposition and mild histologic lesions. However, EM showed extensive effacement of the foot processes, similar to that observed in MCD, thus defining it as MCD-IgAN.[3]
- **Diagnosis.** The diagnosis of IgAN can only be confirmed through renal biopsy, with the detection of IgA deposits on IF. This is because, to date, no specific laboratory findings are available to diagnose IgAN. However, renal biopsy also depends on the clinical presentation, which may not be necessary for every patient suspected of having IgAN. In cases of isolated hematuria without proteinuria and impaired renal function, biopsy is typically not performed, as it would not change therapy. However, indications for renal biopsy vary geographically.[1]

- **Lupus Nephritis (LN).** Membranous LN (class V LN) occurs in more than 20% of patients with LN and may coexist with class III or IV LN.[4] There are two mechanisms underlying membranous LN. First, through the formation of auto-antibodies against nuclear antigens and antibodies against C1q, Sm, Ro, chromatin, ribosomes, and others;[1] cationic antigens can penetrate the anionic glomerular base-ment membrane (GBM) and deposit in the subepithelial space, leading to antibody binding and in situ immune complex formation. Second, through the formation of circulating antibodies against podocyte-specific antigens, such as the exostosin 1/ exostosin 2 (EXT1/2) complex and neural cell adhesion molecule 1 (NCAM).[5,6] Both mechanisms can activate local complement; however, the GBM separates chemoattractants from the blood, and immune cell recruitment is minimal. Therefore, injury is confined to podocytes, leading to proteinuria without renal dysfunction in most cases.[1]
- **Diagnosis:** Standard diagnosis requires biopsy. Pure class V LN is characterized by thickening the glomerular capillary wall in LM and subepithelial immune deposits similar to MN in EM. However, typical of class V LN not found in MN are IgA, IgM, IgG, C3, and C1q along more than half of the glomerular capillary loop in IF.[1]

- **Membranoproliferative glomerulonephritis (MPGN).** Subendothelial immune complex deposits characterize MPGN and typically manifest as a combination of nephrotic/nephritic

syndrome and decreased complement C3.[7] The hallmarks of glomerular injury on renal biopsy include (a) thickening or double contour of the GBM on silver staining and (b) endo-capillary and mesangial hypercellularity.[1]

- **Diagnosis.** Renal biopsy is crucial for diagnosing MPGN. The classification falls into immune complex-mediated MPGN (I-MPGN), complement-mediated MPGN (C-MPGN), and without Ig or complement deposition[8] based on IF microscopy findings. C-MPGN is now referred to as C3 glomerulopathy (C3G), which includes two major subtypes—C3 glomerulonephritis (C3GN) and dense deposit disease (DDD)—according to the different patterns of C3 deposition in EM.[9]

- **Membranous nephropathy (MN**). MN is the leading cause of primary NS in adults. The characteristic injury pattern on renal biopsy includes thickening of the GBM and subepithelial Ig deposits with or without minimal cellular proliferation or infiltration. Clinical signs of NS develop slowly as the accumulation of immune complex deposits occurs gradually, often making it challenging to identify its onset. Proteinuria in MN can vary, ranging from subnephrotic to severely nephrotic. Renal function is generally preserved; most patients maintain normal blood pressure.[1]
- **Diagnosis.** Currently, MN is the only possible cause of NS immune-mediated based without renal biopsy. Although many autoantibodies have been identified for diagnosing MN[1], to date, only PLA2R-ab has been shown to help diagnose primary MN. Renal biopsy is unnecessary if anti-PLA2R-ab serology is positive, there is no indication of secondary causes, and renal function remains normal.[10] A biopsy is only indicated if anti-PLA2R-ab is negative, there is impaired renal function, and there is evidence of secondary causes. If the findings are consistent with MN, the biopsy specimen should also be examined for PLA2R staining. Anti-PLA2R-ab levels can also monitor response to therapy.[10] If anti-PLAR2 titers are undetectable, immunosuppressive therapy can be discontinued, and if increasing titers are found, therapy modification is necessary.[1]

Based on the brief description above, it can be concluded that every patient with NS should always undergo a kidney biopsy and standard microscopic examination and staining. Only NS due to MN can be diagnosed without renal biopsy, with positive anti-PLA2R antibodies, provided that renal function is normal and there is no evidence of secondary causes. However, the current evidence is still limited to patients with positive anti-PLA2R antibodies and is unclear for patients with positive THSD7A.

Declarations

Competing interest

The author declares no conflict of interest.

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Original Article

The Determinants of Detrimental Changes in Pulse Pressure During Maintenance Hemodialysis Treatments

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ABSTRACT

Background: Studies indicate that large fluctuations in pulse pressure during hemodialysis are associated with cardiovascular events, cardiovascular mortality, and all-cause mortality.

Objective: We investigated the determinants of detrimental changes in pulse pressure (ΔPP) during hemodialysis.

Methods: This prospective, observational cohort study was conducted from 1 to 30 April 2023 at Dr. Sardjito Hospital Yogyakarta, involving maintenance hemodialysis patients for ≥ 6 months. Patients were categorized into group 1 (detrimental ΔPP, ΔPP >5 mmHg or <−25 mmHg) and group 2 (stable ΔPP, −25 to 5 mmHg). Mann-Whitney, independent-t, chi-square, Fisher exact tests, and logistic regression were applied to evaluate associations between ΔPP groups and clinical variables.

Results: This study involved 136 patients, 75 males (55.1%) with a mean age of 52 (18-87). The most common comorbid was hypertension, present in 85 patients (62.5%). The mean hemodialysis vintage of patients was 47.2 (6.5-330.7) months. We found significant difference between group in post-dialysis systolic blood pressure (SBP) (p=0.003), pre-dialysis diastolic blood pressure (DBP) (p=0.015), post-dialysis DBP (p=0.007), ultrafiltration (p=0.041), pre-dialysis mean-arterial-pressure (MAP) (p=0.013), post-dialysis MAP (p=0.002), and alpha-blocker treatment (p=0.037). Multivariate logistic regression analysis shows a significant association between groups of ΔPP with pre-dialysis DBP (p=0.035; OR=1.153; OR=$Exp^{(10x\mathcal{B})}$ =4.137) and post-dialysis SBP (p=0.007; OR=1.052; OR=$Exp^{(10x\mathcal{B})}$ =1.6487).

Conclusion: Our study demonstrates that group 1, with detrimental changes in pulse pressure during hemodialysis, was found to have higher post-dialysis DBP, pre-dialysis DBP, post-dialysis SBP, pre-dialysis MAP, post-dialysis MAP, alpha-blocker treatment, and ultrafiltration, with significant association with post-dialysis SBP and pre-dialysis DBP.

Keywords: Chronic Kidney Disease, Maintenance Hemodialysis, Detrimental Changes, **Δ** Pulse Pressure**.**

Introduction

In Indonesia, hemodialysis is the most commonly used modality for renal replacement therapy. While essential, hemodialysis may lead to complications arising from changes in blood pressure during the procedure, including intra-dialytic hypotension and intra-dialytic hyper-tension, both of which may negatively impact

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patient outcomes. However, the extent to which blood pressure changes during hemodialysis affect or predict survival remains poorly understood.

Cardiovascular disease is a prevalent complication and the leading cause of mortality among patients with end-stage renal disease undergoing maintenance hemodialysis.[1] These patients frequently exhibit vascular changes, such as arteriosclerosis and atherosclerosis, contributing to increased pulse pressure.[2,3]

Pulse pressure, a recognized prognostic marker of vascular stiffness, is calculated by subtracting diastolic blood pressure (DBP) from systolic blood pressure (SBP).[4] Several key factors influence pulse pressure, including arterial wall compliance, stroke volume, vascular resistance, and patient-specific variables such as age, heart rate, height, underlying disease, endurance aerobic exercise, hormone replacement therapy, salt intake, and anti-hypertensive drugs.

Increased pulse pressure (PP) serves as an independent predictor of cardiovascular events, cardiovascular mortality, and all-cause mortality in both the general population and subgroups such as elderly individuals and those with hypertension.[5,6] Changes in pulse pressure are associated with factors including age, duration of hemodialysis, sex, blood flow rate, ultrafiltration, diabetes mellitus, inflammation, and albumin levels in patients undergoing maintenance hemodialysis.[7]

Compared to age-matched controls with normal renal function, patients on maintenance hemodialysis exhibit higher pulse pressure values, irrespective of mean arterial blood pressure (MAP).[7] Increased pulse pressure and arterial stiffness are associated with higher risks of cardiovascular events, cardiovascular mortality, and all-cause mortality in these patients.[8,9]

Hypervolemia may significantly contribute to changes in pulse pressure (ΔPP) in maintenance hemodialysis patients.[10] Volume overload has been linked to left ventricular hypertrophy and increased mortality.[11–13] Research suggests that decreased pulse pressure during hemodialysis is linked to a lower risk of hospitalization and mortality.[14] Regression models have limited these previous observations, assuming a linear relationship between pulse pressure changes and mortality. As a result, these models may be underpowered to detect a U-shaped association of high mortality with increases or decreases in pulse pressure.[14]

Some studies indicate that significant declines or increases in SBP during hemodialysis are linked to higher rates of cardiovascular events, cardiovascular mortality, and all-cause mortality.[15] Conversely, moderate pulse pressure reductions following hemodialysis are linked to improved survival outcomes. Large declines (>25 mmHg) or increases (>5 mmHg) in pulse pressure have been associated with higher mortality risks.[16] Moreover, increased pre- and post-dialysis pulse pressure have been identified as important predictors of all-cause mortality in hemodialysis patients.[9,17]

Despite various factors influencing pulse pressure changes in maintenance hemodialysis patients, the primary determinants of adverse pulse pressure changes in maintenance hemodialysis patients remain unclear. Therefore, this study aims to identify the factors contributing to detrimental changes in pulse pressure (ΔPP) during hemodialysis to identify the optimal blood pressure management strategies for these patients.

Methods

Design and participants

This prospective cohort study utilized data from patients 18 and older undergoing routine hemodialysis for more than 6 months at the Dr. Sardjito General Hospital hemodialysis center between April 1 and April 30, 2023. A total of 159 patients undergoing routine hemodialysis at Dr. Sardjito Hospital were considered for inclusion. Patient selection methods are illustrated in Figure 1 as a flowchart. After applying the exclusion criteria, the final sample comprised 136 patients.

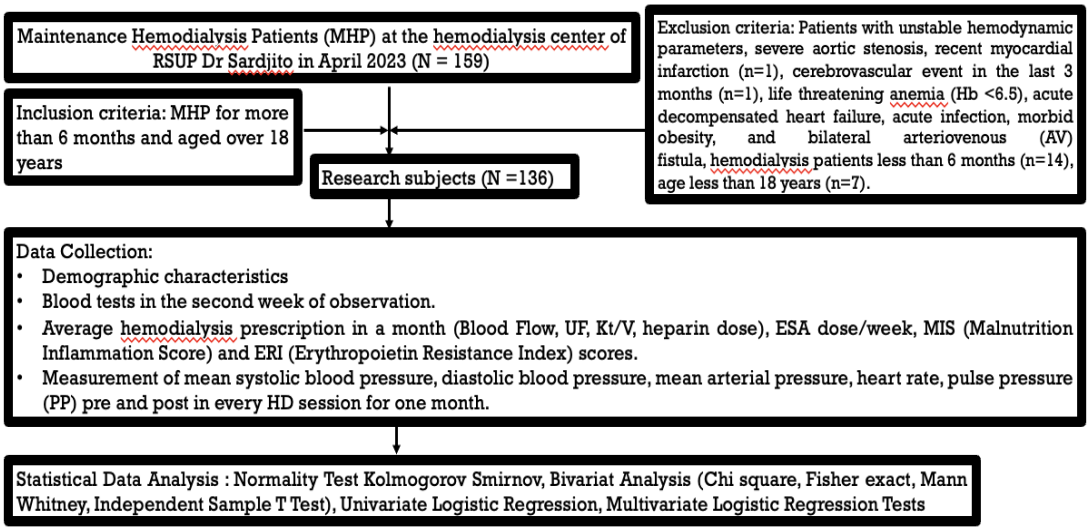

Figure 1. A flowchart of patient selection in our study

Demographic characteristics, including age, gender, duration of hemodialysis, body weight, height, body mass index (BMI), smoking status, causes of end-stage renal disease, routine blood tests, blood chemistry, average hemodialysis prescription over a month (blood flow, ultrafiltration volume, Kt/V, heparin dose), erythropoietin stimulating agents (ESA) dose/week, Malnutrition Inflammation Score (MIS), Erythropoietin Resistance Index (ERI) scores and measurement of mean systolic blood pressure, diastolic blood pressure, mean arterial pressure, heart rate, pulse pressure pre and post in every hemodialysis (HD) session for one month were recorded. All patients underwent an assessment of their hemodialysis records on April 1, 2023. The dialysis prescription lasts 3.5 to 5 hours, with blood flow rates between 120–300 ml/min, using standard bicarbonate dialysis concentrate (Sol-Cart® B-B.Braun) and polyethersulfone hemodialysis filter high permeability (Model SHM-DLPES-P1.6HF®–HOSPITECH®) with an effective surface area of 1.6 m2 and an ultrafiltration rate of 71 ml/h/mmHg. The erythropoiesis stimulant agents administered included Epoetin Alfa (Hemapo®–Kalbe Farma®) and Epoetin Beta (Recormon®-Roche®).

Study Covariates

The primary outcome of this study was to identify factors associated with detrimental changes in pulse pressure during hemodialysis. Detrimental changes in pulse pressure during hemodialysis are defined as significant declines (>–25 mmHg) or increases (>5 mmHg) in pulse pressure, both of which have been associated with higher cardiovascular and all-cause mortality.[16]

The inclusion criteria for this study were all patients aged 18 years and older who had been undergoing routine hemodialysis for more than 6 months at the hemodialysis center of Dr. Sardjito Hospital from April 1 to April 30, 2023. The exclusion criteria included patients with unstable hemodynamic parameters, severe aortic stenosis, recent myocardial infarction, cerebrovascular events in the past 3 months, life-threatening anemia (Hb <6.5), acute decompensated heart failure, acute infection, morbid obesity, bilateral arteriovenous (AV) fistula, those undergoing hemodialysis for less than 6 months, and those under 18 years of age.

The factors analyzed in this study included various demographic characteristics, blood tests, malnutrition status (assessed using the Malnutrition Inflammation Score (MIS) and body mass index (BMI)), iron deficiency

(evaluated based on transferrin saturation, blood iron levels/serum iron (SI) and total iron binding capacity (TIBC), Erythropoietin Resistance Index (ERI) score, dialysis prescription (include data of Kt/V values, blood flow, ultrafiltration volume and duration of hemodialysis) as well as hyper-parathyroid conditions (assessed by a simple examination of calcium levels and serum phosphorus levels) and measurement of mean systolic blood pressure, diastolic blood pressure, mean arterial pressure, heart rate, pulse pressure (PP) pre and post in every HD session for one month period.

Statistical analysis

Data processing was conducted using the SPSS 26.0 software package. Descriptive statistical methods measure central tendencies (mean, median) and summarize the numerical characteristics of the observed research variables. The results of data analysis were considered statistically significant if the p-value <0.05. The normality of data variables was analyzed using the Kolmogorov-Smirnov test. Continuous variables were summarized as mean±standard deviation (normal variables) or median and quartiles (non-normal variables). Categorical variables were presented as percentages.

Bivariate analyses, including Chi-square, Fisher exact, Mann-Whitney, and Independent Sample T-Test were used to determine the correlation significance between various independent factors and detrimental blood pressure changes during hemodialysis. The strength of the relationship between the independent factors and detrimental blood pressure changes during hemodialysis treatment was analyzed using univariate logistic regression, followed by multivariate logistic regression analysis to adjust for potential confounders.

Results

Table 1 presents the basic characteristics of the study sample. Of the 136 patients, 75 (55.1%) were male, and the mean age was 52 years (range 18-87). Hypertension was the most prevalent comorbidity, affecting 85 patients (62.5%). The mean hemodialysis vintage was 47.2 months (6.5-330.7).

Table 1. Baseline characteristic

		Mean ± SD or Median (min-max)	n	%
Age (years)		52 (18-87)		
Gender	Male		75	55.1
	Female		61	44.9
Dialysis Vintage (Months)		47.2 (6.5-330.7)		
DM	Yes		29	21.3
	No		107	78.7
Hypertension	Yes		85	62.5
	No		51	37.5
Obstructive uropathy (stone/stricture urethra/prostate)	Yes		8	5.9
	No		128	94.1
GNC	Yes		11	8.1
	No		125	91.9
Others/unknown	Yes		2	1.5
	No		134	98.5

Weight (kg)	60.53 ± 13.82
Height (cm)	160 (136-184)
BMI	23.3 (14.8-35.1)
Albumin (mg/dl)	4 (2.3-4.9)
EPO dose/weeks	6000 (4000-8000)
SI	52.5 (19-179)
TIBC	195 (97-382)
Transferrin Saturation	28.8 (8.8-99.4)
Hb	9.5 (6.5-13,1)
AL	6 (2.2-12.9)
AT	200 (63-442)
Albumin (mg/dl)	4 (2.3-4.9)
Calcium (mg/dl)	8.9 (2.6-13)
Corrected calcium (calculator)	8.9 (2.5-13.4)
Phosphorus (mg/dl)	4.16 ± 1.58
Corrected calcium x phosphorus (mg/dl)	37.11 ± 14.49

Malignancy	Yes	3	2.2
	No	133	97.8
Steroid	Yes	2	1.5
	No	134	98.5
Smoker	Yes	1	0.7
	No	135	99.3
Infection	Yes	0	0.0
	No	136	100.0
Transfusion	Yes	2	1.5
	No	134	98.5
Hepatitis B	Yes	4	2.9
	No	132	97.1
Hepatitis C	Yes	0	0.0
	No	136	100.0
HIV	Yes	1	0.7
	No	135	99.3
History of hemorrhage within 3 months	Yes	7	5.1
	No	129	94.9
ARB	Yes	98	72.1
	No	38	27.9
CCB	Yes	98	72.1
	No	38	27.9
Beta Blocker	Yes	27	19.9
	No	109	80.1
Statin	Yes	7	5.1
	No	129	94.9
Alpha Blocker	Yes	21	15.4

	No	115	84.6
Calcium Carbonate	Yes	89	65.4
	No	47	34.6
Amount of Anti-Hypertensive Drug Usage	0	30	22.1
	1	10	7.4
	2	63	46.3
	3	25	18.4
	4	8	5.9

Table 2. Factors that influenced detrimental changes during hemodialysis treatment

	Delta Pulse Pressure Category						
	-24.99-4.99			≤-25 or ≥5			P
	Median	Min	Max	Median	Min	Max	
Age (year)	52.5	18	87	48	18	76	0,299*
Dialysis Vintage (months)	47.40	6.5	330.75	46.65	6.60	205.75	0,553*
Height (cm)	159.5	136	184	162	146	176	0,331*
BMI	24.12	14.86	35.11	22.49	16.38	32.89	0,518*
Albumin (mg/dl)	3.99	2.27	4.86	4.05	3.27	4.68	0,889*
EPO dose/week	6000	4000	8000	6000	4000	6000	0,739*
SI	53	27	179	52	19	135	0,724*
TIBC	194.5	97	329	196	126	382	0,640*
Transferrin Saturation	28.70	12.79	99.38	29.73	8.79	73.14	0.962*
Blood Flow	225	130	300	230	150	300	0,053*
Hb	9.45	6.50	12.40	9.55	6.50	13.1	0,752*
AL	5.95	2.20	7.1	6	3.60	12.90	0,900*
AT	202.5	63	442	196	94	442	0,662*
Albumin (mg/dl)	3.99	2.27	4.86	4.05	3.27	4.68	0,889*
Calcium (mg/dl)	8.94	2.60	13	8.78	6.92	12.64	0,392*
Post-dialysis Diastolic Blood Pressure (DBP)	84.12	61	113	87.85	62.25	124.88	0,041*
Pre dialysis Pulse pressure	64.72	33.12	116.89	67.74	30.5	100.5	0,539*
Time of Dialysis (hours)	4.5	3	5	4.5	3	5	0,510*
Ultrafiltration Volume (ml)	3000	300	5000	3500	300	5000	0,046*
ERI SCORE	10.30	5.60	28.74	10.70	4.39	17.26	0,727*
MIS SCORE	4	1	19	5	1	16	0,320*

Cont.

	Delta Pulse Pressure Category				
	-24.99-4.99		≤-25 or ≥5		P
	Mean	SD	Mean	SD	
Body Weight (kg)	60.58	14.78	60.43	11.70	0,954**
KT/V	1.75	.31	1.73	.34	0,795**
Phosphorus (mg/dl)	4.29	1.53	3.88	1.65	0,151**
Corrected calcium x phosphorus (mg/dl)	38.35	14.27	34.53	14.75	0,151**
Pre-Dialysis Systolic Blood Pressure (SBP)	142.92	19.45	149.52	20.56	0,071**
Post Dialysis SBP	143.76	21.75	159.48	35.23	0,002**
Pre-dialysis Heart rate	79.55	11.44	79.92	11.76	0,864**
Post-dialysis Heart rate	77.11	11.23	79.86	12.26	0,197**
Mean of peridialytic heart rate	78.33	10.65	79.89	11.18	0,434**
Pre-dialysis Diastolic Blood Pressure (DBP)	75.50	12.73	81.67	14.33	0,012**
Post-dialysis pulse pressure	59.28	17.60	67.97	23.03	0,016**
Pre-dialysis MAP	97.86	12.91	104.29	14.80	0,011**
Post-dialysis MAP	104.27	12.99	114.15	22.23	0,001**
Hb	9.30	1.46	9.37	1.57	0,795**

*Independent T-test

		Delta Pulse Pressure Category				
		-24.99-4.99		≤-25 or ≥5		P
		N	%	N	%	
Gender	Male	48	64.0	27	36.0	0,313#
	Female	44	72.1	17	27.9	
Others/unknown	Yes	2	100.0	0	0.0	1,000$
	No	90	67.2	44	32.8	
DM	Yes	21	72.4	8	27.6	0,536#
	No	71	66.4	36	33.6	
Hypertension	Yes	54	63.5	31	36.5	0,185#
	No	38	74.5	13	25.5	
Obstructive uropathy (stone/stricture urethra/prostate)	Yes	7	87.5	1	12.5	0,437$
	No	85	66.4	43	33.6	
Glomerulonephritis Chronic	Yes	8	72.7	3	27.3	1,000$
	No	84	67.2	41	32.8	
Vascular dialysis access	AV shunt	85	68.0	40	32.0	0,747$
	Others	7	63.6	4	36.4	
Heparin	Continue	80	65.6	42	34.4	0,217#
	Mini	7	77.8	2	22.2	
	Free	5	100.0	0	0.0%	

Ferrous Sulfate Injection	Yes	10	58.8	7	41.2	0,406#
	No	82	68.9	37	31.1	
Malignancy	Yes	3	100.0	0	0.0	0,551$
	No	89	66.9	44	33.1	
Steroid	Yes	1	50.0	1	50.0	0,544$
	No	91	67.9	43	32.1	
Smoker	Yes	1	100.0	0	0.0	1,000$
	No	91	67.4	44	32.6	
Infection	Yes	0	0.0	0	0.0	-
	No	92	67.6	44	32.4	
Transfusion	Yes	1	50.0	1	50.0	0,544$
	No	91	67.9	43	32.1	
Hepatitis B	Yes	3	75.0	1	25.0	1,000$
	No	89	67.4	43	32.6	
Hepatitis C	Yes	0	0.0	0	0.0	-
	No	92	67.6	44	32.4	
HIV	Yes	1	100.0	0	0.0	1,000$
	No	91	67.4	44	32.6	
Bleeding History	Yes	6	85.7	1	14.3	0,428$
In 3 months	No	86	66.7	43	33.3	
ARB	Yes	62	63.3	36	36.7	0,079#
	No	30	78.9	8	21.1	
CCB	Yes	64	65.3	34	34.7	0,349#
	No	28	73.7	10	26.3	
Beta Blocker	Yes	20	74.1	7	25.9	0,425#
	No	72	66.1	37	33.9	
Statin	Yes	7	100.0	0	0.0	0,096$
	No	85	65.9	44	34.1	
Alpha-blocker	Yes	10	47.6	11	52.4	0,033#
	No	82	71.3	33	28.7	
Calcium carbonate	Yes	60	67.4	29	32.6	0,937#
	No	32	68.1	15	31.9	
Amount of antihypertensive	0	24	80.0	6	20.0	0,581#
drug treatment usage	1	7	70.0	3	30.0	
	2	40	63.5	23	36.5	
	3	16	64.0	9	36.0	
	4	5	62.5	3	37.5	
Corrected ca x phosphorus	<=55	82	66.7	41	33.3	0,547$
	>55	10	76.9	3	23.1	

Notes:
*Mann Whitney test, **Independent T test, # Chi-Square test, $ Fisher exact test.

Bivariate analysis revealed significant mean differences between study groups, with the ultrafiltration volume, pre-hemodialysis diastolic blood pressure, post-hemodialysis systolic blood pressure, post-hemodialysis diastolic blood pressure, pre, and post-hemodialysis mean arterial pressure, post-hemodialysis pulse pressure and the use of alpha-blockers were found higher in the group 1 with detrimental pulse pressure changes ($\Delta PP = \leq -25$ or ≥ 5) ($p < 0.05$).

Table 3. Factors that influenced detrimental changes during hemodialysis treatment

	P	OR	CI 95%
Ultrafiltration Volume	0,041	1,00	1,00-1,01
Post-dialysis SBP	0,003	1,02	1,01-1,04
Pre-dialysis DBP	0,015	1,04	1,01-1,06
Post-dialysis DBP	0,007	1,04	1,01-1,07
Pre-dialysis MAP	0,013	1,04	1,01-1,06
Post-dialysis MAP	0,002	1,04	1,01-1,06
Alpha-blocker	0,037	2,73	1,06-7,05

Notes: The analysis method uses univariate logistic regression

Univariate logistic regression analysis indicated that the incidence of detrimental PP changes was positively influenced by ultrafiltration volume, pre-HD diastolic blood pressure, post-HD systolic blood pressure, post-HD diastolic blood pressure, pre-HD MAP, post-HD MAP, and the use of alpha-blockers.

Table 4. Factors that influenced detrimental changes during hemodialysis treatment

					95% C.I.	
	B	P	OR	$Exp^{(\triangle \mathcal{B})}$	Lower	Upper
Ultrafiltration Volume	0.000	.033*	1.000	1	1.000	1.001
Post-dialysis SBP	0.050	.007	1.052	△=10 mmHg =(1.6487)	1.014	1.091
Pre-dialysis DBP	0.142	.035*	1.153	△=10 mmHg =(4.137)	1.010	1.316
Post-dialysis DBP	-0.067	.113	.935		.861	1.016
Pre-dialysis MAP	-0.119	.051	.887		.787	1.000
Alpha-blocker	0.553	.360	1.739		.532	5.687
Constant	-2.960	.111	.052			

Notes: The analysis method uses multivariate logistic regression

Multivariate logistic regression analysis revealed ultrafiltration volume was not associated with detrimental pulse pressure changes (p = 0.33; OR = 1). However, higher pre-HD diastolic blood pressure (OR = 1.153; p = 0.035; OR = $Exp^{(10x\mathcal{B})}$ = 4.137) increased the odds of detrimental pulse pressure changes by 1.153 times for every 10 mmHg increase. Higher post-HD systolic blood pressure (OR = 1.052; p = 0.007; OR = $Exp^{(10x\mathcal{B})}$ = 1.6487) increased the likelihood of detrimental changes by 1.052 times for every 10 mmHg increase.

Discussion

In this cohort of 136 maintenance hemodialysis patients, we observed that those with detrimental pulse pressure changes during hemodialysis exhibited higher post-dialysis DBP, pre-dialysis MAP, post-dialysis MAP, alpha-blocker treatment, and ultrafiltration volume. These patients also showed significant association with post-dialysis SBP and pre-dialysis DBP.

This study found that pre-HD diastolic blood pressure has a significant association with detrimental pulse pressure change during hemodialysis (p=0.035; OR=1.153; 95% C.I (1.010-1.316)) with OR 4.137 for every 10 mmHg increase. This finding is consistent with that of Hara M. et al., who demonstrated that higher pre-HD diastolic blood pressure increases the risk of cardiovascular disease and all-cause mortality in hemodialysis patients in Japan.[18]

Both increases and decreases in post-HD systolic blood pressure exceeding 5 mmHg were associated with the highest risk of cardio-

vascular events and all-cause mortality compared to patients with stable post-dialysis BP changes (within -5 to 5 mmHg).[19] Furthermore, an increase in post-dialysis systolic blood pressure is associated with subclinical volume overload.[19] In our study, post-HD systolic blood pressure also showed a significant association with detrimental pulse pressure changes during hemodialysis (p=0.07; OR=1.052; 95% C.I 1.014-1.091) with an OR of 1.6487 for every 10 mmH increase.

A study by Lertdumrongluk found that ultrafiltration volume per session and spKt/V were negatively correlated with delta pulse pressure changes (ΔPP).[16] In contrast, our study found no significant association between ultrafiltration volume (p=0.033; OR=1) and detrimental pulse pressure changes during hemodialysis. However, patients with detrimental pulse pressure changes post-hemodialysis underwent greater fluid removal during treatment (3500 cc vs 3000 cc).

Therefore, these findings suggest that appropriate therapeutic strategies could help mitigate the long-term complications associated with excessive pulse pressure changes during hemodialysis treatment. Such strategies may include:

1. Adjusting ultrafiltration volume by optimizing dry weight calculations, educating patients on nutrition, salt restriction, and fluid intake to reduce excessive inter-dialytic weight gain, and increasing the frequency and duration of hemodialysis in patients with large inter-dialytic weight gains.

2. Modifying hemodialysis prescriptions (e.g., atrium and ultrafiltration profiling, blood flow, and ultrafiltration volume) to prevent intradialytic hypertension or intradialytic hypotension.

3. Optimizing hypertension management to achieve appropriate blood pressure targets during hemodialysis (intradialytic and peridialytic hypertension) and inter-dialytic periods (<140/90 mmHg) while minimizing the use of alpha-blockers whenever possible.

Conclusion

This study demonstrates that among the independent variables, pre-dialysis diastolic and post-dialysis systolic blood pressure have significant associations with detrimental changes in pulse pressure during hemodialysis. These factors may serve as key risk indicators for cardiovascular disease, arrhythmias, and both cardiovascular and all-cause mortality in maintenance hemodialysis patients. Future research employing more robust study designs and larger sample sizes must identify additional factors significantly contributing to detrimental pulse pressure changes during hemodialysis. Such studies will aid in developing targeted therapeutic strategies to modify pulse pressure responses during hemodialysis, potentially improving survival outcomes for maintenance hemodialysis patients.

Limitations of the Study

Several limitations in this study should be considered. First, we did not measure intrinsic factors that could influence preload, afterload, and heart muscle contractility changes, which may affect changes in pulse pressure during hemodialysis. Additionally, the study's relatively short duration limits our ability to conclude causal relationships between the independent and dependent variables. Finally, since the study was conducted at a single hemodialysis center, the generalizability of our findings to the broader population of hemodialysis patients may be limited.

Declarations

Ethics approval and consent to participate

This article complied with all ethical rules at the research site.

Competing interests

There are no conflicts of interest in writing this article.

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None.

Author's Contribution

Idea/concept: RD. Design: RD. Control/supervision: MP. Data collection/ processing: RD. Analysis/interpretation: RD. Literature review: RD. Writing the article: RD, Critical review: YW. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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Original Article

Observational Study on How the Frequency of Dialyzer Reuse Impacts Hemodialysis Effectiveness

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ABSTRACT

Background: The increasing practice of dialyzer reuse in hemodialysis raises critical concerns regarding its impact on efficacy, infection risks, and essential metrics such as Urea Reduction Ratio (URR) and Kt/V values. Addressing these concerns is paramount to establishing safe and optimal reuse limits through comprehensive performance assessments.

Objective: To evaluate the feasibility of dialyzer reuse by assessing Kt/V and URR measurements.

Methods: A prospective cohort study was conducted at RSUD Dr. Saiful Anwar's Hemodialysis Unit from November 2021 to January 2022. Data collection employed a standardized pilot form designed to collate Kt/V and URR data from all participants. Statistical analyses included repeated measures ANOVA to detect temporal changes in average Kt/V and URR, alongside Spearman correlation analysis to explore variable relationships.

Results: The study encompassed 15 participants, revealing a statistically significant decline in both Kt/V and URR values across each reuse group ($p < 0.05$). Specifically, each subsequent reuse of the dialyzer corresponded to a decrement of 0.0469 units in Kt/V and 1.003 units in URR. Notably, by the 7th reuse, hemodialysis adequacy remained satisfactory, achieving an average Kt/V of 1.61. Furthermore, the study indicated that even up to 11 reuses could achieve a Kt/V > 1.4. Similarly, the average URR value for the 7th reuse was 70.207%, with the potential to maintain URR > 65% even after up to 13 reuses.

Conclusion: This study unequivocally affirms that hemodialysis adequacy remains satisfactory up to the 7th reuse of dialyzers, despite observed declines in Kt/V and URR values over successive reuses.

Keywords: Hemodialysis; Kt/V; Urea Reduction Ratio; Reuse Dialyzer; Adequacy.

Introduction

Chronic kidney disease (CKD) represents a substantial global health challenge, affecting a significant portion of the population across various stages.[1] Globally, 13.4% of individuals experience CKD stages 1–5, with 10.6% progressing to stages 3–5. In 2017 alone, CKD accounted for 1.2 million deaths, highlighting its severe impact on mortality rates.[2] Over the period from 1990 to 2017, there was a concerning 41.5% increase in the global all-age mortality rate attributed to CKD.[3] Patients with CKD stages 4 and 5 face particularly high mortality risks, comparable to those undergoing

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dialysis. Specifically, individuals in these advanced stages experience mortality rates three-fold and sixfold higher, respectively, compared to those with an estimated glomerular filtration rate (eGFR) of 60 or higher.[4] Hemodialysis has been a cornerstone therapy for end-stage CKD patients since its inception in the 1960s, effectively managing the condition.[5] However, its implementation comes with significant challenges, notably the substantial financial burden.[6]

The dialyzer device, a critical and expensive component of the treatment process, is a pivotal contributor to the high costs associated with hemodialysis. This expense poses a significant challenge for patients reliant on hemodialysis for kidney function support. Consequently, the reuse of dialyzers has emerged as a promising strategy to mitigate costs.[6] Originating in 1964, the practice of dialyzer reuse has gained widespread adoption,[7] particularly in Indonesia where 92% of dialysis centers engage in reuse practices, averaging between 2 and 10 reuses per dialyzer. This approach has been shown to yield cost savings ranging from 11% to 42%.[8] Despite its cost-effectiveness, dialyzer reuse is not without concerns. Issues such as diminished membrane surface area, which can lead to inadequate dialysis, and infection risks associated with sterilization procedures have been documented.[9] Moreover, prolonged exposure to sterilizing agents poses long-term risks to both patients and equipment. Additionally, repeated use of dialyzers can impact essential metrics of hemodialysis effectiveness, notably reducing Urea Reduction Ratio (URR) and Kt/V values, thereby potentially compromising treatment efficacy.[10] As is well known, both URR and Kt/V are essential for evaluating the outcomes of dialysis. URR provides an assessment of urea removal efficiency, while Kt/V evaluates urea clearance over a specific period and body fluid volume. The implications of not maintaining adequate URR and Kt/V values are highly significant. This can affect patient survival, quality of life, and healthcare costs. Regular monitoring and adjustments in dialysis treatment are crucial to ensure that these parameters meet the recommended targets. This is aimed at improving patient outcomes and reducing the burden on healthcare systems. To address these challenges, guidelines such as those from PERNEFRI recommend limiting dialyzer reuse to seven times to balance cost-effectiveness with safety and efficacy considerations.[11] Given these complexities, it is crucial to determine the optimal number of re-uses for each dialyzer to ensure adequate and safe hemodialysis. This study aimed to assess the feasibility of safe dialyzer reuse by evaluating Kt/V and URR measurements, providing insights into maintaining hemodialysis adequacy amidst cost-saving practices. This study is expected to provide information on the safety and efficacy of dialyzer reuse, including the maximum number of times it can be safely used for patients.

Methods

Design and participants

The study, a single-center study, was designed as a prospective cohort study conducted at the hemodialysis unit of RSUD Dr. Saiful Anwar between November 2021 and January 2022. The primary objective was to evaluate the efficacy of hemodialysis in patients with chronic kidney disease, comparing those who used reused dialyzers with those who did not. Key parameters assessed included Kt/V and URR. Protocols and procedures throughout the study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for prospective cohort studies.[12]

The sample size for this study was determined based on a prevalence rate of 13.4% among hemodialysis patients,[13] with a minimum power of 80%.[14] This calculation required a minimum of 110 patients in our study. The selection sample method employed was consecutive sampling. Inclusion criteria encompassed patients diagnosed with chronic kidney disease undergoing routine hemodialysis at our hospital and who provided written informed consent to participate. Exclusion criteria included patients with hepatitis B and HIV, as well as those who

had not undergone reuse of the dialyzer more than seven times. Dropout criteria included patients who did not participate in the study during the study period or who passed away before undergoing dialyzer reuse seven times.

Data collection

The study was conducted at the Hemodialysis Unit of RSUD Dr. Saiful Anwar between November 2021 and January 2022. Data collection utilized a standardized pilot form designed to gather Kt/V and URR data from all participants.

Covariates

The predictor covariate in our study was the use of reused dialyzers, while the outcome covariate was the assessment of hemodialysis adequacy, measured by Kt/V and URR. These covariates were used to evaluate the effectiveness of hemodialysis treatment among participants in our study.

Statistical analysis

In our study, data were presented as mean ± standard deviation (SD) for numerical variables and n (%) for categorical variables. The normality of the data was assessed using the Kolmogorov-Smirnov test, with a p-value less than 0.05 indicating non-normal distribution and a p-value greater than or equal to 0.05 indicating normal distribution. To assess the main findings, repeated measures ANOVA was employed to determine differences in average Kt/V and URR. The selection of the ANOVA test in this study was based on the fact that the variables in this study are numerical and consist of more than two variables. Additionally, Spearman correlation analysis was conducted to examine correlations between variables. The Spearman test was conducted to assess the correlation between variables, as the variables in this study are ordinal and numerical. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS; IBM SPSS; Chicago, US).

Results

Baseline characteristics of patients included in our study

The characteristics of the subjects in this study (Table 1) revealed that 54.8% (63 participants) were male and 45.2% (52 participants) were female. The majority of patients, 96.5% (111 participants), underwent hemodialysis twice a week, while a minority, 3.5% (4 participants), received treatment three times a week. Regarding hemodialysis access, 66.1% (76 participants) had AV-shunt access, 14.8% (17 participants) had double-lumen access, and 19.1% (22 participants) had manual vascular access. Additionally, 0.68% (1 participant) did not have any identified risk factors, 25.85% (38 participants) had risk factors for diabetes mellitus, 67.35% (99 participants) had risk factors for hypertension, 4.08% (6 participants) had risk factors for hyperuricemia, and 0.68% (1 participant) had risk factors for prostate cancer.

Table 1. Baseline characteristics of patients included in our study

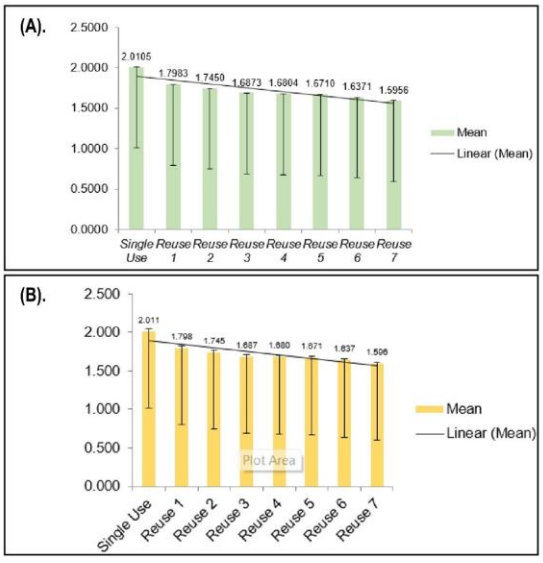
Variables	Percentage
Gender	
Male	63 (54.8%)
Female	52 (45.2%)
Hemodialysis Freq.	
2 times/week	111 (96.5%)
3 times/week	4 (3.5%)
Vascular access	
AV-Shunt	76 (66.1%)
Double lumen	17 (14.8%)
Vein insertion	22 (19.1%)
Risk factor	
Diabetes mellitus	38 (25.85%)
Hypertension	99 (67.35%)
Hyperuricemia	6 (4.08%)
Prostate cancer	1 (0.68%)

Note: data were presented in n (%).

Reuse dialyzer impact on Kt/V

The Kt/V data for single use (new dialyzer) and reuse 1 through reuse 7 exhibited a normal distribution (Figure 1A). This finding allowed for parametric testing. The mean values of Kt/V were 2.011, 1.798, 1.745, 1.687, 1.680,

1.671, 1.637, and 1.596 units, respectively, for each level of dialyzer reuse (Figure 1B). Significant differences ($p < 0.05$) were observed between single-use and each reuse level (reuse 1 through reuse 7), as well as among different reuse levels (e.g., reuse 1 *vs.* single-use and reuse 2 through reuse 7). However, comparisons between specific reuse levels (e.g., reuse 3 *vs.* reuse 4 and reuse 5) did not show significant differences ($p > 0.05$) (Figure 1C). Correlation analysis (Table 2) revealed a negative correlation coefficient of -0.262 with $p = 0.000$ ($p < 0.05$), indicating a significant relationship between the frequency of dialyzer reuse and Kt/V. This negative correlation suggested that as the frequency of dialyzer reuse increased, Kt/V decreased, while shorter reuse durations were associated with higher Kt/V values. Additionally, a strong correlation coefficient of 0.920 underscored the relationship between dialyzer reuse and Kt/V. Regression analysis yielded the equation: $Y = 1.9392 - 0.0469X$, where Y represents Kt/V and X represents the frequency of reuse dialyzer. This equation indicated that Kt/V tended to remain high at 1.9392 units but decreased by 0.0469 units with each additional reuse of the dialyzer.



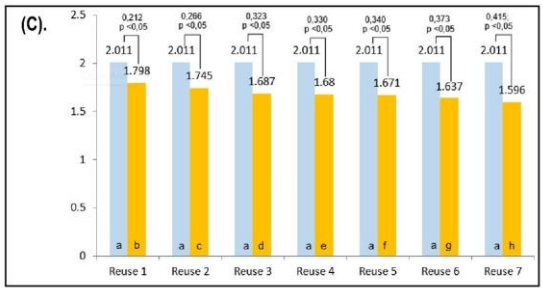


Figure 1. Test outcomes of reuse dialyzer on Kt/V. (A). Normality test outcomes for Kt/V with reused dialyzers. (B). Estimation of the use of dialyzer reuse against Kt/V. (C). Average reduction in Kt/V with reused dialyzers.

Table 2. Correlation test findings for reused dialyzer impact on Kt/V

		Kt/V	Frequency of reuse dialyzer
Pearson correlation	Kt/v	1.000	-.262
	Frequency of reuse dialyzer	-.262	1.000
Sig.(1-tailed)	Kt/v		.000
	Frequency of reuse dialyzer	.000	
N	Kt/v	.920	.920
	Frequency of reuse dialyzer	.920	.920

*Significant if $p<0.05$

The impact of reuse dialyzers on URR

The URR data for single use (new dialyzer) and reuse 1 through reuse 7 exhibited a normal distribution, allowing for parametric testing (Figure 2A). The average URR values were 78.600, 76.218, 75.308, 74.377, 73.435, 73.191, 72.574, and 70.207 units, respectively, for each level of dialyzer reuse (Figure 2B). Significant differences ($p < 0.05$) were found between single-use and each level of reuse (reuse 1 through reuse 7), as well as among different levels of reuse (e.g., reuse 1 *vs.* single-use and reuse 2 through reuse 7). Notably, comparisons between specific reuse levels (e.g., reuse 4 *vs.* reuse 5 and reuse 6) did not show significant differences ($p > 0.05$) (Figure 2C). Correlation analysis (Table 3) revealed a

negative correlation coefficient of -0.382 with p = 0.000 ($p < 0.05$), indicating a significant relationship between the frequency of dialyzer reuse and URR. This negative correlation implied that as the frequency of dialyzer reuse increased, URR decreased, while shorter reuse durations were associated with higher URR values. A strong correlation coefficient of 0.920 further emphasized the relationship between dialyzer re-use and URR. Regression analysis yielded the equation: Y = 78.754 - 1.003X, where Y represented URR and X represented the frequency of dialyzer reuse. This equation suggested that while URR tended to remain high at 78.754 units, each additional use of the reused dialyzer was associated with a decrease of 1.003 units in URR.

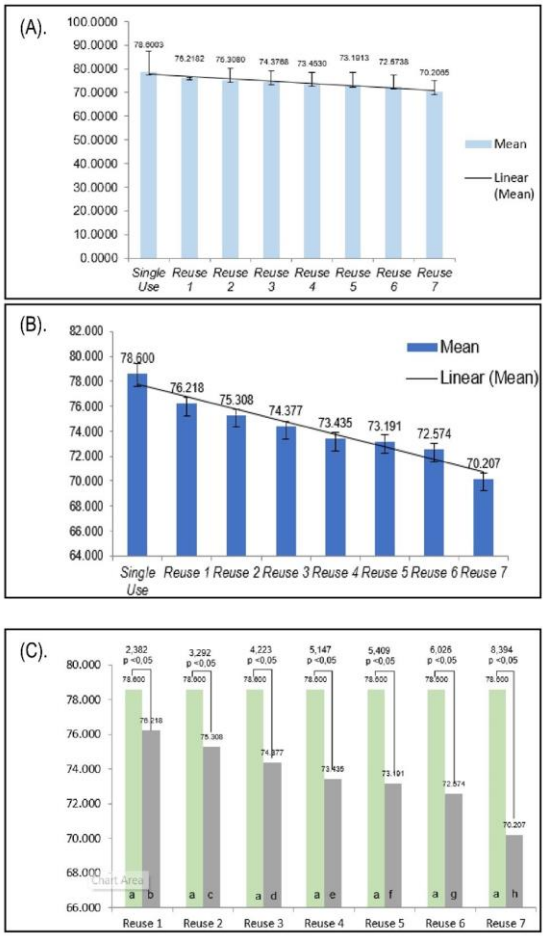


Figure 2. Impact of dialyzer reuse on URR results. (A). Normality test outcomes of dialyzer reuse on URR. (B). Estimate of dialyzer reuse impact on URR. (C). Average decrease in URR with reused dialyzers.

Table 3. Correlation test findings for reused dialyzer impact on URR

		URR	Frequency of reuse dialyzer
Pearson correlation	URR	1.000	-.382
	Frequency of reuse dialyzer	-.382	1.000
Sig.(1-tailed)	URR		.000
	Frequency of reuse dialyzer	.000	
N	URR	.920	.920
	Frequency of reuse dialyzer	.920	.920

*Significant if $p<0.05$

Discussion

Our study found that the use of a dialyzer up to reuse 7 produced an average Kt/V value of 1.6109 and an average URR value of 71.733. These results are consistent with previous studies that evaluated the impact of dialyzer reuse on Kt/V and URR. Earlier studies reported Kt/V and URR levels of 1.6 ± 0.3 and 74 ± 5, respectively. Furthermore, they indicated that reusing dialyzers up to the 12th reuse was safe from clinical, microbiological, and inflammatory perspectives.[15] Another study demonstrated no significant difference in Kt/V (1.4 ± 0.4) between reused and single-use dialyzers. Additionally, they suggested that reused dialyzers were associated with improved survival rates and lower levels of inflammatory markers, although nutritional markers were not assessed.[16] Moreover, further study revealed no difference in adequacy between single-use and reused dialyzers.[8] These studies supported our findings, indicating that the use of reused dialyzers is safe in terms of hemodialysis adequacy for patients.

In our study, the Kt/V value with reuse of the dialyzer up to the 7th reuse was 1.6109,

indicating effective hemodialysis. Previous studies have established safety and adequacy thresholds for Kt/V values. For instance, a study monitoring 80 hemodialysis patients receiving thrice-weekly treatment found that Kt/V values below 1.3 were significantly associated with higher one-year mortality (25%) and shorter survival times (3.3%). Conversely, Kt/V values above 1.4 were linked to lower one-year mortality rates.[17] Another study recommended a Kt/V dose of 1.2 for thrice-weekly hemodialysis,[18] supported by guidelines from the European Renal Best Practice Group (EBPG), which emphasize achieving a Kt/V value ≥1 for optimal treatment outcomes. Values below this threshold are associated with poorer prognoses, whereas a Kt/V above 1.4 is linked with better outcomes compared to values below 1.3.[19] Additionally, further study indicated that a Kt/V above 1.45 is necessary to meet adequate hemodialysis targets. Therefore, our study's finding of a Kt/V of 1.6109 with reused dialyzers underscores their safety and effectiveness in achieving adequacy for hemodialysis patients.[20]

In our study, the URR value with reused dialyzers up to the 7th reuse was 71.733%, indicating effective hemodialysis. Previous studies have assessed the safety and adequacy thresholds of URR values. For example, one study determined that a minimum URR of 65% was necessary for adequate dialysis and found that reused dialyzers could be used up to 13 times while maintaining recommended URR levels.[21] Moreover, a study in India involving 35 patients undergoing long-term hemodialysis showed that an average URR of 66.4% per dialysis was associated with positive outcomes.[22] Similarly, a three-month study in Baghdad on patients with advanced chronic kidney disease identified a minimum URR of 65% as linked to favorable outcomes.[23] Therefore, our study's finding of a URR of 71.733% with reused dialyzers confirms their safety and efficacy in achieving hemodialysis adequacy.

This study has several clinical implications. First, we found that the use of re-used dialyzers was safe, as evaluated based on Kt/V and URR levels. This suggests that reusing dialyzers up to the seventh reuse is highly recommended and safe. Our study confirmed that dialyzer reuse could safely extend to seven cycles without compromising hemodialysis adequacy, highlighting its practical relevance. Given the substantial financial resources required for treatment, this finding is significant for the cost-effectiveness of managing hemodialysis patients.[6] Second, the safety findings regarding reused dialyzers suggest that they do not necessarily need to be new for dialysis patients, as modifications in their reuse can still provide adequate treatment. This could lead to significant cost savings without compromising patient care. Third, however, our study also revealed a decrease in hemodialysis adequacy with reused dialyzers, raising concerns about the safe limit for their reuse. While not substantial in our findings, the decrease indicates the need for ongoing monitoring and assessment to ensure patients receive optimal care. Nonetheless, the complications associated with reused dialyzers, such as infection risk, cardiovascular complications, and impact on patient quality of life, must be carefully considered.[9] While our study supports the safety and efficacy of dialyzer reuse up to seven times, healthcare providers must weigh these benefits against potential risks and ensure that protocols are in place to mitigate any adverse effects.

Conclusion

In conclusion, our study determined that by the 7th reuse of dialyzers, hemodialysis adequacy remained satisfactory with an average Kt/V value of 1.61, above the standard threshold of 1.4, despite a decrease of 0.0469. Similarly, the average URR value on the 7th reuse was 70.207%, exceeding the standard URR of 65%, with a decrease of 1.003. These findings highlight the potential for safe and effective reuse of dialyzers up to the seventh use, which can have significant cost-saving implications for the management of hemodialysis patients. However, future studies should assess factors such as membrane biocompatibility, infection risk, cardiovascular events, quality of life, and cost-effectiveness to better understand the

implications of dialyzer reuse. Addressing these aspects and using samples from larger or multi-center studies may help optimize hemodialysis treatment protocols and ensure patient safety and well-being.

Limitations of the Study

This study had several limitations. First, the sample size was small, requiring caution in interpreting the findings. A larger sample size would provide more robust data and allow for more generalized conclusions. Second, potential confounding factors such as underlying diseases, hemodialysis dosage, and comorbidities were not analyzed, necessitating careful consideration when interpreting the results. These factors could influence hemodialysis outcomes and should be included in future studies to provide a more comprehensive understanding. Third, the study did not assess complications associated with reused dialyzers, such as infection risk, cardio-vascular complications, and intradialytic events. These complications are critical to understanding the full impact of dialyzer reuse on patient safety and quality of life.[9] Fourth, membrane bio-compatibility, known to influence hemodialysis adequacy significantly, was not evaluated. Different dialyzer membranes can have varying effects on patient outcomes,[24] and future studies should examine this aspect to determine the best options for dialyzer reuse. Finally, despite the primary objective of cost-effectiveness, the financial aspects of using reused dialyzers were not evaluated. Understanding the economic impact of dialyzer reuse is crucial for healthcare providers and policymakers to make informed decisions about treatment protocols and resource allocation.[6]

Declarations

Ethics approval and consent to participate

The study protocol received approval from the local ethics committee (approval number 070/17231/102.7/2022), adhering to institutional guidelines and the Declaration of Helsinki principles.[25] Participants provided written informed consent after receiving detailed information about the study's aims, potential risks, and benefits. Participants were assured of their voluntary participation and the option to withdraw without consequences.

Competing interests

There are no conflicts of interest in writing this article. This article is written neutrally with actual results.

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Author's Contribution

Idea/concept: RS, AG, NS, AR. Design: RS, AG, NS, AR. Control/supervision: AG, NS, AR. Data collection/processing: RS, AG, NS, AR. Analysis/interpretation: RS, AG, NS, AR. Literature review: RS, AG, NS, AR. Writing the article: RS, AG, NS, AR. Critical review: RS, AG, NS, AR. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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Original Article

Characteristics and Clinical Outcomes of COVID-19 in ESRD Patients Undergoing Hemodialysis in Ngudi Waluyo Wlingi General Hospital in 2020-2022

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ABSTRACT

Background: The coronavirus disease (COVID-19) pandemic is a major threat to global health care. Comorbidities, including end-stage renal disease (ESRD), are related to an increased risk of severe infection and mortality.

Objective: To assess determinants related to the clinical outcomes of COVID-19 in ESRD patients undergoing hemodialysis in Ngudi Waluyo Wlingi General Hospital in 2020-2022.

Methods: This study included ESRD patients undergoing maintenance hemodialysis who were hospitalized at Ngudi Waluyo Wlingi General Hospital due to COVID-19 from May 2020 to February 2022. Clinical characteristics were investigated in relation to the severity and survival status.

Results: A total of 26 patients (46.15% male) with a mean age of 52.27±13.65 years met the inclusion criteria. Of these, 42.3% had a mild infection, 23% had a moderate infection, 30.77% had a severe infection, and 3.8% had a critical infection. The mortality rate was 23.08%, with a mean length of stay of 15.19±7 days. Age, oxygen saturation, respiratory rate upon admission, lymphocyte and neutrophil levels, and neutrophil-to-lymphocyte ratio were significantly associated with COVID-19 severity. Length of stay was statistically influenced by respiratory rate upon admission. The mortality rate was correlated with the dialysis vintage, levels of hemoglobin, leukocytes, platelets, neutrophils, neutrophil-to-lymphocyte ratio, serum urea, serum creatinine, eGFR, and length of stay.

Conclusion: COVID-19 in ESRD patients undergoing hemodialysis were more likely to have a poor prognosis. Identifying determinants is crucial for reducing morbidity and mortality.

Keywords: Chronic Kidney Disease, COVID-19, Hemodialysis, Renal Insufficiency, Renal Dialysis.

Introduction

Coronavirus disease (COVID-19), caused by the novel beta-coronavirus SARS-CoV-2, was initially identified on December 31, 2019, in Wuhan, China. Following its declaration as a global pandemic in March 2020, it has presented a major threat to global health care.[1] As of June 7, 2024, there have been 775,522,404 confirmed cases and 7,049,617 deaths reported across 232 countries.[2]

Comorbidities, such as chronic kidney disease (CKD), are associated with an increased risk of complications and mortality. The prevalence of COVID-19 among CKD patients fluctuated between 0.4 and 49.0% in 2022.[3] In

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Indonesia, it was predicted that the number of CKD patients with COVID-19 would reach 52.200 cases.[4] Individuals with CKD who are infected with COVID-19 experience a mortality rate that is 14 to 16 times higher than that of individuals without comorbidities.[5] They produce more pro-inflammatory cytokines and oxidative stress as part of the inflammatory response to infections.[1,6]

COVID-19 in patients undergoing routine hemodialysis is associated with elevated rates of hospitalization, intensive care unit (ICU) admissions, and mortality.[3] About 35.3% of dialysis patients developed COVID-19, and 50.2% of them required hospitalization.[7] Routine hemodialysis patients face a hospitalization risk for COVID-19 that is 3 to 4 times higher than that of patients receiving peritoneal dialysis.[8] Between 6.1% and 35.7% of dialysis patients with COVID-19 experienced respiratory distress, with a mortality rate of 14%.[9] These individuals possess a compromised immune response, and face increased social interactions due to regular hospital visits, making them more susceptible to COVID-19.[5,10]

Despite significant improvement in the prognosis of COVID-19 due to vaccinations and advancements in treatment, outcomes in routine hemodialysis patients remain unclear, particularly in Indonesia. This study aims to identify the determinants related to clinical outcomes of COVID-19 in ESRD patients undergoing hemodialysis at Ngudi Waluyo Wlingi General Hospital between 2020-2022.

Methods

Design and participants

This retrospective study focused on hemodialysis patients who were treated for COVID-19 at Ngudi Waluyo Wlingi General Hospital from May 2020 to February 2022. The study population included patients aged ≥15 years with positive RT-PCR and high serum renal function who were hospitalized between May 2020 and February 2022. Inclusion criteria consisted of a diagnosis of ESRD and adherence to a regular hemodialysis schedule. In our hospital, the standard hemodialysis regimen was biweekly sessions lasting 5 hours each. The exclusion criteria were incomplete medical records. Data was retrieved from medical records, including clinical and laboratory data. The patients were grouped according to the severity of COVID-19 and survival status.

In this study, COVID-19 was confirmed through positive RT-PCR results from nasopharyngeal swabs. The hematology test was conducted using a hematology analyzer. Serum potassium level was measured with an ion-selective electrode. Serum urea was evaluated using Berthelot methods, while serum creatinine was assessed using Jaffe methods. The estimated glomerular filtration rate (eGFR) was determined using the CKD-EPI 2021 formula. CKD was classified into five stages based on the Kidney Disease: Improving Global Outcomes guideline. CKD stage 5 (eGFR <15 ml/min) or ESRD is further divided into dialysis-dependent and dialysis-independent.[3] In this study, all participants were diagnosed with CKD stage 5 and undergoing hemodialysis. Dialysis vintage was defined as the period between the date of hemodialysis initiation and hospitalization, measured by "month."[11]

Data collection

In this study, patients were divided into a group of patients with ≤12 months of dialysis and a group of patients with >12 months of dialysis. The severity of COVID-19 was classified according to the Indonesian COVID-19 Treatment Guideline into the following categories: asymptomatic (no symptoms), mild (symptomatic without evidence of viral pneumonia or hypoxia), moderate (signs of pneumonia without evidence of severe pneumonia), severe (signs of pneumonia with increased respiratory rate >30x/minute, or peripheral oxygen saturation <93% on room air, or severe respiratory distress) and critical infection (sepsis, septic shock, acute respiratory distress syndrome, or conditions requiring mechanical ventilation or vasopressors).[5]

Statistical analysis

Variables were assessed using the Saphiro-Wilk test to determine normality. The Mann-Whitney method (for categorical independent variables) and Spearman method (for numeric independent variables) were used to analyze factors that influence the severity of COVID-19 and length of hospital stay. Meanwhile, the survival status analysis used the Chi-square method (for categorical independent variables) and lambda correlation test (for numeric independent variables). Data analysis was performed using IBM SPSS 25.0, considering a *p-value* of <0.05 as a significance value. This study obtained ethical permission from the Health Research Ethics Committee of Ngudi Waluyo Wlingi General Hospital.

Results

From May 2020 to February 2022, 26 patients met the inclusion criteria, with a mean age of 52.27±13.65 years. A total of 12 (46.15%) patients were male. The majority of patients (46.15%) had unknown comorbidity in addition to CKD, and 38.46% had only one comorbidity, with hypertension identified as the most prevalent (34.62%), followed by type 2 diabetes mellitus (15.38%). The mean dialysis vintage was 22.15±15.80 months, with a maximum of 47 months and a minimum of 1 month. The average length of stay (LOS) was 15.19±7.4 days.

Risk factors of COVID-19 severity in patients with ESRD undergoing hemodialysis

Based on the severity of COVID-19, 11 (42.3%) individuals had a mild infection, 6 (23%) had a moderate infection, 8 (30.77%) had a severe infection, and 1 (3.8%) had a critical infection (Table 1). Patients with critical infection had older age (p=0.027, r=0.450) and exhibited reduced oxygen saturation (SpO2) (*p*<0.001,r=-0.657), increased respiratory rate (RR) (*p*=0.031,r=0.425), reduced lymphocyte levels (*p*=0.049,r=-0.389), and increased neutrophils (*p*=0.017,r=0.462) and neutrophil-to-lymphocyte ratio (NLR) (*p*=0.032,r=0.421).

Table 1. Characteristics of the participants stratified by COVID-19 severity

Characteristic	COVID-19 severity				Total	*p*-value
	Mild	Moderate	Severe	Critical		
	(*n*=11)	(*n*=6)	(*n*=8)	(*n*=1)	(*n*=26)	
Age (mean, in years±SD)	46.81±13.49	48.5±8.57	61.63±13.62	60±0	52.27±13.65	0.027
<60 years, *n*(%)	9(81.81)	6(100)	3(37.5)	-	18(69.23)	
≥60 years, *n*(%)	2(18.18)	-	5(62.5)	1(100)	8(30.77)	
Sex, male, *n*(%)	6(54.54)	2(33.33)	3(37.5)	1(100)	12(46.15)	0.722
Comorbidities, *n*(%)						0.902
0	5(45.45)	2(33.33)	5(62.5)	-	12(46.15)	
1	5(45.45)	2(33.33)	2(25)	1(100)	10 (38.46)	
>1	1(9.09)	2(33.33)	1(12.5)	-	4(15.38)	
Hypertension	4(36.36)	3(50)	1(12.5)	1(100)	9(34.62)	
Type 2 Diabetes mellitus	3(15)	2(33.33)	1(12.5)	-	4(15.38)	
Dialysis vintage (mean, in months±SD)	18.72±16.4	19.5±17.58	28.13±14.69	28±0	22.15±15.80	0.199
≤12 months, *n*(%)	4(36.36)	2(33.33)	1(12.5)	-	7(26.92)	
>12 months, *n*(%)	7(63.63)	4(66.67)	7(87.5)	1(100)	19(73.08)	
SpO2 (mean, in %±SD)	97.72±1.61	96.34±1.86	85±10.85	96±0	93±8.02	<0.001
RR (mean, in x/min±SD)	21±1.84	23±2.10	25±5.86	24±0	22.81±3.86	0.031
Laboratory, mean±SD						
Hemoglobin (g/dl)	7.54±1.98	8.45±1.81	8.81±1.69	6.1±0	8.09±1.87	0.214
Leukocyte (10^3/μL)	6.85 ±2.58	9.41 ± 3.34	8.04 ± 2.30	8.58±0	7.88 ±2.72	0.162
Platelets (10^3/μL)	312.72±134.95	304.17±164.57	271.13±81.50	491±0	304.81±127.82	0.985
Neutrophil (%)	65.54±7.37	78.43±11	77.09±11.66	82.9±0	72.74±11.17	0.017
Lymphocyte (%)	21.61±8.38	14.93±7.89	15.01±7.72	9.3±0	17.57±8.42	0.049
NLR	3.66±1.91	7.77±6.09	7.33±5.36	8.89±0	5.94±4.58	0.032
Serum potassium (mmol/L)	4.61±0.90	4.40±1.13	4.30±0.65	4.76±0	4.47±0.85	0.311
Serum urea(mg/dl)	145.18±45.39	173.5±41.75	116.5±55.65	435±0	154.041±75.98	0.143
Serum creatinine (mg/dl)	10.29±3.58	10.19±2.22	8.10±3.83	18.85±0	9.92±3.81	0.315
eGFR (mL/min/1.73 m^2)	7.66±3.68	6.84±1.62	13.41±14.97	2.88±0	9.06±8.85	0.986

Hospitalization duration in days (mean,±SD)	15.09±6.55	15±8.15	16.25±8.94	9±0	15.19±7.40	0.557
Death, *n*(%)	2(18.18)	1(16.67)	2(25)	1(100)	6(23.08)	0.303

eGFR, estimated glomerulus filtration rate; HHD, hypertensive heart disease; NLR, neutrophil-leukocyte ratio; RR, respiratory rate; SpO2, peripheral oxygen saturation.

Risk factors of length of hospital stay of COVID-19 in patients with ESRD undergoing hemodialysis

Length of stay (LOS) was significantly affected by respiratory rate upon admission (p=0.012, r=-0.484). The analysis of determinants related to LOS is provided in Table 2.

Table 2. Correlation of risk factors of length of hospital stay

Variable	*r*	*p*-value
Age	-0.018	0.932
Sex	-	0.327
Comorbidities	0.006	0.978
Dialysis vintage	-0.013	0.948
SpO2 on the admission	0.054	0.792
RR on the admission	-0.484	0.012
Laboratory		
Hemoglobin	-0.024	0.908
Leukocyte	0.097	0.638
Platelets	-0.028	0.892
Neutrophil	-0.211	0.300
Lymphocyte	0.167	0.414
NLR	-0.093	0.653
Serum potassium	0.057	0.786
Serum urea	0.122	0.561
Serum creatinine	0.292	0.157
eGFR	0.025	0.905

Risk factors of mortality of COVID-19 in ESRD patients undergoing hemodialysis

The characteristics of patients according to survival status are summarized in Table 3. A total of 6 (23.07%) patients died. The number of deaths in each infection group was as follows: mild (2 deaths, 18.18%), moderate (1 deaths, 16.67%), severe (2 deaths, 25%), and critical infection (1 deaths, 100%). Factors such as dialysis vintage (p=0.041), levels of hemoglobin (p=0.009), leukocytes (p=0.009), platelets (p=0.009), neutrophils (p=0.009), NLR (p=0.009), serum urea (p=0.019), serum creatinine (p=0.008), eGFR (p=0.002), and length of hospitalization (p=0.02) were significantly associated with the mortality rate. The causes of death were mostly uremic encephalopathy, disseminated intravascular coagulation, acute respiratory distress syndrome, and septic shock.

Table 3. Characteristics of the participants stratified by survival status

Characteristic	Survival status			*p*-value
	Non-survivor	Survivor	Total	
	(*n*=6)	(*n*=20)	(*n*=26)	
Age (mean, in years±SD)	54.67±13.88	51.55±13.86	52.27±13.65	0.245
<60 years, *n*(%)	3(50)	15(75)	18(69.23)	
≥60 years, *n*(%)	3(50)	5(25)	8(30.77)	
Sex, male, *n*(%)	3(50)	9(45)	12(46.15)	0.829
Comorbidities, *n*(%)				0.958
0	3(50)	9(45)	12(46.15)	
1	2(33.33)	8(40)	10 (38.46)	
>1	1(16.67)	3(15)	4(15.38)	
Hypertension	2(33.33)	7(35)	9(34.62)	
Type 2 Diabetes mellitus	2(33.33)	2(10)	4(15.38)	
Dialysis vintage (mean, in months±SD)	31.67±10.98	19.3±16.11	22.15±15.80	0.041
≤12 months, *n*(%)	-	7(35)	7(26.92)	
>12 months, *n*(%)	6(100)	13(65)	19(73.08)	
SpO2 on the admission (mean, in %±SD)	92.67±6.62	93.10±8.55	93±8.02	0.475
RR on the admission (mean, in x/min±SD)	28.83±3.25	22.5±4.05	22.81±3.86	0.066

Laboratory, mean±SD				
Hemoglobin (g/dl)	8±1.73	8.11±1.96	8.09±1.87	0.009
Leukocyte (10^3/μL)	6.76±0.97	8.21±3	7.88 ±2.72	0.009
Platelets (10^3/μL)	309.67±107.42	303.35±135.84	304.81±127.82	0.009
Neutrophil (%)	76.68±11.01	71.56±11.22	72.74±11.17	0.009
Lymphocyte (%)	15.97±8.14	18.05±8.65	17.57±8.42	0.115
NLR	6.27±3.73	5.84±4.89	5.94±4.58	0.009
Serum potassium (mmol/L)	5.26±0.84	4.24±0.72	4.47±0.85	0.114
Serum urea (mg/dl)	213.67±115.27	136.15±51.39	154.041±75.98	0.019
Serum creatinine (mg/dl)	10.41±4.78	9.78±3.61	9.92±3.81	0.008
eGFR (mL/min/1.73 m²)	7.70±4.50	9.46±9.84	9.06±8.85	0.002
Hospitalization duration in days (mean,±SD)	16.5±13.32	14.80±4.96	15.19±7.40	0.020

eGFR, estimated glomerulus filtration rate; HHD, hypertensive heart disease; NLR, neutrophil-leukocyte ratio; RR, respiratory rate; SpO2, peripheral oxygen saturation.

Discussion

Patients with CKD undergoing hemodialysis are more susceptible to infections due to various comorbidities, advanced age, and reduced immune function.[9] This is related to accelerated immune aging characterized by reduced CD8+ and CD4+ T cells, as well as B lymphocytes. Hemodialysis can also lead to increased neutrophil apoptosis and the release of myeloperoxidase. Uremic toxins and non-self-antigens from hemodialysis materials contribute to chronic inflammation.[12] Furthermore, regular hospital visits further increase the risk of transmission.[8]

Dialysis patients have vitamin D and erythropoietin deficiencies that exacerbate pro-inflammatory effects while diminishing anti-inflammatory responses.[9] COVID-19 causes hyperinflammation, leading to increased production of cytokines, chemokines, inflammatory monocytes, and macrophages.[12] Angiotensin-converting enzyme 2, the COVID-19 target organ, is expressed in proximal tubule cells. This allows the virus to invade cells and disrupt fluid, acid-base, and electrolyte balance, further damaging the kidneys.[6,13] This contributes to a "cytokine storm" and further renal vascularization impairment.

A retrospective study in Indonesia found that the average age of CKD patients with COVID-19 was between 46 and 55 years.[14] The elderly were reported to have a worse infection and higher incidence of death.[1,15] A study documented that the 28-day mortality rate among dialysis patients aged 75 years or older could reach as high as 31.4%.[3] Several other studies have also indicated that the average age of those who died was older.[16,17] This is attributed to immune system degeneration in the elderly, which is characterized by a reduction in cellular quantity, immune receptors, and B lymphocyte differentiation.[18] This is consistent with our study findings, which showed that age correlated with the severity of COVID-19 but not with the survival status and length of stay.

Male patients are associated with a higher risk of death, possibly due to their role as breadwinners, which often entails greater social activity and, consequently, increased social contact.[6,7,15,19] Moreover, the protective effects of sex hormones and the X chromosome may influence the immune response.[6] Smoking and alcohol consumption, which are more prevalent among men, could also increase susceptibility. A retrospective study in Indonesia found that male patients had an increased risk of COVID-19.[14,20] In contrast, similar to our study's findings, a cohort study found no association between sex,

disease severity, length of stay, and survival status.[17,21]

ESRD patients with comorbidities tend to experience more severe COVID-19 symptoms and have a higher risk of death.[1,3,22,23] Chronic diseases can impair the immune system, making individuals more vulnerable to infections like COVID-19, leading to worse outcomes. The presence of comorbidities increases the likelihood of being admitted to ICU due to severe infection.[18] In Indonesia, hypertension and diabetes mellitus are the most common comorbidities in CKD with COVID-19.[14] Several studies and meta-analyses showed that cardiovascular disease, hypertension, and diabetes were linked to higher mortality rates and greater severity of COVID-19. Another meta-analysis reported that individuals with diabetes mellitus, cardiovascular disease, cancer, and hypertension face a higher risk of death from COVID-10 compared to those without these conditions.[3] Among comorbidities, diabetes mellitus with complications and severe liver disease were identified as the highest risk factors for hospitalization. Other conditions, such as dementia and coronary artery disease, were associated with higher mortality.[24] Patients with hemoglobin disorders are reported to have the longest hospital stay, followed by those with severe obesity and diabetes. Those with multiple comorbidities tend to have longer stays in the ICU and hospital admission compared with those with just one comorbidity.[25] In this study, the majority of the participants had unknown comorbidities. However, despite the presence of comorbidities, there was no statistically significant association between these comorbidities and the severity, mortality, or length of hospital stay due to COVID-19 infection.

Increased dialysis vintage is associated with impaired cardiovascular functional capacity. A cross-sectional study showed that individuals with dialysis vintage >12 months developed a lower oxygen uptake at peak exercise compared to those with dialysis vintage ≤12 months.[26] Moreover, higher dialysis vintage was also associated with a higher prevalence of unpleasant symptoms, lower hemoglobin levels, iron stores, and dialysis adequacy levels.[11] It was also identified as an independent predictor of a poor serological response.[27] In this study, we found that higher dialysis vintage was associated with a higher rate of mortality.

Severe respiratory impairment is indicated by decreased SpO2 and increased RR.[28] An observational study found that more patients with CKD required oxygen support than those without CKD (55.9% vs 31.8%). Moreover, in patients undergoing routine hemodialysis with COVID-19, a SpO2 level below 95% was linked to ICU admission and had a mortality rate 16.6 times higher than those with higher oxygen saturation levels.[15,19,21] These studies align with our results, which showed that SpO2 was statistically related to the severity of COVID-19. Additionally, the RR was statistically associated with both COVID-19 severity and LOS.

Patients with CKD typically have lower hemoglobin levels compared to individuals with normal eGFR due to reduced kidney function.[22] Moreover, COVID-19 can lead to hemolysis, which further decreases hemoglobin levels.[29] A multicenter study found that CKD patients with COVID-19 had a higher incidence of anemia compared to those without CKD.[30,31] A cross-sectional study in Indonesia found that patients who survived COVID-19 had higher levels of hemoglobin, platelets, and albumin.[20] We also found that hemoglobin levels were statistically related to survival status.

COVID-19 patients often exhibit elevated levels of leukocytes, neutrophils, and NLR, while their lymphocyte counts are typically decreased.[21] Moreover, uremia negatively impacts lymphocyte production and impairs neutrophil functions.[24] In routine hemodialysis patients with COVID-19, lower lymphocyte counts, higher levels of pro-inflammatory cytokines, and activated monocytes have been observed. Lymphopenia may result from a decrease in CD4+ T, CD8+ T, and B lymphocytes.[12] In the non-survivor group, patients exhibited lower lymphocyte counts alongside higher leukocyte counts and NLR, suggesting a correlation

between these immune markers and poor outcomes.[15,17,32] A cross-sectional study in Bali found that 87.2% of hemodialysis patients with COVID-19 had elevated NLR levels, which were associated with higher D-Dimer values.[4] A study in Malang also reported higher neutrophil counts and NLR in ESRD patients. An NLR value of 1 or more was associated with a 1.3 times higher mortality rate compared to an NLR value below 1.[33] These findings align with our study, which also found a statistical association between neutrophils, lymphocytes, and NLR levels with the severity of COVID-19. Moreover, leukocytes, neutrophils, and NLR levels were associated with the survival status in this population.

Thrombocytopenia is often associated with COVID-19 infection, with younger patients generally exhibiting higher platelet counts.[21] The "cytokine storm" in COVID-19 can lead to hypercoagulability, which contributes to thrombocytopenia.[29] Damage to lung tissue caused by COVID-19 triggers platelet activation and thrombus formation, leading to increased platelet consumption. A significant association between platelet counts and survival status was also found in this study.

Hyperkalemia is associated with unfavorable outcomes in ESRD patients undergoing hemodialysis with COVID-19, especially when there are delays in receiving dialysis sessions.[28] However, consistent with our findings, several studies have indicated no significant relationship between potassium levels and the severity, LOS, or mortality of COVID-19.[1,28]

Some studies, including in Indonesia, found that non-survivors of COVID-19 tend to have elevated levels of urea and creatine.[20,21,34] In this study, serum urea and creatinine levels were statistically linked to survival status. Moreover, estimated GFR at admission was linked to 28-day mortality in ESRD patients undergoing hemodialysis and COVID-19.[2] A study found that individuals with an eGFR between 30-50mL/min/1.73 m^2 had an increasing 60-day mortality risk prior to admission.[24] Another study reported that non-survivors had lower eGFR values compared to survivors. In our study, eGFR was found to be related to disease mortality.

The prognosis for COVID-19 in ESRD patients undergoing hemodialysis is worse than in the general population. Around 64.4% of these patients require hospitalization due to the severity of the disease.[6,28] CKD patients, especially those with ESRD, are at a 2-3 times greater risk of severe COVID-19.[3,10,24] Several factors, such as critical infection, advanced age, elevated ferritin levels, high aspartate aminotransferase levels, and low platelet count, are related to an increased risk of death.[29] However, our study did not find a significant correlation between disease severity and mortality.

In our study, LOS in the hospital was linked to disease mortality. A study reported that hemodialysis patients with COVID-19 had an average hospitalization of 18.5 days and a mortality rate of 44.9%.[35] Another study reported an average hospital stay of 19.2±12 days, with a mortality rate of 15%.[15] Dialysis patients face a higher risk of hospitalization and mortality compared to individuals not on dialysis. They often present with atypical symptoms, experience rapid changes in mental status, and are more likely to be admitted to the ICU at an earlier stage of the disease.[32] Approximately 17.6% of hemodialysis patients with COVID-19 required intensive care, with contributing factors including advanced age, nosocomial pneumonia, gastrointestinal bleeding, arrhythmia, and SpO2 levels below 95% at admission.[35] However, it was reported that patients receiving maintenance hemodialysis had a 15-day longer survival rate than those receiving emergency hemodialysis.[4]

The mortality rate for COVID-19 in ESRD patients undergoing hemodialysis is 24%, which is higher compared to individuals without CKD.[6,28,30] A retrospective study in Indonesia showed a mortality rate of 23.6% among this

population.[20] CKD patients on dialysis face a 1.41-fold higher risk of 28-day mortality, while those who are not on dialysis have 1.25-fold increased risks compared to individuals without CKD. The primary causes of death in these patients were respiratory failure, kidney failure, and septic shock.[32] In our study, several factors, such as dialysis vintage, levels of hemoglobin, leukocytes, platelet counts, neutrophils, NLR, serum urea, serum creatinine, eGFR, and length of hospitalization, were significantly associated with the mortality rate.

SARS-CoV-2 variants significantly influence the transmission, severity, and mortality of COVID-19. In Indonesia, some variants of concern have been identified. Alpha variant (B.1.1.7) is associated with a higher transmission rate, an increased secondary attack rate, more frequent hospitalization, and reduced neutralizing activity in monoclonal antibody-based therapies with a similar risk of reinfection. Beta variant (B.1.351) also leads to higher transmission and hospitalization rates, along with diminished neutralizing activity.[36] Delta variant (B.1.617.2) is linked to even higher transmission rates, ICU admission, and mortality, characterized by higher viral load for longer periods, and a shorter latent period. The Omicron variant (B.1.1.529) has the highest transmission rate but is associated with higher survival and reinfection rates. Its clinical symptoms tend to be milder compared to other variants.[37] In this study, genome sequencing of COVID-19 was not performed due to limited resources.

This study emphasizes that patients with ESRD undergoing hemodialysis need special care and attention when dealing with COVID-19, as they are at higher risk for severe outcomes. Screening for COVID-19-related signs and symptoms is essential for early diagnosis of the infection, allowing for timely intervention. These patients should be closely monitored to minimize the risk of morbidity and mortality.

Conclusion

Several risk factors influence clinical outcomes in ESRD patients undergoing hemodialysis with COVID-19. Age, oxygen saturation, respiratory rate upon admission, lymphocyte and neutrophil levels, and neutrophil-to-lymphocyte ratio were significantly associated with COVID-19 severity. Length of stay was statistically influenced by respiratory rate upon admission. The mortality rate was correlated with dialysis vintage, hemoglobin, leukocytes, platelets, neutrophils, neutrophil-to-lymphocyte ratio, serum urea, serum creatinine, eGFR levels, and length of stay.

Limitations of the Study

This study has several limitations. First, there was no information on how COVID-19 progressed over time, making it impossible to track the natural history of the disease. Second, the data were not adjusted for confounding factors. Additionally, SARS-CoV-2 variants and immunization status were not collected during the hospitalization. Moreover, this study was conducted with a small sample size from a single center. Further investigation with a larger sample size across multicenter is recommended to yield more reliable and comprehensive results.

Declarations

Ethics approval and consent to participate

This study received approval from the Ethics Committee of Ngudi Waluyo General Hospital.

Competing interests

There are no conflicts of interest in writing this article. This article is written neutrally with actual results.

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Author's Contribution

Idea/concept: FHW. Design: AZI. Control/supervision: FHW. Data collection/ processing: AZI, SM. Analysis/interpretation: AZI. Literature review: FHW, AZI. Writing the article: AZI. Critical review: AZI. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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Original Article

Association Between Fluid Administration and Hemoglobin Changes During Perioperative Kidney Transplantation

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ABSTRACT

Background: Chronic Kidney Disease (CKD) is a leading cause of mortality worldwide, particularly in Indonesia, so it requires effective treatment options like kidney transplantation. Optimal fluid therapy during the perioperative period is important for stable hemodynamics and graft function. However, guidelines for fluid administration remain lacking.

Objective: This study investigates the association between fluid therapy and changes in hemoglobin levels in patients undergoing renal transplantation.

Methods: A retrospective observational cross-sectional study was conducted at RSUP Prof. DR. I.G.N.G. Ngoerah Denpasar from January 2016 to August 2024. Data were collected from medical records of patients who underwent kidney transplantation, excluding those with incomplete data. Key variables included daily fluid intake and hemoglobin levels. The coefficient of variance was calculated and continued with correlation analyses utilizing Pearson correlation and linear regression to assess relationships between fluid administration and hemoglobin changes.

Results: Of 28 patients, 10 met inclusion criteria, consisting of 4 males and 6 females. Analysis showed a strong correlation between the variance of fluid intake and the variance of hemoglobin levels ($R = 0.86$; $R^2 = 0.74$; $P < 0.001$).

Conclusion: This study demonstrates a significant relationship between post-operative variance of fluid administration and variance of hemoglobin levels following kidney transplantation. It may have an impact on the management of post-operative reduction in hemoglobin levels.

Keywords: Fluid, Hemoglobin Changes, Kidney Transplant, Association, Perioperative.

Introduction

Chronic Kidney Disease (CKD) has become one of the leading causes of death worldwide, especially in Indonesia. Hypertension and Diabetes Mellitus have been identified as the main contributing factors. End-Stage Renal Disease (ESRD), or late stage of CKD, requires renal replacement therapy, such as hemodialysis, peritoneal dialysis, or kidney transplantation. Kidney transplantation is one of the most effective therapies, as it can restore the excretory, secretory, and endocrine functions of the kidney nearly perfectly. The kidney donor may come from a living donor or a cadaveric donor.[1,2]

Administering optimal fluid therapy to achieve stable hemodynamics during kidney transplant surgery is important. Proper fluid

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administration can increase microvascular flow, give a better oxygen distribution, and prevent cellular hypoxia, leading to immediate graft function. It also helps avoid hypovolemia during the perioperative period. However, there is no standardized guideline specifying how much fluid should be given during the perioperative period after a kidney transplant.[3,4]

The old theory suggested that providing fluids to fulfill the kidney's need for 25% of cardiac output would optimize graft function. However, this approach increases the risk of hypervolemia and pulmonary edema. Several studies have compared various parameters, such as Central Venous Pressure (CVP) and Mean Arterial Pressure (MAP), to assess fluid adequacy, but no definitive numbers have been established, making fluid administration more individualized. Retrospective studies on kidney transplant patients indicated that intraoperative CVP values of less than 8 mmHg, even reaching less than 6 mmHg, were significant predictors of delayed graft function or primary non-function. A retrospective study of 1,966 patients showed that CVP above 11 mmHg was a predictor of chronic graft dysfunction, while fluid administration of more than 2,500 mL was an independent risk factor for graft failure. Other prospective and retrospective studies suggested that aggressive fluid administration during graft ischemia, increasing CVP from 5 mmHg to 15 mmHg, was associated with better graft function, reduced use of vasopressors and diuretics, and less post-operative tissue edema.[3–5]

Fluid administration may also trigger a relative, but not absolute, condition known as dilutional anemia, characterized by decreased hemoglobin concentration. Iatrogenic hemodilution is often seen in critically ill patients receiving colloid therapy as part of perioperative treatment goals, where there is no increase in cardiac output after intravenous fluid loading. In septic shock patients receiving fluid therapy to reach a target CVP of 8–12 mmHg, MAP of 65–70, urine output of >0.5 mL/kg/hr, and oxygen saturation >70% within the first 6 hours, a complete blood count often reveals a 30% reduction in hematocrit within 3 hours post-resuscitation. The administration of 500 ml IV fluid can reduce hemoglobin level by 1 gr/dL.[5,6] Iatrogenic hemodilution can increase the risk of unnecessary blood transfusions without significant bleeding. In a randomized controlled trial (RCT) study comparing patients receiving goal-directed therapy (GDT) with a control population, it was found that the GDT group had twice the rate of blood transfusions. It was concluded that many patients in the GDT group experienced a drop in hemoglobin levels below the threshold for transfusion due to hemodilution.[6–8]

Kidney transplant patients also receive large volumes of fluid during the perioperative period to prevent delayed graft function. However, no studies have explored the association between fluid administration and changes in hemoglobin levels during the perioperative period following kidney transplantation. This study investigates the correlation between fluid administration and hemoglobin changes to avoid unnecessary blood transfusions without signs of significant bleeding.

Methods

Design and participants

This retrospective observational cross-sectional study involves all patients who underwent kidney transplantation at RSUP Prof. DR. I.G.N.G. Ngoerah Denpasar from January 16, 2016, to August 31, 2024. Data were collected from medical records, and patients with incomplete data were excluded. Descriptive statistical analysis was performed on social patient data, including age, sex, relationship with the donor, human leukocyte antigen **(**HLA) matching, baseline hemoglobin levels, daily hemoglobin levels, and the amount of fluid administered daily during hospitalization. The variables studied were hemoglobin levels and daily fluid intake.

Ethics approval and consent to participate

Not applicable.

Data collection

Data were gathered from medical records, with patients with incomplete information excluded. A descriptive statistical analysis was conducted on social patient data, encompassing factors such as age, sex, relationship with the donor, human leukocyte antigen (HLA) matching, baseline hemoglobin levels, daily hemoglobin levels, and the amount of fluid administered daily during hospitalization. The study focused on the variables of hemoglobin levels and daily fluid intake.

Statistical analysis

A coefficient variation analysis was conducted for both parameters to assess the variability of hemoglobin levels and fluid intake in each sample. The linearity of the results was analyzed using Pearson correlation and linear regression, as well as nonlinear correlation (power correlation), to determine the correlation coefficient (R), coefficient of determination (R^2), and regression coefficient (B). A p-value of less than 0.05 was considered statistically significant. The data were presented in the form of box plots and scatter plots.

Results

A total of 28 patients with chronic kidney disease underwent kidney transplant surgery at RSUP Prof. DR. I.G.N.G. Ngoerah Denpasar, consisting of 17 male and 11 female patients, with a mean recipient age of 31.14 (±7.26) years. Of these, 18 patients were excluded due to incomplete data, leaving only 10 patients in the study. Table 1 shows the basic characteristics of the patients.

Table 1. Characteristics data of patients

Characteristics	Mean	SD	n
Age	28.9	5.54	
Sex			
Male			4
Female			6
Body mass index (BMI)	23.52	2.01	
Hemoglobin (g/dL)	12.26	1.54	
Creatinine (mg/dL)	13.91	2.58	
HD Duration (mo's)	37.8		
Relation with donor			
Father			4
Mother			5
Sibling			1

Hemoglobin levels and the amount of fluid administered after kidney transplant surgery were recorded and analyzed to determine the average values, standard deviation, and co-efficient of variation. Table 2 below shows the daily hemoglobin levels and the daily fluid intake.

Table 2. Daily hemoglobin levels and daily fluid intake

		N	Mean	SD	Minimum	Maximum
Fluid intake (ml/24h)	1	10	8,246	3,625	4,005	15,167
	2	10	6,703	3,395	3,625	15,670
	3	10	5,555	1,539	3,650	8,960
	4	10	5,720	1,685	3,225	8,766
	5	10	5,948	2,056	3,830	9,950
	6	10	5,552	1,375	3,280	7,100
	7	10	5,825	2,245	3,300	11,100
	8	10	5,989	1,593	3,590	9,180
	Total	80	6,192	2,386	3,225	15,670

Cont.

Hb (g/dl)	1	10	11.2	2.1	8.1	14.5
	2	10	9.5	2.1	6.1	12.3
	3	10	8.7	1.9	5.4	11.2
	4	10	8.8	1.8	5.7	12.4
	5	10	9.2	1.1	7.1	10.5
	6	10	9.4	1.0	7.5	10.5
	7	10	9.2	1.4	7.0	11.3
	8	10	9.5	1.8	7.1	12.8
	Total	80	9.5	1.8	5.4	14.5

The changes in hemoglobin levels per day and the amount of fluid intake can be seen in the following figures 1 and 2.

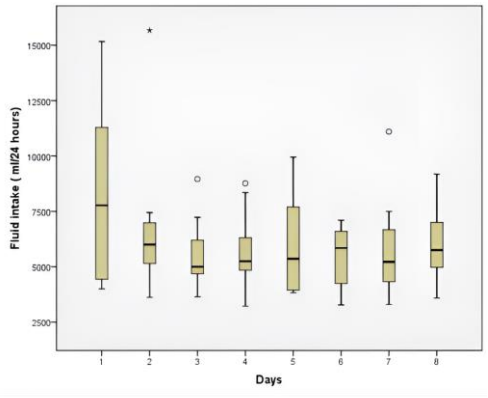

Figure 1. Changes in fluid intake per day

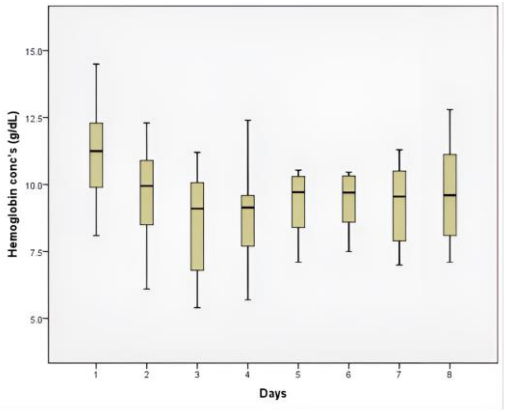

Figure 2. Changes in hemoglobin per day

Figure 1 shows that the fluid intake has the largest variance range on the first day, which then decreases and tends to stabilize on the second, third, and fourth days. It increases again on the fifth day before stabilizing until the eighth day. Meanwhile, in Figure 2, hemoglobin levels show a downward trend, reaching their lowest point on the third day before rising again until the eighth day. An analysis was conducted to determine the coefficient of variation for daily fluid intake and hemoglobin levels, as shown in Table 3.

Table 3. average and standard deviation of fluid intake and hemoglobin levels, as well as coefficient of variation for each patient

No.	Mean*	SD*	Mean**	SD**	CoV*	CoV**
1.	6,389	2,271	10.96	1.11	0.36	0.10
2.	8,467	4,520	10.45	0.95	0.53	0.09
3.	5,000	1,223	9.75	0.76	0.24	0.08
4.	6,778	1,758	7.77	1.39	0.26	0.18
5.	5,913	1,742	11.36	1.43	0.29	0.13
6.	5,652	1,780	11.45	1.37	0.32	0.12
7	5,900	1,106	8.98	0.68	0.19	0.08
8.	8,625	1,900	7.53	0.85	0.22	0.11
9.	4,584	890	8.34	1.71	0.19	0.21
10.	4,614	1,086	8.41	1.35	0.24	0.16

*Fluid intake (ml/day); **Hb level (g/dL)

Using Pearson Correlation and Linear Regression, followed by a power correlation test, the results showed a strong relationship between the coefficient of variation for fluid intake and the coefficient of variation for hemoglobin levels ($R = 0.86$; $R^2 = 0.74$; $B = 0.38$; $P < 0.001$), as illustrated in the line diagram below (Figure 3).

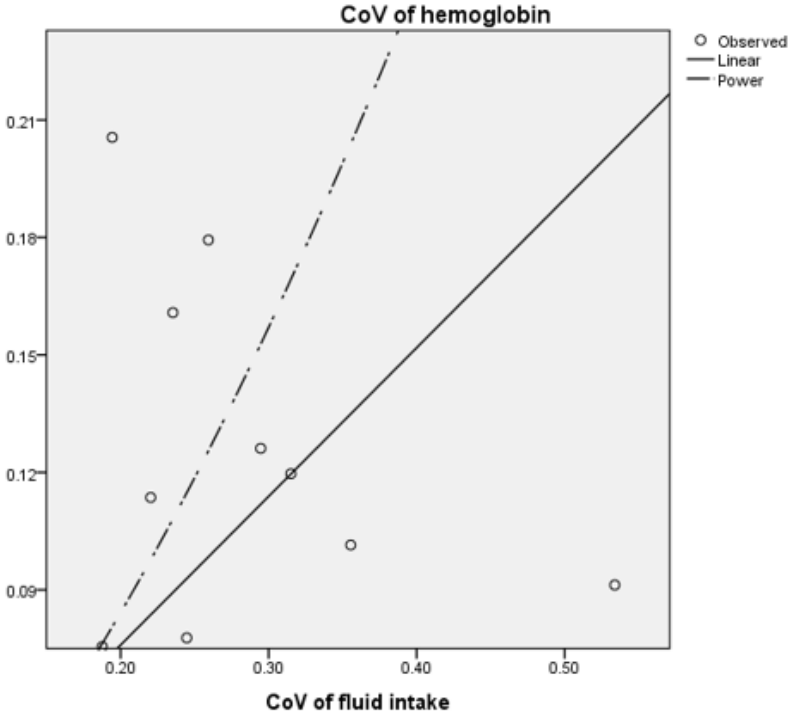

Figure 3. The relationship between the coefficient of variation for fluid intake and variance of hemoglobin levels was analyzed using linear regression ($R = 0.86$; $R^2 = 0.74$; $B = 0.38$; $P < 0.001$) and power correlation ($R = 0.96$; $R^2 = 0.91$; $B = 1.54$; $P < 0.001$).

Discussion

Optimal fluid administration targets achieving immediate graft function, which is the most critical aspect of perioperative management after kidney transplantation. Since there is no standardized consensus or guidelines on the exact volume of fluid that should be administered, the amount of fluid given is individualized for each kidney transplant recipient. It is known that administering 500 ml of fluid can result in a hemoglobin decrease of 1 g/dL, a condition known as relative and temporary hemodilution. However, hemodilution can reduce the oxygen delivery capacity to tissues due to the lowered hemoglobin levels.[4–6,8]

In major surgery, preoperative fluid administration to achieve acute normovolemic hemodilution (ANH) is often to be done. The main concept is that exchange with crystalloids or colloids is given for every blood loss to maintain normovolemia. The target hematocrit with ANH is variable, but it is often around 25% to 30%. More extreme hemodilution is likely to be more efficacious in preventing allogenic blood transfusion, but the risks are greater, particularly in some patients with pre-existing medical conditions. Hemoglobin concentrations are influenced by plasma. An increase in the plasma volume by the intravenous administration of fluids may cause significant hemodilution and decreased hemoglobin levels. Critical hemoglobin level denotes the efficacy of ANH, and for humans, the decrease of hemoglobin levels between 4 to 5 gr/dL was considered safe.[9,10]

To our knowledge, our study is the first to investigate the effect of fluid administration in

the perioperative period after kidney transplantation on hemoglobin. This study observed a strong relationship between the decrease in hemoglobin levels and fluid administration to achieve immediate graft function. This hemoglobin decrease is temporary and will recover on its own without the need for blood transfusion. Iatrogenic hemodilution, which is temporary, was confirmed during the perioperative period after kidney transplantation in this study. Careful monitoring is necessary to avoid unnecessary blood transfusions.

Conclusion

There is a relationship between perioperative fluid administration after kidney transplantation and a temporary decrease in hemoglobin levels, suggesting that blood transfusion should only be administered when significant bleeding is evident.

Limitations of the Study

This study is a preliminary observation of hemodilution during the perioperative period after kidney transplantation, and it has limitations, including a small sample size and the lack of analysis regarding intraoperative bleeding and the volume of fluids administered during the procedure.

Declarations

Ethics approval and consent to participate

Not applicable.

Competing interests

There are no conflicts of interest in writing this article.

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None.

Author's Contribution

Idea/concept: AS. Design: AS. Control/supervision: IGRW, GWM, YK, NPA, IGNATE. Data collection/processing: AS. Analysis/interpretation: AS, IGRW. Literature review: AS. Writing the article: AS. Critical review: IGRW, AS. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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Review Article

Pathogenesis of Immune-Mediated Glomerulonephritis

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ABSTRACT

Most forms of glomerulonephritis (GN) are characterized by a pathogenic immune response, which is mediated by the action of various immune system elements, both innate and adaptive. What is clear is that the immunopathogenesis of GN is very broad and complex. Deposits of immune complexes in the glomeruli activate complement and glomerular injury due to the involvement of circulating inflammatory cells and glomerular intrinsic cells, ultimately resulting in a wide variety of clinical manifestations, which depend in part on the location and immunopathology of the patient, including genetic and environmental factors, from asymptomatic to rapidly progressive GN. Most of the treatment strategies for GN are non-specific, consisting of corticosteroids and cytotoxic agents. Thus, an advanced understanding of GN immunopathogenesis may offer many opportunities for future therapeutic interventions on an individual basis. To further facilitate understanding of the pathogenesis of GN, the author also includes a graphical abstract.

Keywords: Antibody-Mediated Glomerular Injury, Humoral and Cellular Component, Circulating Inflammatory Cells, Intrinsic Glomerular Cells Injury, Permeability Factors.

Introduction

A substantial body of immunological, clinical, and experimental data supports the hypothesis that immunological mechanisms are the primary cause of most forms of human glomerulonephritis (GN).[1] The etiology of GN in humans remains largely unidentified and elusive.[2,3] The development of immune responses that can cause GN is influenced by genetic predisposition in certain individuals.[4–6] The unique glomerular physiology also facilitates trapping immune aggregates or exogenous antigens in the glomerular capillaries. Indeed, the immunopathogenesis of GN is broad and complex, involving a nephritogenic immune response, both cellular and humoral, resulting in diverse clinical and pathological manifestations, ranging from asymptomatic urinary abnormalities to acute kidney injury (AKI) or end-stage renal disease (ESRD).[1,7] The humoral immune response causes immunoglobulin (Ig) deposition to form, subsequently triggering an inflammatory response by activating the complement factor cascade.[1,8] Meanwhile, the cellular immune facilitates the infiltration of circulating mononuclear inflammatory cells in the glomerulus and crescent formation.[9] There is a close and integrated interaction between intrinsic glomerular cells under physiological and illness or injury conditions.[10] In inflammatory lesions, glomerular hypercellularity may be seen due to infiltration of hematopoietic cells (mainly macrophages and neutrophils), intrinsic

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glomerular cell proliferation, or a combination of both. These effector cells further instigate various pathological changes, including thrombosis, necrosis, and crescent formation, potentially culminating in renal insufficiency and rapidly progressive GN (RPGN). Meanwhile, non-inflammatory lesions caused by immune injury typically involve podocytes as the primary effector cells and are associated with increased protein permeability.[9]

A further understanding of GN's pathogenic mechanisms can lead to more appropriate diagnostic considerations and treatment options for the halting or interrupting pathophysiology underlying individual disease, which causes significant and progressive glomerular disease. The author has also included a graphical summary at the end of this article to facilitate better understanding.

The role of glomerular physiology in immune-mediated injury

The glomerulus can be thought of as a "capillary network" that produces ultrafiltrate. Glomerular filtration is determined by glomerular blood flow and ultrafiltration pressure, regulated by arterial tone, which generates a pressure gradient, and the filtration surface area, which is affected by mesangial contractility. With their fenestrations, glomerular endothelial cells (GECs) can prevent blood cell filtration but cannot prevent water movement. The glycocalyx covers the GEC, which contains negatively charged glycosaminoglycans, which block the diffusion of negatively charged molecules and have anti-thrombotic and anti-adhesive properties. The glycocalyx is also crucial in regulating capillary permeability, mediating interactions between leukocytes and GECs, and transducing shear stress.[11]

Overall, the glomerular endothelium (with the glycocalyx), glomerular basement membrane (GBM), and podocytes collectively constitute the glomerular filtration barrier (GFB). This specialized structure facilitates the substantial filtration of solutes and water while also acting on the physicochemical and electrostatic charge of a molecule. Although the structure of the glomerular capillaries is typically designed to serve as a barrier to the passage of solutes, especially proteins, on the other hand, they are vulnerable to inflammatory injury from various causes, resulting in multiple causes of GN.[12] Conditions that can increase the vulnerability of the glomerulus to injury include: (1) the kidneys receiving 25% of high cardiac output; (2) high hydrostatic pressures within the glomerular capillaries; (3) highly fenestrated endothelium; and (4) sieving effect of glomerular filter. These conditions can maximize contact between reactants and GBM and concentrate substances potentially injuring the glomerulus, including circulating antigen-antibody complexes. The filtering ability of the glomerular capillaries for solutes is inversely related to the size of the substance. Large negatively charged molecules will be more readily filtered than positively charged molecules of the same size.[13] The inherent characteristic physiological conditions of the glomerulus will make it easier for the filtered substances to be trapped in certain places in the glomerulus, which in turn can trigger pathological processes in the kidney.

Components of the nephritogenic immune response in glomerular injury

A. **Humoral component**. The leading cause of glomerular injury is the humoral immune response. This glomerular injury is mediated by immune complexes (ICs) containing Ig and components of complements. This immune-mediated injury can occur directly, i.e., antibodies with intrinsic antigens (endogenous antigens as fixed-antigens), or indirectly, i.e., antibodies with embedded exogenous antigens (implanted antigens) and entrapment of circulating antigen-antibody complexes.[14] Immune deposits form as a result of antibodies targeting these antigens:

   a. Normal glomerular constituents

   - In anti-glomerular basement membrane (anti-GBM) disease:

interactions between antibodies and glomerular intrinsic antigen (as Goodpasture antigen), i.e., type IV collagen alpha-3 chains.[15,16]

- In membranous nephropathy (MN): interaction of antibodies against podocyte-specific antigens, such as phospholipase A2 receptor type-M (PLA2R), thrombospondin type-1 containing domain 7A (THSD7A)[17,18], and the third antigen, consisting of exostosins 1 and 2 (EXT1 and EXT2), neural epidermal growth factor-like 1 (NELL-1), neutral endopeptidase (NEP), Semaphorin 3B (Sema3B), protocadherin-7 (PCDH7), high-temperature recombinant protein A1 (HTRA1) and neural cell adhesion molecule 1 (NCAM-1).[19]

- In congenital nephrotic syndrome Finnish type (CNF): anti-nephrin antibodies in the diaphragmatic cleft can induce proteinuria without immune deposits and inflammation.[20]

b. Non-glomerular endogenous antigens localized to glomeruli

- In lupus nephritis (LN): DNA nucleosome complexes.[21]
- In IgA nephropathy (IgAN): abnormally glycosylated IgA.[22]
- On antineutrophil cytoplasmic antibody (ANCA) - associated vasculitis (AVV): myeloperoxidase (MPO) or proteinase 3 (PR3).[23]

The localization of non-glomerular endogenous antigens within the glomeruli occurs due to passive trapping through their interaction with the glomerular capillary wall, i.e., at negatively charged sites or through spontaneous aggregation.[9]

c. Immune aggregates or exogenous antigens localized in the glomerular capillaries. This process occurs through various mechanisms, including passive trapping, local precipitation of macromolecular aggregates, or loading affinity for glomerular structures.

- In membranoproliferative GN (MPGN) associated with hepatitis C virus (HCV): Cryoglobulin containing HCV antigen.[24]

However, in asymptomatic individuals, autoantibodies to MPO, PR3, and GBM may also be found, and anti-PLA2R antibodies may develop months or years before the onset of MN.[25] This shows that humoral immunity to target antigens does not always show pathogenicity.

B. **Cellular components.** Pathogenic T-cell responses in immune-mediated GN are linked to the most severe forms of GN, i.e., crescentic GN (cGN), which pathologically consists of immune complex (IC), pauci-immune, and anti-GBM GN. T helper-1 (Th1) cells recruit monocytes to the kidney by promoting the expression of chemokines in glomerular intrinsic cells. Further, an increase in interferon ɣ (IFNɣ) by activated Th1 cells and glomerular intrinsic cells promotes macrophage recruitment and differentiation of monocytes into inflammatory M1 macrophages, which mediate tissue damage and crescent formation. T helper-2 (Th2) cells are involved in driving immune complex deposition, which subsequently induces glomerular infiltration of neutrophils. These neutrophils contribute to tissue damage through reactive oxygen species (ROS) production, neutrophil extracellular traps (NET) formation, and serine protease degranulation.[26]

Immune mechanism responses to glomerular injury

A. Inflammatory injury. The cellular inflammatory response occurs due to the deposit of immune complexes with the

activation of complement factor cascades in the glomerulus.[8,27] The inflammation it causes is influenced by the site where the IC deposits occur. For example, IC is deposited on the GBM in anti-GBM antibodies disease, subendothelial deposition in class III or IV LN and MPGN, and deposits in the mesangium in IgAN and LN.[9] Besides occurring due to the influence of IC deposits, severe inflammation can also happen without IC deposits, as seen in conditions like vasculitis (ANCA-positive necrotizing GN).[1] In the presence of inflammatory changes, glomerular hypercellularity results from the infiltration of macrophages and neutrophils, proliferation of intrinsic glomerular cells, or both. Furthermore, these effector cells can further contribute to necrosis, thrombosis, and crescent formation, leading to renal insufficiency and RPGN.[1]

B. **Non-inflammatory injury**. Non-inflammatory lesions caused by immune injury typically involve podocytes as primary effector cells, leading to increased glomerular permeability to albumin and other proteins without detectable light microscopic damage.[1] The main clinical features of this non-inflammatory glomerular lesion are proteinuria and nephrotic syndrome (NS).[9]

Effector cells and mediator in the inflammatory GN

The inflammatory response involves the coordinated activation of signaling pathways that control the production of inflammatory mediators in resident tissue cells and blood-derived recruited inflammatory cells.[28] This mechanism is commonly observed in inflammatory response processes, as with glomerular injury. The glomerular injury also typically driven by the activation of effector cells (i.e., neutrophils, macrophages, natural killer (NK) cells, T cells, and platelets as well as glomerular intrinsic cells) and release of inflammatory mediators (i.e., complement activation products, oxidants, and proteases; and various cytokines, chemokines, growth factors (GFs), and other vasoactive agents).[2,9,29]

A. Role of circulating inflammatory cells

Role of Neutrophils - Neutrophils are among the first leukocyte subsets recruited to deposit IC, consisting of autoantibodies or antibodies essential in promoting glomerular injury.[30] This is evidenced by the presence of neutrophils in kidney biopsies from patients with antibody-mediated GN such as PSGN, MPGN, IgA vasculitis (Henoch-Schoenlein purpura), LN, anti-GBM disease, and some forms of cGN.[31] Based on its cellularity, GN can be classified into two categories: proliferative forms due to the influx of immune cells and intrinsic cell proliferation and non-proliferative forms. Leukocytes play a central role in developing proliferative GN at multiple levels, including influencing the development of adaptive and humoral immune responses and modulating local effector mechanisms that directly contribute to glomerular damage.[30] Although the role of neutrophils in glomerular injury is recognized, the molecular mechanisms underlying immune complex-mediated recruitment of neutrophils in the glomerulus, where capillaries serve as the main site of leukocyte recruitment, remain indeterminate.[32] In general, some of the important roles of neutrophils in glomerular injury include:

- Neutrophils phagocytose immune complex aggregates, leading to their activation and the initiation of a respiratory burst that produces ROS. These ROS contribute to glomerular injury by interacting with MPO, a cationic enzyme derived from neutrophils that localizes in the glomerulus due to its positive charge.[9]

- Neutrophils are the storage site for cationic serine proteases, including cathepsin G and elastase, in azurophilic granules, released upon neutrophil activation, which can further degrade elements of the glomerular capillary wall.[9]

- Neutrophils generate NETs, as in AGN and LN. NETs are net-like histone structures decorated with peptides, proteases, and enzymes, which are also detrimental.[33]

- Role of neutrophils in ANCA-associated vasculitis (AAV)— Neutrophil involvement in AAV is linked to cationic proteases, PR3, and MPO, localized in neutrophil primary granules. Upon activation by certain cytokines, these proteases are translocated to the surface of neutrophils, making them accessible to circulating ANCA antibodies targeting PR3 or MPO, contributing to the pathogenesis of glomerular injury.[9,34]

Role of Macrophages — Macrophages are innate immune cells and major components of the mononuclear phagocytic system. They are involved in numerous cellular processes crucial in maintaining tissue homeostasis.[35] IC or cells of the adaptive immune system (T lymphocytes and their cytokines) can activate macrophages. In renal disease, macrophage activation is typically secondary to the activation of complementary or effector T cells, which are triggered by antigens that are not specific to the kidney. This suggests that macrophages may not be the primary initiators of renal disease.[36] However, in immune-mediated GN, there is an increased number of macrophages in the kidney.[37] In some glomerular lesions, especially those showing crescent formation, macrophages are the prominent constituents.[29,38] The following aspects should be addressed regarding the role and function of macrophages in human GN:

- In proliferative GN, the number of glomerula macrophages correlates with disease severity. Macrophages were observed in the glomerular tuft in nearly all types of GNs, whose staining varied from "positive" to "intense." The intensity of this stain correlates with the cellular intensity of the glomerulus, either intrinsic glomerular cells or circulating inflammatory cells. Macrophage staining was more intense on cGNs, i.e., LN and AAV, whereas staining was less intense on less proliferative GNs, i.e., IgAN and MN.[39]

- In most severe lesions, macrophages are localized in the glomeruli. AGN and cryoglobulinemia GN are 2 diseases characterized by comparable massive macrophage glomerular infiltration, though they differ in their localization. In AGN, macrophage accumulates mainly in areas of extra-capillary proliferation (crescent) and granulomatous glomerular lesions. Contrarily, in cryoglobulinemic GN, macrophages are more homogeneously distributed throughout the glomerular tufts but are absent from the periglomerular interstitium.[38]

- Macrophages are recruited to glomeruli and glomerular lesions by chemokines secreted by intrinsic glomerular cells. Monocyte chemoattractant protein-1 (MCP-1) has been identified in IgAN, LN and GPA. Additionally, MCP-1 and its chemokine receptor 2B (CCR2B) are expressed in human cGN, with CD68+ cells being the primary glomerular cell type that expresses CCR2B.[40] Macrophages are also easily recruited by molecules derived from lymphocytes, like macrophage migration inhibitory (MIF), produced during interactions between T cells, particularly those with specific sensitivities and intraglomerular antigens.[41]

- Macrophages that are attracted become activated in proliferative glomerular lesions. In addition to differences in number and localization, AGN and cryoglobulinemic GN macrophages exhibit significant differences in cytokine production, activation, adhesion, and proliferation. De novo production of glomerular vascular cell adhesion molecule 1 (VCAM-1) was observed exclusively in AGN and was restricted to necrotizing extra-capillary lesions.[38] Likewise, the production of TNF-α and IL-1β is prominent in AGN. AGN differs from cryoglobulinemic GN in macrophage properties, contributing to its more severe disease progression. Macrophages are also seen in Henoch-Schönlein syndrome, necrotizing IgA nephritis, and GN associated with endocarditis and have not been seen in other glomerular diseases.[42,43]

Overall, it has been shown that acute macrophage activation immediately affects the production of proinflammatory cytokines in the glomeruli and adhesion molecules in the endothelium, thereby exacerbating the severity of the disease.[39] In addition, macrophages release tissue factor, which triggers crescent formation and fibrin deposition, as well as transforming growth factor (TGF)-ß, leading to extracellular matrix (ECM) synthesis and development of glomerular sclerosis.[9]

Role of T Cells – T cells are detectable in conditions primarily characterized by macrophage-mediated mechanisms, such as cGN.[2,29,31] The functional role of T cells in cGN pathogenesis was first demonstrated in a study of athymic nude mice treated with human renal GBM. This study demonstrated that without T cells, neither autologous anti-GBM antibodies nor glomerular injury developed.[44] The significance of T cells in LN disease pathology was highlighted in MRL-lpr mice. T cell depletion led to less severe renal disease in this genetic autoimmune model mice strain.[45] The important role of CD4+ T cells in disease pathology was also demonstrated in anti-MPO GN. In this context, depletion of CD4+ T cells reduced renal immune cell infiltration and mitigated cGN.[46,47]

While experimental evidence suggests that systemic T cells can induce glomerular injury without antibody deposition, evidence supporting that glomerular T cells alone are nephritogenic is limited, except for T cell-derived permeability factors.[48,49] T-cell-mediated injury primarily presents through the release of chemokines and the subsequent recruitment of macrophages, which serve as effector cells.

Role of T helper 17 cells. All T cell subsets are involved in GN, but IL17-producing T helper 17 (Th17) cells are likely the primary contributors to T cell-induced inflammation. Th17 cells in kidney biopsies in several forms of human GN.[50] These cells also facilitate anti-MPO-mediated GN through the secretion of IL-17a. IL-17a-deficient mice are protected against anti-MPO-mediated GN and have reduced accumulation of renal macrophages.[51] Th17 cells are recruited via chemokine and receptor interactions, releasing cytokines including IL9, IL17, IL21, IL22, and TNFα. These cytokines stimulate other cells to produce additional proinflammatory chemokines, attracting neutrophils and monocytes while activating intrinsic glomerular cells.[50]

Role of Regulatory T Cells — In contrast to effector T cells like Th17 cells, which exacerbate glomerular injury, regulatory T cells (Tregs) have been shown to aid in injury repair and promote tolerance.[52–54] Tregs are known to suppress innate and adaptive immune responses in the kidney, and abnormalities in their number or function have been reported in certain forms of GN.[55]

Tregs were identified as T-cells that express high levels of the IL-2 receptor alpha (CD25) and the transcription factor forkhead box P3 (Foxp3), a hallmark of their control function of Treg cells. IL-2 is the master regulator of Treg, and a deficiency in IL-2 has an important influence on decreasing the number and function of Treg cells.[52,56] The functions of Tregs include controlling innate and adaptive immunity, regulating cell damage, and promoting repair.[52] In SLE, there is immune dysregulation, with deficiency of IL-2 production, excessive production of proinflammatory cytokines, and resistance to Treg-mediated suppression. Given the role of Tregs, many new therapeutic strategies are currently being developed that target Treg enhancement. It has been demonstrated that the cytokines IL-2, IL-2/mCD25, IL-6, and IL233 directly promote strong Treg expansion, preventing autoimmunity and LN.[52]

Role of Platelets - Some glomerular lesions have prominent platelets, especially in lesions involving intraglomerular thrombosis, such as thrombotic microangiopathy and anti-phospholipid antibody syndrome. While platelets are best known for their involvement in thrombotic processes associated with endothelial cell injury, they also secrete various bioactive substances that contribute to and exacerbate

glomerular injury. These include chemotactic, mitogenic, and vasoactive substances.[9]

A. Role of Glomerular Intrinsic Cells Injury

Endothelial, mesangial, parietal epithelial, and visceral epithelial cells (podocytes) in the glomerulus all have unique and specific roles, which are essential for the normal functioning of the glomerulus. However, these glomerular intrinsic cells are also the main target of various disease processes, including immune injury. Response to injury depends on the damage's duration, nature, and magnitude. An overview of the typical intrinsic cell responses to injury is provided in Table 1.[31]

Table 1. Key functions and responses to injury of intrinsic glomerular cells[31]

Cell Type	Normal Function and Features	Responses to Injury	Relevant Glomerular Diseases (Examples)
Mesangial cells	Maintain structural architecture of glomerulus Mesangial matrix homeostasis Regulate filtration surface area Phagocytose apoptotic cells	Lysis with healthy remodeling Apoptosis Hypertrophy Proliferation and matrix expansion leading to glomerulosclerosis	IgA nephropathy Diabetic nephropathy
Glomerular endothelial cells	Fenestrations and glycocalyx facilitate selective permeability and filtration	Apoptosis Loss of fenestrations Widening of cell-cell junctions, transcellular holes Glycocalyx damage, loss of GAG synthesis	ANCA-associated GN Lupus nephritis (Class III and IV) Hemolytic uremic syndrome Diabetic nephropathy
Podocytes	Foot processes wrap around capillaries Adherence to GBM Slit diaphragm regulates filtration	Apoptosis Foot process effacement Detachment from GBM, podocyte loss Loss of slit diaphragm	Minimal change disease FSGS Diabetic nephropathy
Parietal epithelial cells	Line Bowman's capsule Several subsets of cells likely with different functions Subset of cells may be able to differentiate into podocytes and play a reparative function	Apoptosis Migration to glomerular tuft, production of ECM proteins leading to glomerulosclerosis Proliferation leading to crescent and pseudocrescent formation	Crescentic GN FSGS

GAG, glycosaminoglycan; GBM, glomerular basement membrane; ECM, extracellular matrix

There are intimate and integrated interactions among cellular components of the glomerulus under physiological conditions and in disease or injury. Podocytes, mesangial cells, and endothelial cells engage in complex, multi-directional cross-talk both among themselves and with leukocytes.[10] Although a particular disease may primarily target a particular cell type, it typically indirectly affects other cells.[31] Podocyte injury can lead to mesangial cell proliferation, while mesangial cell injury can result in thinning and fusion of podocyte foot processes. Additionally, signals from mesangial and endothelial cells are essential for the normal function of podocytes.[57]

a. **Injury of glomerular endothelial cells (GEC).** GECs, with their unique properties and functions as previously described, are more prone to become major targets of injury in hemolytic uremic syndrome, certain forms of vasculitis, and preeclamptic toxemia in pregnancy.[58] GECs injury can lead to cell proliferation, detachment, apoptosis, adhesion of leukocytes, and thrombosis.[59,60] The above conditions underlying GEC injury are commonly associated with proliferative GN, which may mediate the progression of cGN. The proliferation of mesangial and endothelial cells, along with leukocyte infiltration, causes endocapillary proliferation, resulting in narrowing and occlusion of the glomerular capillary lumen.[61]

b. **Injury of glomerular mesangial cell.** Glomerular mesangial cell injury is observed in IgAN and LN, where immune deposits occur and involve the mesangium.[62,63] Mesangial cell activation generally results in proliferation and hypertrophy, production of ROS, and excessive matrix production.[62] Mesangial cell activation also produces cytokines and chemokines, which influence mesangial and glomerular cells and other leukocytes. In response, these leukocytes release mediators that affect the mesangial cells, forming a paracrine loop.[63] The expansion of the mesangial matrix and the release of vasoactive mediators lead to a decrease in glomerular surface area and changes in glomerular hemodynamics, ultimately decreasing GFR.[62,63] Several mediators have been identified that can activate mesangial cells, i.e., cytokines, GFs; C5b-9, the complement MAC; immune complexes, and ROS.[9]

c. **Injury of glomerular parietal epithelial cell (PEC).** Compared with the other 3 intrinsic glomerular cell types, the occurrence of well-defined glomerular disease primarily due to abnormalities arising in PECs is lacking.[64] However, evidence based on GN mouse models targeting early injury to glomerular endothelial cells and GBM suggests that the ensuing proliferation of glomerular PEC results in a significant increase in cell numbers within the crescent.[65] This is consistent with the main feature of cGN, i.e., PEC proliferation.[9] Besides proliferating, activated PEC (which is induced by fibrin) also migrates and produces ECM.[66,67] The proliferated or increased PECs can attenuate urine flow and release cytokines and chemokines, which can interfere with the function of the affected glomerulus. Conversely, PEC may migrate from Bowman's capsule to capillary bundles and differentiate into podocytes in response to injury.[68,69] It suggests a regenerative and reparative role when podocytes are lost. PECs presenting cellular crescents undergo epithelial-to-mesenchymal transition (EMT) with increased ECM synthesis, which ultimately leads to the formation of classical honeycomb-like lesions.[70]

d. **Injury of glomerular visceral epithelial cells (podocyte).** Podocytes are the most sensitive component of the glomerulus to injury and are frequently damaged or dysfunctional.[71] Besides their important role in preventing proteinuria, podocytes also contribute to crescent formation through the formation of cellular masses due to proliferation.[72,73] Podocyte injury may also be involved in PEC proliferation and crescent formation by reducing the expression of Krüppel-like factor 4, a zinc-finger transcription factor critical for maintaining

podocyte homeostasis and keeping PEC in a quiescent state.[74,75]

During development and in various forms of renal pathology, podocytes, and PEC are interdependent. Rapid loss of podocytes in diseases, including RPGN and collapsing and cellular subtypes of FSGS, is associated with the proliferation and migration of PEC toward capillary bundles, leading to the formation of crescents and pseudo-crescents.[76] The occurrence of severe proteinuria in IgAN is another illustration of the interaction between various glomerular cell types. Mesangial expansion can cause compression of individual podocytes leading to effacement of their foot processes, changes in the filtration slits, shedding of podocytes, and proteinuria.[77,78]

Role of the location of deposit immune complexes in glomerular injury

Different places or locations of injury in the glomerulus can give a different clinical picture according to the physiological function of each part of the glomerulus. Therefore, the primary factor in determining whether a patient develops nephritic or nephrotic syndrome is the site of glomerular injury.[9] Table 2 lists examples of GN caused by IC deposition.[14]

Table 2. Immune complex-mediated glomerulonephritis[14]

Location of glomerular immune complex deposits	Associated glomerulonephritides, with examples	Associated diseases involving loss of immune homeostasis, examples
Subendothelial	Membranoproliferative GN IgA nephropathy Lupus nephritis (classes III & IV)	Autoimmune disease (e.g., Sjogren's syndrome, scleroderma, SLE)
Mesangial	Membranoproliferative GN IgA nephropathy Lupus nephritis (classes I & II)	Autoimmune disease (e.g., Coeliac disease, SLE) Inflammatory disease (Crohn's disease)
Subepithelial	Membranoproliferative GN Infection-related GN MN Lupus nephritis (class V)	Autoimmune disease (e.g. SLE, anti-PLA2R disease)

- **Endothelial cells and glomerular mesangium**: Formation or deposition of IC in the subendothelial space or mesangial matrix often results in glomerular inflammation and nephritic syndrome (the subendothelial deposition of IC is more severe than the mesangium because the mesangium is relatively localized). Injury to the endothelium and subendothelial causes recruitment of leukocytes with consequent inflammatory GN, impaired hemostasis causing thrombotic microangiopathy, and vasoconstriction and contraction of mesangial cells, eventually leading to AKI. This deposition in the sub-endothelial causes the formation of chemotactic factors, which will attract infiltrating leukocytes and mononuclear cells. These cells will phagocytize ICs and release mediators such as chemo-kines and cytokines, which then cause inflammation of the glomerulus, which clinically displays active sediment in the urine, such as hematuria, pyuria, and proteinuria.[9]

- **Visceral epithelial cells or podocytes**: Injured podocytes will give the dominant picture through massive proteinuria and nephrotic range or NS (MCD; FSGS) and do not cause active inflammation.[9]

- **Subepithelial and basement membranes**. As with podocyte injury, injury or IC that deposits in the capillary wall adjacent to the podocytes (sub-epithelial deposits) does not produce an inflammatory response due to GBM, a separator of immune deposits from the systemic circulation.[9] Deposits of antigen-antibody complexes on the basolateral surface of podocytes activate the C5b-9 membrane attack complex (MAC), leading to oxidative damage and DNA injury to podocytes. This, in turn, results in damage to the actin cytoskeleton. Collapse of the actin cytoskeleton, loss of GBM adhesion, and loss of diaphragmatic cleft integrity lead to proteinuria.[79]

- **Parietal epithelial cell**. Injury to the parietal epithelial cells results in the formation of crescents, which are clinically indicated by a rapid decrease in glomerular filtration. This glomerular crescent formation is considered a non-specific response to severe injury to the glomerular capillary wall. This condition involves multiple upstream immune mechanisms, such as the deposition of autoantibodies and IC, complement activation, and recruitment of inflammatory cells.[80]

Role of other factors in glomerular injury

Apart from the location of glomerular injury as described above, other factors can cause glomerular injury, namely:

1. Biological properties of the Ig that forms the deposit. Inflammation is more severe when caused by IgG subtypes, such as IgG1 and IgG3, compared to IgA and IgG4, which activate complement poorly.[81]

2. Mechanism of deposit formation. Compared with passive trapping of circulating IC, local complement activation resulting from the formation of IC in situ is much more nephritogenic.[82,83]

3. The magnitude of the formation of immune deposits. A positive relationship exists between the amount of immune deposits and the degree of tissue injury.[9]

4. Recognized nature of the epitopes. There is a relationship between kidney injury and pathogenic antibodies to the linear epitope on the Goodpasture antigen.[84] Similarly, certain disease-specific MPO epitopes for active ANCA have been found[85,86], whereas other epitopes persist during remission or in healthy individuals.[85,86]

Despite immune deposits, significant tissue injury can occur due to immunoglobulin alone, as in patients with CNF, which is linked to

mutations in the nephrin gene, in which anti-nephrin antibodies can induce proteinuria without inflammation.[20]

Antibody-mediated injury without immune complex

Antineutrophil Cytoplasmic Antibodies - Associated Vasculitis (AAV)

AAV is a group of autoimmune disorders that includes granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA), and their localized forms.[87] The most common manifestation of AAV is ANCA-associated GN (AGN).[88] The clinical presentation of renal involvement in AAV includes proteinuria, hematuria, or RPGN, depending on the degree of vasculitic kidney damage. The extent of renal involvement in AAV varies based on the different ANCA serologies. Patients with PR3-ANCA showed minor kidney involvement compared to those with MPO-ANCA patients.[89,90] Conversely, patients with PR3-ANCA are more likely to experience extra-renal organ manifestations compared to those patients with MPO-ANCA.[91] The characteristic lesion in AGN patients is necrotizing crescent-immune GN, often presenting as crescentic or necrotizing GN without Ig deposition.[88]

The disease diagnosis is based on findings on ANCA staining, which can be either a cytoplasmic pattern (c-ANCA) or a perinuclear pattern (p-ANCA). c-ANCA is a neutrophil antigen, usually PR3, a constituent of primary neutrophil granules, whereas p-ANCA is usually an MPO antigen, another granule constituent that migrates to the perinuclear region.

C3 nephritic factor

C3 nephritic factor (C3NF) is a group of autoantibodies that allow continuous activation of alternative complement pathways.[92] This IgG autoantibody, C3NF, stabilizes C3 conversion, causing uncontrolled C3 activation leading to very low C3 levels but normal C4. Consequently, deleterious C3 deposits can form in the glomerulus, triggering downstream inflammatory cascades and increasing leukocyte infiltration.[14] In dense deposition disease (DDD), small bands of electron-dense deposits form along the GBM, causing it to thicken and become dysfunctional.[93] In addition to GBM deposits, C3 glomerulopathy exhibits varying degrees of mesangial C3 deposits, contributing to mesangial cell proliferation and matrix expansion. C3NF is most common in MPGN (C3 glomerulonephritis). Currently, DDD with isolated intramembrane C3 deposition and MPGN is classified as C3 glomerulopathy.[94,95]

The clinical features of DDD and C3 glomerulonephritis (C3GN), classified as C3 glomerulopathy, vary widely.[96] The diagnosis of C3GN or DDD is made through an immuno-fluorescence examination of a kidney biopsy specimen, along with studies of the complement system. An electron microscope is required to distinguish DDD from C3GN. DDD is characterized by highly electron-dense deposits in the GBM ('sausage-like deposits), whereas subendothelial and mesangial electron-dense deposits of lower intensity characterize C3GN.[96,97]

Non-inflammatory mechanisms of immune glomerular injury

In contrast to inflammatory injury, non-inflammatory immune glomerular injury usually results in proteinuria with little or no hematuria. Among non-inflammatory immune glomerular injuries, MCD, FSGS, and MN are the most prevalent causes. This disorder is characterized by increased glomerular permeability, corresponding to the main target of injury, i.e., podocytes.[9]

Evidence for the role of circulating factors

Evidence supporting the patho-physiological role of circulating factors influencing podocyte function and structure are: (1) resolved nephrotic proteinuria in children of mothers with FSGS and NS.[98] (2) transplant success in diabetic patients with grafts derived from transplanted FSGS recipients due to intractable recurrent massive proteinuria and renal insufficiency[99]; (3) perfused rat glomeruli

isolated with plasma from patients with FSGS-induced increased glomerular capillary permeability to albumin[100]; (4) The occurrence of massive proteinuria and FSGS histological lesions after kidney organ transplantation from healthy donors in approximately 30% of patients with FSGS[101]; (5) with prior plasma exchange, some patients were successfully treated[101]; (6) The risk of FSGS recurrence (rFSGS) following transplantation can be reduced by preemptive plasmapheresis[102]; (7) one year after transplantation, kidneys from a donor with FSGS transplanted into two uremic recipients showed no signs of proteinuria and had normal renal function.[103]

Glomerular permeability factors

- **Cardiotrophin-like cytokine factor 1 (CLC-1).** CLC-1, a member of the IL-6 family, is detected in the plasma fraction of patients with FSGS. CLC-1 increases glomerular albumin permeability, and its injection induces proteinuria in rats.[100]

- **Radical oxygen species (ROS).** Oxidative stress in isolated rat glomeruli induces proteinuria.[104] Resting PMNs from idiopathic NS (INS) patients demonstrated a tenfold higher ROS production than normal PMNs. This oxidative burst by PMNs is highly regulated by T lymphocytes, especially Tregs, through soluble factors. However, this regulatory circuitry is altered in INS.[105]

- **Hemopexin**. Hemopexin is a heme scavenger protein that increases during acute phase reactions to inflammation. Upon activation, hemopexin alters the function of both glomerular endothelium and podocytes.[106] It has been shown that activated hemopexin induces reversible proteinuria in rats, accompanied by podocyte foot process effacement. Similarly, hemopexin levels are elevated in children during relapsing MCD.[107] However, the cause of hemopexin activation is still unclear, possibly involving the inhibition of hemopexin inhibitors or their leakage into urine. In the second scenario, hemopexin activation should only be a secondary event, dependent on the increased permeability of the GFB to proteins.[108]

- **Soluble urokinase-type plasminogen activator receptor (su-PAR).** Urokinase plasminogen activator receptor (uPAR), a cell membrane glycosylphosphatidylinositol (GPI)-anchored membrane glycoprotein, contributes to the migration of activated T-lymphocytes, monocytes, and neutrophils to sites of inflammation.[106] The role of uPAR in its soluble form (suPAR) in the pathogenesis of human FSGS remains a topic of ongoing debate.[108] Therefore, further research is needed using tests to differentiate the various forms of circulating suPAR across different glomerular pathologies.

- **Angiopoietin-like 4 protein (Angptl4).** Podocyte Angtpl4 has been suggested to contribute to the development of proteinuria in MCD.[109,110] Angptl4 podocyte overexpression has been observed in MCD in relapse[110–112] and other human glomerular diseases.[113,114] However, studies have proven that Angptl4 is not a good biomarker in MCD.[115] Increased urinary agptl4 in glomerular disease appears to reflect more with the degree of proteinuria than with the specific disease.

- **Calcium/calmodulin-dependent serine/threonine kinase (CASK).** CASK was produced mostly by monocytes and M2 macrophages rather than by T or B lymphocytes via exosomes to alter the GFB in patients with USGS.[116] A soluble form of CASK acts as a permeability factor in patients with rFSGS.[117]

- **Anti-nephrin antibodies**. Anti-nephrin antibodies are the newest candidates for permeability factors in MCD. In the Nephrotic Syndrome Study Network (NEPTUNE) cohort, 11 out of 18 patients with positive anti-nephrin antibodies during active disease showed a reduction or complete absence of these antibodies during remission.[118] Based on the NEPTUNE cohort, a new molecular classification of

MCD nephrin autoantibodies has been proposed. This classification provides a framework for initiating precise therapy for these patients.

Although clinical and experimental data indicate that circulating permeability factors induce glomerular proteinuria and NS, one suspected responsible factor remains un-identified. The identity of permeability factors and mechanisms for increasing glomerular permeability in humans with NS are uncertain. Likewise, the correlation with clinical activity is inconsistent.

Conclusion

Available evidence has shown that most forms of human GN result from immunological mechanisms, although the etiology of the majority remains unknown. The precipitating factor is thought to be infection, cancer, drug or toxin exposure, which in turn triggers a nephritogenic immune response, which includes cellular and humoral components, as well as intrinsic glomerular cell involvement and their cross-talk, resulting in various manifestations of GN. Genetic and environmental factors also influence the nature of the immune response that causes GN and the individuals who develop it.

The humoral immune response causes the deposition of IC in the glomeruli, triggering an inflammatory response and activation of the complement factor cascade. Meanwhile, the cellular immune response leads to circulating mononuclear inflammatory cell infiltration in the glomerulus, promoting crescent formation. In inflammatory lesions, hematopoietic cells infiltrate (mainly macrophages and neutrophils) and proliferation of intrinsic glomerular cells, leading to glomerular hypercellularity. These effector cells can also induce thrombosis, necrosis, and crescent formation, leading to RPGN. Immune injury that produces non-inflammatory lesions usually involves podocytes as the primary effector cells and is associated with increased protein permeability.

The site of glomerular injury is the key factor determining whether a patient presents with an inflammatory injury characterized by active urinary sediment (nephritic syndrome) or a non-inflammatory injury marked by proteinuria and minimal or absent hematuria (nephrotic syndrome). Injury to GEC and mesangial cells usually results in inflammatory injury. In contrast, a glomerular injury that primarily involves podocytes generally results in non-inflammatory injury. Additional factors modulating glomerular injury include the biological nature of the Ig involved in forming immune deposits, i.e., IC formed in situ or trapped of circulating IC; the quantity of formation of immune deposits; epitope properties; and diffusion of the immune response (spread of epitopes).

Perspective

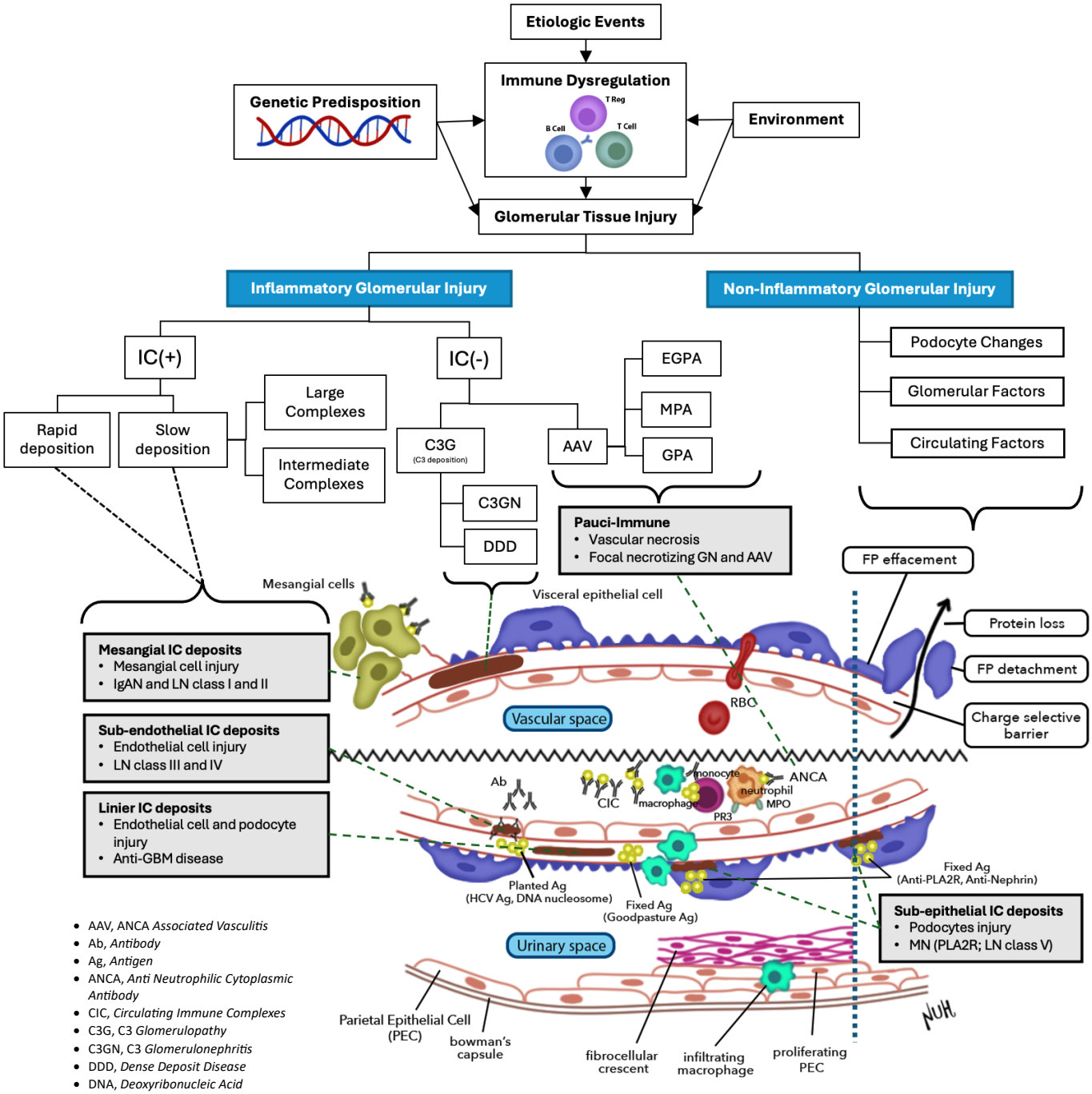
Indeed, a comprehensive understanding of the pathogenesis of immune-mediated GN may lead to a more precise diagnosis. However, because of the breadth and complexity of the pathogenesis of GN, it undoubtedly poses many challenges in the work-up of patients with the clinical presentation of glomerular disease. GN is indeed a highly variable and unpredictable condition, ranging from benign and spontaneous remission to rapidly progressive. These conditions can contribute to a delay in the diagnosis of GN, coupled with uncertainty in prognosis and therapy, all of which can lead to poor patient outcomes.

Renal biopsy remains the gold standard of diagnosis for almost all adult GN. However, it has been shown that biopsies often fail to predict clinical course or response to therapy. The existence of heterogeneous pathogenetic mechanisms causes a histological picture that cannot be distinguished from the clinical picture, the progression rate, and the therapy response. In cases of MN, the disease's diagnosis, treatment, and prognosis may be assessed without biopsy, based solely on the patient's serum anti-PLAR2 Ab titer. However, anti-PLA2R antibodies can appear months or years before the development of MN.[25] Similarly, antibodies to MPO, PR3, and

GBM can be found in asymptomatic individuals, complicating interpretation.

Based on the conditions above, the management of GN seems to require a paradigm shift. For diagnosing GN, biomarkers, diagnostic panels, or scoring/classification systems may be needed to make the diagnosis more specific. There is a need for biomarkers that reflect the molecular mechanisms underlying clinical pathology diagnosis. By identifying new biomarkers, it is hoped that it can improve diagnosis, predict prognosis, and make appropriate therapeutic decisions. The presence of biomarkers of glomerular disease across the genotype-phenotype continuum, in turn, provides an opportunity to shift to precision medicine, i.e., therapies that maximize efficacy and minimize toxicity

Graphical Summary: Pathogenesis of Immune-mediated Glomerulonephritis



- AAV, ANCA *Associated Vasculitis*
- Ab, *Antibody*
- Ag, *Antigen*
- ANCA, *Anti Neutrophilic Cytoplasmic Antibody*
- CIC, *Circulating Immune Complexes*
- C3G, C3 *Glomerulopathy*
- C3GN, C3 *Glomerulonephritis*
- DDD, *Dense Deposit Disease*
- DNA, *Deoxyribonucleic Acid*
- EGPA, *Eosinophilic Granulomatosis with Polyangiitis*
- FP, *Foot Processes*
- GPA, *Granulomatosis with Polyangiitis*
- GBM, *Glomerular Basement Membrane*
- HCV, *Hepatitis C Virus*
- IC, *Immune Complexes*
- IgAN, *Immunoglobulin A Nephropathy*
- LN, *Lupus Nephritis*
- MN, *Membranous Nephropathy*
- MPA, *Microscopic Polyangiitis*
- MPO, *Myeloperoxidase*
- PLA2R, *Phospholipase A2 Receptor*
- PR3, *Proteinase 3*
- RBC, *Red Blood Cell*

Declarations

Competing interests

The author declares no conflict of interest.

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Author's Contribution

Idea/concept, design, control/ supervision, data collection/processing, analysis/ interpretation, literature review, writing the article, critical review: NS. Author has critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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Case Report

Acute Kidney Injury with Characteristics of Rapidly Progressive Glomerulonephritis Due to Suspected IgA Nephropathy: A Case Report

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ABSTRACT

Acute kidney damage (AKI) in glomerular disease is typically characterized by rapidly progressive glomerulonephritis (RPGN). RPGN in IgA nephropathy is uncommon, occurring in less than 10% of patients. RPGN presents diagnostic issues in resource-limited settings. A 34-year-old male patient had acute kidney injury with RPGN characteristics based on clinical symptoms of hypertension, pitting edema, anuria, and hematuria after an upper respiratory tract infection, as well as laboratory findings of proteinuria, persistent microscopic hematuria, and positive erythrocyte casts. Serum creatinine levels rose sharply. Corticosteroids, antihypertensives, and hemodialysis resulted in clinical improvement and fast kidney function recovery. Due to limited resources, no kidney biopsy was conducted. This case provides a diagnostic approach to RPGN in IgA nephropathy in resource-limited settings, along with comprehensive therapy.

Keywords: RPGN, Rapidly Progressive Glomerulonephritis, IgA Nephropathy, Acute Kidney Injury, Case Report.

Introduction

Glomerulonephritis (GN) is a spectrum of illnesses caused by diverse immune responses and marked by inflammation in the kidney filtration units.[1] Immune complex glomerulonephritis (which includes infection-associated glomerulonephritis, IgA nephropathy, lupus nephritis, and cryoglobulinaemic glomerulonephritis), anti-neutrophil cytoplasmic antibody-associated glomerulonephritis (pauci-immune), anti-glomerular basement membrane glomerulonephritis, C3 glomerulopathy, and monoclonal immunoglobulin-associated glomerulonephritis are the four main types of glomerulonephritis.[2]

IgA nephropathy is the most prevalent primary glomerulonephritis globally.[3–5] Its prevalence varies among areas. Primary IgA nephropathy is the most common kind of primary glomerulopathy in adults, accounting for 2.5 occurrences per 100,000 persons worldwide each year. It is most prevalent in East Asia (45 cases per million people in Japan), Europe (31 cases per million in France), and Africa.[4,6] Some cases of IgA nephropathy have been documented in Indonesia, but no research has found a prevalence.

Glomerulonephritis is responsible for roughly 10% of acute kidney injury (AKI) cases in adults. AKI episodes in glomerular disorders

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are frequently triggered by Rapidly Progressive Glomerulonephritis (RPGN).[3] RPGN in IgA nephropathy occurs in less than 10% of patients.[7] RPGN is distinguished by a nephritic syndrome (hematuria, proteinuria, oliguria, edema, and hypertension) followed by a fast and progressive loss in kidney function over days or weeks, which can lead to end-stage renal failure if not treated rapidly.[8] Histopathologically, RPGN is distinguished by crescentic or crescent-shaped characteristics in some glomeruli.[9] RPGN results in nephritic urine examination, which includes proteinuria, microscopic or macroscopic hematuria, dysmorphic red blood cells, and red blood cell casts. The diagnosis is based on history, urinalysis, serologic testing, and a kidney biopsy. RPGN is a challenging diagnosis, particularly in resource-limited settings. Early diagnosis, adequate therapy, and evaluation are required to prevent a poor outcome. We present a comprehensive approach to identifying and managing acute kidney injury with RPGN features due to suspected IgA nephropathy in a low-resource setting.

Case Illustration

A 34-year-old male was taken to a tertiary hospital after complaining of weakness for the last two weeks, which was accompanied by edema in his lower legs. The edema had been present for the past week. During the past week, the patient also complained of reduced urination with a reddish hue. The patient acknowledged to have had a prior cough and cold. On physical examination, the blood pressure was 170/100 mmHg, and all other vital signs were within normal range. There was pitting edema in both lower legs. The patient was anuric. The examination of the head, chest, and abdomen revealed no abnormalities. A full blood count showed hemoglobin 14.3 mg/dL, leukocytes 31,910/L, and platelets 289,000/L.

The kidney function tests revealed serum creatinine 7.9 mg/dL, urea 316 mg/dL, and blood urea nitrogen (BUN) 147.66 mg/dL. Kidney function testing two weeks before revealed serum creatinine 3.1 mg/dL, urea 73 mg/dL, and BUN 34.11 mg/dL. The albumin level was 3.4 g/dL, total cholesterol 124 mg/dL, and triglycerides 239 mg/dL. Urinalysis revealed +3 protein levels, >400/LPB leukocyte sediment, 100-150/LPB red blood cell sediment, and positive red blood cell casts. Proteinuria was 4878 mg/24 hours. The anti-streptolysin O (ASTO) test was negative, as did the antinuclear antibody-immunofluorescence (ANA-IF) test. The C3 level was normal. The chest X-ray revealed normal lungs. Abdominal ultrasound revealed thickening of bilateral kidney parenchyma, with no stones or space-occupying lesions. The patient was diagnosed with acute kidney injury caused by acute glomerulonephritis from suspected IgA nephropathy with RPGN features. The acute condition in chronic renal disease served as a differential diagnosis. The patient had a methylprednisolone pulse dose of 2 x 500 mg for 3 days, followed by prednisone 2 x 20 mg. Candesartan (1x8 mg) was used to manage blood pressure. Renal support therapy with hemodialysis was conducted five times. After two weeks of medication, the patient's symptoms improved. The patient was discharged after continuous corticosteroid therapy, and hemodialysis was discontinued. At the 10-day follow-up, blood pressure was 120/60 mmHg. Kidney function tests revealed urea 45 mg/dL, serum creatinine 0.8 mg/dL, and BUN 21.03 mg/dL. Urine analysis revealed +1 protein, +1 blood, and 15-20/LPB red blood cell sediment.

Discussion

The most frequent signs of acute glomerulonephritis are elevated blood pressure (hypertension), proteinuria (excess protein in the urine), and hematuria. GN with dominant podocyte damage causes nephrotic syndrome, which is characterized by severe proteinuria and leg edema.[1] The patient's clinical findings included hypertension (blood pressure 170/100 mmHg), pitting edema in both lower limbs, and laboratory results that showed 24-hour urine protein of 4878 mg, microscopic hematuria with erythrocyte sediment 100-150/HPF, erythrocyte casts (+), and +3 proteinuria, all of which were

consistent with GN. Proteinuria implies podocyte damage, whereas hematuria shows damage to the glomerular basement membrane.[1] RPGN often causes acute episodes of glomerulonephritis in glomerular disorders.[3] RPGN is a type of acute glomerulonephritis characterized by a sudden and progressive decline in kidney function followed by kidney failure, as indicated by a more than two-fold increase in blood creatinine within days to weeks, as well as edema, hypertension, oliguria to anuria, and active urine sediment.[8] The primary causes of RPGN are small vessel vasculitis and anti-GBM illness. However, IgA nephropathy, thrombotic microangiopathy, lupus nephritis, and post-streptococcal glomerulonephritis can all induce RPGN.[3]

Blood Test	
Haemoglobin	14.3 mg/dL
Leukocytes	**31.910/µL ↑**
Platelets	289.000/µL
Haematocrit	**43 % ↑**
Serum creatinine	**7.9 mg/dL ↑**
Ureum	**316 mg/dL ↑**
Blood Urea Nitrogen (BUN)	**147.66 mg/dL ↑**
Natrium	**124 mmol/L ↓**
Potassium	4.5 mmol/L
Chlorida	**89 mmol/L ↓**
Albumin	**3.4 g/dL ↓**
Total cholesterol	124 mg/dL
Triglycerides	**239 mg/dL ↑**
ASTO	<200 **N**
ANA-IF	Negative **N**
C3	89mg/dL

Urine Test	
Protein	**+3 ↑**
Leukocyte sediment	**>400/LPB ↑**
Red blood cell sediment	100-150/LPB
Red blood cell casts	**Positive**
Proteinuria	**4878 mg per 24 hours ↑**

Figure 1. Laboratory Result

Figure 2. Patient's kidney function during hospitalization

IgA nephropathy appears clinically as recurring episodes of macroscopic hematuria during or after upper respiratory tract infections, frequently accompanied by chronic proteinuria or microscopic hematuria.[10] Kidney biopsy specimens with dominant or codominant immunoglobulin A mesangial deposits must be histopathologically examined to confirm IgA nephropathy. Primary IgA nephropathy is diagnosed when the disease affects only the kidneys. However, IgA may arise as a secondary extrarenal clinical manifestation in illnesses such as chronic liver disease, diabetes, hypertension, and lupus, referred to as secondary IgA nephropathy.[3]

According to Kidney Disease: Improving Global Outcomes (KDIGO) 2021, rapidly progressive IgA nephropathy is defined as a progressive increase in serum creatinine by 50% or higher over three months or faster, with other causes of RPGN (e.g., ANCA-associated vasculitis, anti-GBM disease) and reversible causes (e.g., drug toxicity, pre- and post-kidney etiology) have been excluded. A kidney biopsy is required to diagnose IgA nephropathy with RPGN characteristics, showing mesangial and endocapillary hypercellularity and crescents accompanied by focal necrosis in a high proportion of kidney glomeruli.[11]

In our case, a more than two-fold rise in creatinine levels, edema, hypertension, anuria, proteinuria, microscopic hematuria, and erythrocyte casts raises the possibility of RPGN. The examination findings do not indicate pre-renal variables and chronic kidney failure or post-renal factors, which are not suggested by ultrasonography. After starting corticosteroid medication, the patient's kidney function quickly recovered, and his clinical condition improved. However, due to a lack of availability in our facility, a kidney biopsy could not be done, making it impossible to determine the precise cause of RPGN. By obtaining negative ANA IF and ASTO values, lupus nephritis and post-streptococcal glomerulonephritis can be ruled out as causes of RPGN. The patient's clinical signs and symptoms matched those of IgA

nephropathy. The patient denied having fever, hemoptysis, shortness of breath, arthralgia/arthritis, or purpura. An X-ray of the chest showed no abnormalities. The levels of hemoglobin and platelets were within normal ranges. The clinical signs that were accessible and the supporting exams conducted did not indicate small vessel vasculitis, anti-GBM disease, or thrombotic microangiopathy, despite the limitations in anti-GBM antibody and antineutrophil cytoplasmic antibody (ANCA) tests.[2,11]

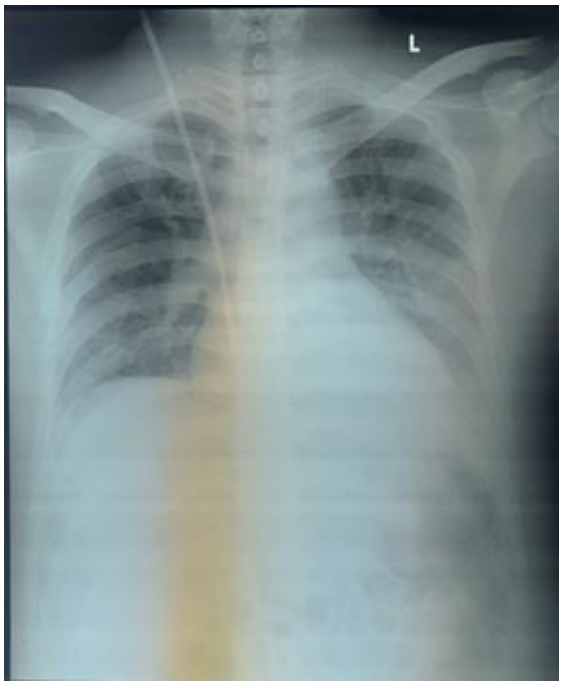

Figure 3. Chest x-ray result. Cor and Pulmo are within normal limits

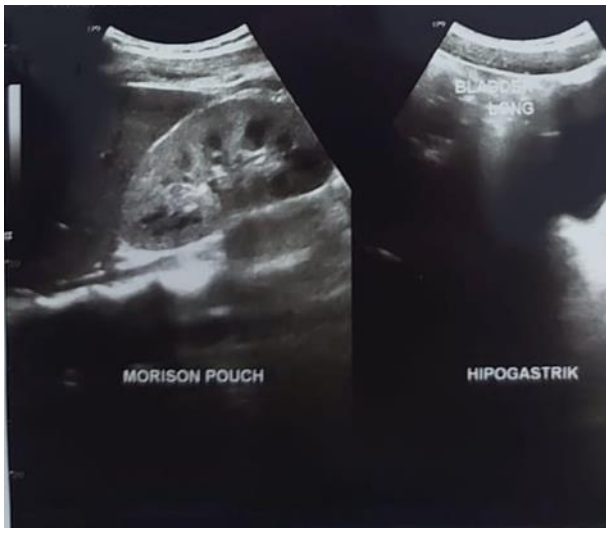

Figure 4. Patient's Abdominal Ultrasound result. Right and left kidney: normal shape and size. Increased parenchymal echogenicity. No stones or space-occupying lesions (SOL) were detected.

Uncontrolled hypertension increases proteinuria levels and leads to a faster decrease in renal function. The goal is to maintain systolic blood pressure below 120 mmHg, with ACE-I and ARB being the preferred antihypertensive medicines.[11] Oral corticosteroids and oral cyclophosphamide are used to treat RPGN, with pulse dose methylprednisolone being a key component in the treatment plan.[12]

Combining cyclophosphamide or azathioprine with corticosteroid is only recommended when crescentic IgA nephropathy is detected.[3] This patient received 500 mg/day of methylprednisolone pulse treatment, followed by two doses of 20 mg of prednisone. Candesartan 1 × 8 mg was used as an initial dosage to manage blood pressure. Hemodialysis was conducted as renal support five times before being terminated. The patient responded well to medication, as seen by stable blood pressure and improved renal function, with an initial serum creatinine level of 7.9 mg/dL dropping to 0.8. Corticosteroids and antihypertensive medication have been proven in studies to enhance outcomes.[13] Other studies needed dialysis due to steroid resistance.[14] In this study, dialysis was begun concurrently with corticosteroid and antihypertensive medication.[15] Anuria, leg edema, and a blood creatinine level were all considered indications for hemodialysis.

Conclusion

Diagnosing RPGN and its etiology is challenging, particularly in resource-limited situations. Due to limited resources, no kidney biopsy was conducted in this case. Clinical symptoms and primary diagnostic tests might be beneficial, such as renal function tests, urinalysis, urine protein levels, abdominal ultrasonography, and serological testing. The patient received corticosteroids, antihypertensives, and hemodialysis, which resulted in rapidly improved clinical and renal function.

Declarations

Competing interests

The authors declare no conflict of interest.

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None.

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