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Ramy is currently a professor and chair of the Department of Microbiology and Immunology at the Faculty of Pharmacy-Cairo University. He earned his PhD in microbiology and immunology from the University of Tennessee Health Science Center, USA in 2005, and, since then performed postdoctoral research at the University of Chicago, San Diego State University, and the University of California San Diego. His research interests span molecular epidemiology, systems biology and genomics of microbial pathogens, microbial, viral, and bacteriophage genomics and metagenomics, resistome and microbiome analysis, and lately pharmacomicrobiomics.

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Soham is an academic clinician at Oxford University Clinical Academic Graduate School and Milton Keynes University Hospital. As part of his academic responsibilities, he is a lecturer in medicine for Oxford University, a neuroanatomy demonstrator for Oxford Medical School, and a Teaching Associate for the Oxford University Global Surgery Group. His primary academic interest is research, particularly in global health and neurosurgery. He is passionate about bringing the voices of patients and the general public to the table when discussing research or advocacy efforts. He is committed to research being accessible to all.

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Julie is a Postdoc in the Department of Organismal Biology at the University of Uppsala. Her work focuses on genome evolution, and specifically transposable elements. Julie is also interested in scientific publishing and how pre-prints will change the scene in the coming years.

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Munya is a Research Fellow in medical statistics at the University of Sheffield. His interests are around the routine use of innovative and efficient statistical methods in clinical trials. Munya is leading initiatives to educate researchers and to improve the appropriate use and transparent adequate reporting of adaptive clinical trial designs. He serves on many data monitoring and trial steering committees, a scientific peer reviewer for many leading medical journals, a BMC Medicine Editorial Board member, a BMC Trials Associate Editor, and an advisory board member for highly efficient clinical trials at The Bill & Melinda Gates Foundation.

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Amiel received his B.Sc. degree at the Faculty of Agriculture, Food and Environment of the Hebrew University, Rehovot, Israel. In parallel to his bachelor's studies, he worked as a laboratory assistant in the Department of Plant Sciences at the Weizmann Institute of Science, where he was exposed to the world of transposable elements and homologous recombination. He then decided to pursue his studies in the field of human genetics. Dr. Dror received his M.D. and Ph.D degrees from the Sackler School of Medicine at Tel Aviv University, Tel Aviv, Israel. His Ph.D., obtained in 2012, focused on studying the mechanisms that underlie deafness as a result of SLC26A4 mutations. Human mutations in SLC26A4 lead to a non-syndromic (DFNB4) and syndromic form of deafness with enlargement of the thyroid gland (Pendred syndrome). In particular, he

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Dr. Alma Zecevic Faust

Alma is the President of Faust Research Services where she provides research development support to academic institutions in the area of biomedical sciences. Prior to this, she was the Director of Office of Research for the College of Liberal Arts and Sciences at the University of Illinois at Chicago and the Administrative Director of the Center for Radiation Oncology Research at MD Anderson Cancer Center. Dr. Faust holds a bachelor's degree in Chemistry and Art History from Hanover College in Hanover, IN and a doctorate in Medical Sciences from Brown University in Providence, RI. She completed her postdoctoral training with Dr. William Plunkett at MD Anderson Cancer Center where she also transitioned into academic research administration. Since early 2011, Dr. Faust has served in various positions within the field of Research Development, including as a Grant Administrator, Scientific Writer, and Scientific Program Manager. In these positions, she worked with all aspects of academic research, including preparation of grant proposals and manuscripts for publications. During her career, Dr. Faust has witnessed the enormous impact preprints can have on grant funding success and currently considers them an invaluable part of demonstrating productivity of a research team.

Dr. Jennifer B. Griffin

Jennifer is a Supervising Epidemiologist at Los Angeles County Department of Public Health. Dr. Griffin has conducted research domestically and in Southeast Asia, South Asia, and sub-Saharan Africa for 18 years and is experienced in study design, quantitative methods and analysis, and technical writing, particularly for maternal, neonatal, child health, family planning, and sexual and reproductive health. As a researcher, Dr. Griffin is particularly interested in the intersection of infectious disease and perinatal epidemiology and has consulted on vaccine safety and efficacy during pregnancy, HIV, malaria, avian influenza, and hepatitis C virus. Dr. Griffin has been an adjunct professor at the Gillings School of Global Public Health at the University of North Carolina (UNC) since 2011.

Dr. Carole Lunny

Carole is a postdoc research methodologist with the Cochrane Hypertension Review Group, the Therapeutics Initiative at the University of British Columbia, and the SPOR Evidence Alliance at the University of Toronto. She specialises in methods for research synthesis and critical appraisal of systematic reviews with pairwise and network meta-analysis, randomised controlled trials, and observational studies (cohort, case control). Her current research focuses on the development of a risk of bias tool for network meta-analyses, methods issues in clinical practice guidelines and 'overviews of reviews'. Her list of publications can be found here. She completed her PhD training as an epidemiologist at Cochrane Australia at Monash University. She is a member of the Cochrane Collaborations Statistical methods group, and the Open Science Taskforce at UBC. She is also an academic editor for PeerJ.

Dr. Leslie McIntosh

Leslie is the founder and CEO of Ripeta, a company formed to improve scientific research quality and reproducibility. Now part of Digital Science, the company leads efforts in rapidly assessing scientific research to make better science easier. She served as the inaugural executive director for the US region of the Research Data Alliance and is still very active with the RDA. She has experience leading diverse teams to develop and deliver meaningful data to improve scientific decisions. Dr. McIntosh is an accomplished biomedical informatician and data scientist as well as an internationally known consultant, speaker, and trainer who is passionate about mentoring the next generation of data scientists.She holds a Masters and PhD in Public Health with concentrations in Biostatistics and Epidemiology from Saint Louis University and a Certificate in Women's Leadership Forum from Washington University Olin's School of Business.

Dr. Ali Mobasheri

Ali is President of the Osteoarthritis Research Society International (OARSI) and is ranked as one of the top 10 leading experts in the world on osteoarthritis on expertscape.com. He is Professor of Musculoskeletal Biology in the Research Unit of Medical Imaging, Physics and Technology within the Faculty of Medicine at the University of Oulu in Finland. Ali holds the position of Chief Researcher in the State

Rheumatology and Clinical Immunology at University Medical Centre Utrecht in the Netherlands. Since April 2020 Ali has held a visiting professorship at Harvard University. Ali was educated at Imperial College London, the University of Toronto and the University of Oxford, where he obtained his doctorate from Wolfson College Oxford. He has served on the BMC and Springer Open journals Editors' Advisory Group (EAG), a group of Editors across who provide feedback on editorial policies and project development. Ali is an editor for leading international journals in his field and is an advocate of Open Access and Open Science.

Dr. Pritam Sukul

Pritam is a senior medical scientist at the University Medicine Rostock (Germany), where he obtained his Doctor of Medical Sciences (DSc.) on Experimental Anesthesiology in 2017. His research combines physiology and medicine with analytical chemistry and biotechnology. His expertise includes physio-metabolic profiling, breathomics of diseases, infections and aging, non-invasive therapeutic monitoring, volatile metabolomics, and translational research. He is a recipient of the 2013 Marie-Curie ESR fellowship, amongst the most competitive and prestigious awards in Europe supporting the most promising young minds. His earlier foundations (in England and India) are based on experimental medicine, clinical research, pharmaceutical management, and zoology. Besides designing and conducting basic and applied studies to bridge bench with bedside, he enjoys communicating STI and its known unknowns to university students and to the public. Since 2019, he also acts as a consultative non-resident scientific advisor (honorary) for the Government of India. He is motivated to involve and promote young researchers (especially women) into cross-disciplinary science and trans-national research/exchange frameworks. He is dedicated to fostering open science and open communications for society.

Dr. Sowmya Swaminathan

Sowmya steers editorial policy development, including policies and initiatives that advance transparency, integrity, open research practices and inclusion in scholarly publishing. She represents Nature and Springer Nature on multiple community and industry forums and collaborations, and has most recently been involved in the development of The MDAR Framework, aligned minimum standards for transparent reporting and open research practices in the life sciences. Sowmya is the Chair of Springer Nature's Research Publishing DEI Programme and a member of the Springer Nature DEI Council. She is a strong advocate of working in coalition with diverse stakeholders across the research ecosystem toward solutions that benefit the research community.

Dr. Karin Verspoor

Karin is Professor and Deputy Head of Research in the School of Information Systems at the University of Melbourne, as well as Deputy Director of the Centre for Digital Transformation of Health. Her research focuses on biomedical text and data analysis, with particular emphasis on knowledge discovery from the published scientific literature. Karin has made a strong investment in scientific peer review as a reviewer and through editorial board memberships.

Dr. Heather Wilkins

Heather earned a Microbiology degree at Kansas State University in 2008. Following completion of her undergraduate degree she joined a research laboratory at the University of Denver for PhD training. The focus of her dissertation was mitochondrial oxidative stress in Amyotrophic Lateral Sclerosis. Upon receipt of her PhD, Dr. Wilkins joined the KU Alzheimer's Disease Center as a postdoctoral fellow in August 2013 with Dr. Russell Swerdlow. Dr. Wilkins was awarded a K99/R00 from the National Institute on Aging in 2017 and transitioned to faculty in 2019. Dr. Wilkins' research interests are understanding how brain energy influences Alzheimer's disease pathology. Dr. Wilkins works with induced pluripotent stem cell models to understand mechanisms of Alzheimer's Disease. She is the associate director of the biomarker core for the KU Alzheimer's Disease Center where she oversees novel biomarker development.

1 - 10 of 58,042 Preprints

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Ernawati Ernawati, Agus Sulistyono, Aditiawardana Aditiawardana, Kamalia Kamalia, Salsabila Nabilah Rifdah, M. Ilham Aldika Akbar, Erry Gumilar, and 1 more authors

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The risk of persistent hypertension and chronic kidney disease in early and late-onset preeclampsia, a report from a low middle income country

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Research Article

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Abstract

Background

Early-onset preeclampsia (EOP) and late-onset preeclampsia (LOP) are associated with different maternal and fetal outcomes, biochemical markers, and clinical characteristics. Nevertheless, only a few data were presented about its long-term effects on kidney function later in life.

Objective

This study aimed to explore the risk of persistent hypertension and kidney failure in EOP and LOP in five years after delivery. **Study Design**: This retrospective cohort study included women with prior history of severe preeclampsia or normotensive pregnancy admitted to one of tertiary hospitals in Indonesia. The blood pressure, body mass index, urea and creatinine serum, and protein urine were analyzed, and risk of chronic kidney disease (CKD) was performed using KDIGO classification.

Results

A total of 27 EOP, 35 LOP and 30 normotensive cases were included. Mean blood pressure after five years recorded respectively 115.6 ± 14.25 mmHg in normotensive group, 131.82 ± 19.34 mmHg in LOP group, and 154.96 ± 23.48 mmHg in EOP group. Percentage of women with positive protein urine varied from 13.3–31.4% and 66.7% in normotensive, LOP, and EOP, respectively. According to KDIGO classification, normotensive group had 90% of low-risk CKD, whereas the severe preeclampsia group had 41.9% of high-risk CKD. In the severe preeclampsia group, the risk of CKD was 20.94 times higher compared to normotensive women (OR 20.94; 95% CI [2.67-163.72], p = 0.004). Then risk of CKD in EOP group was 6.75 times higher than LOP group (OR 6.75; 95% CI [2.19–20.76], p = 0.001), whereas persistent hypertension in EOP group was 5.78 times higher than LOP group (OR 5.78; 95% CI [1.91-17.395], p = 0.002).

Conclusions

Preeclampsia women have a higher risk of CKD than normotensive women. Women with a history of EOP are more likely to develop persistent hypertension and CKD than women with prior LOP history.

Introduction

Pre-eclampsia (PE), a multisystem disorder characterized by hypertension and frequently coinciding with new-onset proteinuria, is associated with a number of problems that place women and their fetuses at a disproportionate risk for further complications, as well as life-long sequelae.[1] PE has been

disproportionately prevalent in developing countries and constitutes a leading cause of maternal mortality in low-income countries.[2] Women with PE in developing countries have a higher risk of mortality than those in developed countries, and hypertension is one of the leading causes of maternal mortality in PE.[3,4] Currently, PE is generally classified into EOP and LOP, which exhibit different clinical manifestations and pathogenesis. EOP is associated with placental insufficiency and defective vascular remodelling, whereas LOP is most likely caused by maternal factors, particularly vascular maladaptation.[5,6,7]

Prior research has linked PE to permanent kidney damage, including an increased risk of albuminuria[8], chronic kidney disease (CKD)[9], and end-stage kidney disease (ESKD).[10] Some studies report that kidney dysfunction can resolve in most women with a history of PE[11,12], however, some women with PE may experience persistently decreased GFR and/or proteinuria and/or an increased risk of CKD.[13,14] Only few data were presented about its long-term effects on kidney function later in life, mostly in early-onset preeclampsia (EOP) and late-onset preeclampsia (LOP). Since EOP and LOP are associated with different maternal and fetal outcomes, biochemical markers, and clinical characteristics.[15] It is thought that EOP poses a substantial risk to both mother and fetus[16], whereas LOP may manifest with less severe clinical symptoms.[17] It has been suggested that EOP and LOP have different risks of developing renal impairment in women with preeclampsia. Unfortunately, to our knowledge there is no data or international publication on the risk of CKD following preeclampsia from developing country. Thus, this study intends to explore the risk of renal failure in EOP and LOP five years after preeclampsia in Indonesia as one of low middle income country in South East Asia.

Methods

This was a retrospective cohort study of women who had previously been diagnosed with severe PE or eclampsia and delivered in Dr. Soetomo Academic Hospital, the largest tertiary referral hospitals in East Indonesia between January 2013 and June 2014. Using the medical records, we identified all patients who met our criteria and included them in the exposed group, whereas women who recorded having uncomplicated pregnancy constituted as control group. All exposed cases who lived in Surabaya and willing to engage in this study were then enrolled. However, women with pre-existing comorbidities such as chronic hypertension, kidney disease, autoimmune disease, cardiac disease at the time of their pregnancy, women who had twins or multiple fetuses, and patients who died over the course of this study were excluded. All samples were contacted and/or visited at their residences before being invited to the hospital for a medical examination and blood sampling test.

PE or eclampsia were defined according to revised ISSHP criteria: the presence of hypertension (systolic blood pressure ≥140mmHg and/or diastolic blood pressure ≥90mmHg), which developed after 20 weeks of pregnancy and the coexistence of one or more of new onset conditions: proteinuria (spot urine protein/creatinine ratio 430mg/mmol or 4,300 mg protein/24 h or at least “2+” on dipstick testing), and/or other maternal organ dysfunction and/or suspected of intrauterine growth restriction (IUGR). Depending on time, EOP was defined as PE that develops before 34 weeks of gestation, whereas LOP was defined as

PE that develops at or after 34 weeks of gestation.[18] An uncomplicated pregnancy history was defined as women who giving birth between 37 and 42 weeks of gestation and having a normal blood pressure and with absence of IUGR.

The primary outcome of the study was risk of chronic kidney disease defined according to Kidney Disease Improvement Global Outcomes (KDIGO) 2012 definitions for the classification of chronic kidney disease based on renal function measured by GFR. Renal function was measured using serum creatinine values determined by the Jaffe method and calibrated using isotope dilution mass spectrometry (IDMS) method. Estimated GFR (eGFR) was calculated using the modified Cockcroft and Gault: GFR = {((l40 – age (year)) x weight (kg)) / (72 x serum creatinin (mg/dL))}x 0.85. Proteinuria was measured using urinalysis examination. According to these criteria, risk of chronic kidney disease classified into low risk if the eGFR ≥60 mL/min/1.73m^2 and proteinuria < 30 mg/g, whereas high risk if the eGFR 30–44 mL/min/1.73m^2 and proteinuria < 30mg/g or the eGFR ≥60 mL/min/1.73m^2 and proteinuria > 300 mg/g.[19]

Basic characteristics data were presented for women with priorly diagnosed EOP or LOP compared to those healthy pregnant woman. Categorical data was presented as frequencies (percentage), while continuous variables was presented either as mean (standard deviation/SD) or median (interquartile range/IQR). Differences were analyzed using Kruskal Wallis and the Fisher exact test was applied as an alternative test. Differences in values between groups considered statistically significant if the P-value was < 0.05. Odds ratios for the primary outcomes were calculated using logistic regression with 95% confidence intervals (CI). All statistical analysis were performed using SPSS 21 software (IBM Corp, Armonk, NY). The Human Research and Ethics Committee for Basic Science and Clinical Research of Dr. Soetomo General Academic Hospital approved the research protocol (Ref. No: 0842/KEPK/XII/2018). Informed consent was obtained from all participants before the initiation of the study.

Results

During periods of study, 673 women who were previously diagnosed with PE between January 2013 and June 2014 were listed from medical record. At the beginning, all patients were assessed for eligibility criteria and of whom 235 who met inclusion and exclusion criteria were enrolled to this study. After excluding some patients due to some reasons, finally we included 62 exposed women with prior PE history, consisting of 27 with EOP and 35 with LOP. We also recruited 30 healthy pregnant women to participate in this study as control group. Details regarding the study selection are documented in Fig. 1.

Basic characteristics and laboratory outcomes of included participants when first diagnosed with PE were presented on Table 1. Our study obtained that women with prior PE tend to have a higher mean of maternal age compared to control group with normotensive blood pressure at the time of delivery. The LOP group was dominated by multiparity, whereas in the EOP group was dominated by nulliparity. Our results also obtained that women with EOP had significantly higher mean of body mass index (BMI) compared to women with LOP and control group (p = 0.019) and were more likely to have chronic

hypertension, kidney disease and diabetes. However, those with chronic hypertension or CKD at baseline were excluded from further analysis. As expected, the mean systolic blood pressure of women with prior EOP and LOP were significantly higher compared to control group (p = 0.001), as well as diastolic blood pressure (p = 0.001). Our study also obtained that gestational age at delivery were significantly differed between groups (p = 0.001). Moreover, there was no statistically significant difference of eGFR between EOP, LOP and control group (p = 0.577).

Table 1
Baseline characteristics of the sample at delivery

Characteristics	Control	Pre-eclampsia		P-value		
	(*n* = 30)	LOP (n = 35)	EOP (n = 27)	C LOP	C EOP	LOP EOP
Age, mean (SD), years	30.1 ± 6.06	34.46 ± 7.38	33.07 ± 7.01	0.058		
Parity, *n* (%)						
Nullipara	11 (36.6)	14 (40)	20 (74.1)	0.785	0.005*	0.006*
Multipara	19 (63.4)	21 (60)	7 (25.9)			
BMI, mean (SD), (kg/m^2)	28.27 ± 4.07	27.07 ± 4.51	30.23 ± 4.94	0.019*		
Gestational age at delivery, mean (SD), (weeks)	38.89 ± 1.38	37.20 ± 2.86	33.3 ± 3.01	0.001*		
Blood pressure at admission mean (SD), (mmHg)						
Systolic	111.66 ± 12.05	160.34 ± 18.22	168.88 ± 15.63	0.001*		
Diastolic	70.66 ± 9.07	102.11 ± 8.20	90.00 ± 16.40	0.001*		
Renal function test at admission						
BUN, *n* (%) BUN > 21 mg/dL	0 (0)	2 (5.7)	5 (18.5)	0.187	0.014*	1.117
Serum creatinine, *n* (%) Cr > 1.1 mg/dL	1 (3.3)	0 (0)	2 (7.4)	0.280	0.495	0.104
eGFR, mean (SD) ($ml/min/1.73m^2$)	194.93 ± 33.03	171.37 ± 50.86	163.79 ± 57.78	0.577		
Proteinuria (+), *n* (%)	0 (0)	35 (100)	27 (100)	0.001*	0.001*	

*P-value from Kruskal-Wallis test for three groups, while fisher exact test for each two groups; C, control group; EOP, early-onset severe preeclampsia; LOP, late-onset severe preeclampsia; SD, standard deviation; BMI, body mass index; BUN, blood urea nitrogen; Cr, serum creatinine; eGFR, estimated glomerular filtration rate.

After five years from being first diagnosed with severe PE, the mean systolic and diastolic blood pressure showed significantly higher result in EOP group compared to all groups ($p = 0.001$). We obtained that women with EOP also had higher mean of BMI (30.23 ± 4.94 kg/m^2) compared to LOP and control group (27.07 ± 4.51 kg/m^2 and 28.27 ± 4.07 kg/m^2, respectively), although failed to show significant difference ($p = 0.084$). All parameters in renal function showed statistically significant difference between groups, except for the number of positive proteinuria and abnormal protein-to-creatinine ratio between LOP compared to control group ($p > 0.05$). Additionally, our analysis obtained that women with prior EOP history showed a significant decrease of eGFR compared to all groups ($p = 0.001$), indicating that the group with prior history of EOP may pose worse renal outcome compared to other groups. Detailed information regarding other characteristics is documented in Table 2.

Table 2
Characteristics of the sample five years after delivery

Characteristics	Control	Pre-eclampsia		P-value		
	(*n* = 30)	LOP	EOP	C	C	LOP
		(n = 35)	(n = 27)	LOP	EOP	EOP
BMI, mean (SD), (kg/m^2)	28.27 ± 4.07	27.07 ± 4.51	30.23 ± 4.94	0.084		
Blood pressure at admission mean (SD), (mmHg)						
Systolic	115.6 ± 14.25	131.82 ± 19.34	154.96 ± 23.48	0.001*		
Diastolic	66.53 ± 11.41	81.74 ± 14.49	96.00 ± 16.16	0.001*		
Persistent hypertension, *n* (%)	0 (0)	9 (25.7)	18 (66.7)	0.003*	0.001*	0.001*
Renal function test, mean (SD)						
BUN, *n* (%) BUN > 21 mg/dL	0 (0)	0 (0)	10 (37.1)		0.001*	0.001*
Serum creatinine, *n* (%) Cr > 1.1 mg/dL	0 (0)	0 (0)	10 (37.1)		0.001*	0.001*
eGFR, mean (SD) (ml/min/1.73m^2)	143.67 ± 33.77	120.80 ± 42.81	97.22 ± 28.71	0.001*		
Proteinuria (+), *n* (%)	4 (13.3)	11 (31.4)	18 (66.7)	0.087	0.001*	0.006*
Abnormal albumine-to-cratinine ratio, *n* (%)	4 (13.3)	13 (37.1)	19 (70.4)	0.031*	0.001*	0.010*
Abnormal protein-to-creatinine ratio, *n* (%)	6 (20)	9 (25.7)	18 (66.7)	0.589	0.001*	0.001*
Persistent proteinuria, *n* (%)	0 (0)	11 (31.4)	18 (66.7)	0.001*	0.001*	0.006*

*P-value from Kruskal-Wallis test for three groups, while fisher exact test for each two groups; C, control group; EOP, early-onset severe preeclampsia; LOP, late-onset severe preeclampsia; SD, standard deviation; BMI, body mass index; BUN, blood urea nitrogen; Cr, serum creatinine; eGFR, estimated glomerular filtration rate.

Further analysis regarding the incidence of persistent hypertension among women with prior history of PE were varied from 66.7% and 25.7% in EOP and LOP groups respectively. According to the logistic regression analysis, RR of developing peristent hypertension is significantly higher among women with

prior history of EOP (RR 5.778; P-value = 0.002; 95% CI 1.919–17.395), as well as the risk of developing CKD (RR 6.75; P-value = 0.001; 95% CI 2.194–20.764) compared to women with prior history of LOP (Table 3). Likewise, according to KDIQO 2012 classification, women with prior severe PE history had significantly higher risk of further developing CKD (RR 20.94; P-value = 0.004; 95% CI 2.679–163.723) compared to normotensive control group.

Table 3
The association between the type of PE with the incidence of persistent hypertension and the risk of developing CKD 5 years after diagnosis.

Variables	Type of PE		Total	P-value	RR (95%CI)
	LOP	EOP			
Persistent Hypertension					
Yes	9 (25.7%)	18 (66.7%)	27	0.002*	5.778 (1.919–17.395)
No	26 (74.3%)	9 (33.3%)	35		
Risk of CKD					
High	8 (22.9%)	18 (66.7%)	26	0.001*	6.75 (2.194–20.764)
Low	27(77.1%)	9 (33.3%)	36		

*P-value from Kruskal-Wallis test for three groups; PE, pre-eclampsia; EOP, early-onset pre-eclampsia; LOP, late-onset pre-eclampsia; CKD, chronic kidney disease; RR, relative risk; CI, confidence interval.

Table 4
Association between severe PE and risk of developing CKD five years after diagnosis.

Variable	CKD risk		Total	P-value	RR(95%CI)
	High	Low			
Severe PE					
Yes	26 (28.3%)	36 (39.1%)	62	0.004*	20.94 (2.679–163.723)
No	3 (3.2%)	27 (29.3%)	30		

*P-value from Kruskal-Wallis test between groups; PE, pre-eclampsia; CKD, chronic kidney disease; RR, relative risk; CI, confidence interval.

Discussion

This study revealed that 5 years after delivery, women with a history of preeclampsia were at risk for persistent hypertension. EOP and LOP cases had higher blood pressure than normal pregnant women. Result from prior study indicated that roughly 20% and 8% of women with a history of PE still had

hypertension and proteinuria six months postpartum, respectively.[20] The study by Berks et al., showed 39% and 14% of women with a prior history of PE remained had high blood pressure and proteinuria three months postpartum, while 18% and 8% remained had hypertension and proteinuria two years afterwards.[21] Lykke et al., found that women with a history of severe PE had the higher risk of chronic or persistent hypertension compared to those with PE (RR 6.07 vs. 3.61).[22]

Our study found that women with EOP have a higher blood pressure than LOP. Women with EOP have a risk of developing persistent hypertension 5.7 times higher than LOP. Study by Veerbeek et al. observed that over nearly half of women with a history of EOP developed persistent postpartum hypertension. Moreover, the blood pressure of women with an EOP history and pregnancy-induced hypertension was considerably greater than that of women with a LOP history.[6] Comparing EOP and LOP, the maternal vascular response and remodelling pattern revealed distinct vascular adaptations. Therefore, increased vascular resistance can contribute to systolic and diastolic dysfunction and could be a driving force behind the development of chronic hypertension in women with EOP.[7] Consequently, our findings support the idea that cardiovascular risk during pregnancy is predictive of cardiovascular risk later in life, particularly the risk of persistent hypertension.[23,24]

Our study indicated that women with a history of severe PE had a greater risk of CKD than the normotensive group. The risk of developing CKD at 5 years after delivery in severe PE patients is 20 times higher than in normal pregnancies. Patients with a previous history of preeclampsia presented lower eGFR and had more cases of persistent protein urine than normal pregnant women. Moreover, eGFR was the lowest in the EOP group. Previous report including a large cohort study found hypertensive disorders of pregnancy are associated with an increased risk of subsequent CKD. Renal impairment was also found earlier in women with GH and PE than in normotensive women.[13] Another study also reported closely association between PE and gestational Hipertension with risk of renal disorder in the the future.[9,25–27]

Risk of CKD in EOP and LOP differed significantly in this study. EOP had higher risk to develop CKD than LOP. The large cohort study by Vikse et al., with a sample of 570,433 women, showed that preeclampsia was a risk factor for the development of end-stage renal disease (ESRD). The risk is higher in preeclampsia patients who give birth to premature babies or children with low birth weight, which indicates EOP cases.[25] Irreversible vascular damage due to more severe endothelial damage and inflammatory stress in EOP than in LOP cannot be disregarded.[28] Renal histology of postpartum biopsies on PE patients showed glomerular endotheliosis and vascular injury as classic pathologies features[29] support this finding. Preeclampsia is suggested to develop kidney disease by causing acute renal impairment, endothelial damage, and podocyte loss.[30]

Endothelial dysfunction induced by PE persists after preeclampsia in many patients.[31] The remaining endothelial dysfunction is unknown; It could be assumed that endothelial cell disturbance enhances by a high level of sFlt1 in women with a history of preeclampsia and also due to epigenetic changes induced by preeclampsia.[32]

Increased levels of sFlt1 have been found in formerly preeclamptic women.[33,34] This persistence of elevated levels of sFlt1 in women with a history of preeclampsia is expected due to an extra-placental source such as endothelial cells and monocytes. This increased sFlt1 may lead to changes in the vascular endothelium, increasing the risk of renovascular diseases in later life. Interestingly, increasing sFlt1 was also found in CKD patients without a history of preeclampsia, which positively correlates with proteinuria.[35]

This fact follows EOP. The combination of insufficient immune tolerance to the fetus and poor placentation resulted in the elevation of serum sFlt-1 and decreasing of PlGF level, thus causing vascular endothelial dysfunction, which led to Preeclampsia manifestation by 34 weeks gestation.[36] It may explain that the risk of developing CKD was higher in EOP than in LOP.

The strengths of this study are mostly related to our hospital (Dr. Soetomo General Academic Hospital), a level 3 and top referral centre hospital in eastern Indonesia. At level 3, we have many cases of preeclampsia, and almost all cases of early-onset preeclampsia and all conservative management are referred to our hospital. Therefore, we have a large number of EOP and LOP cases.

As the limitation of the study, we have to consider that this was a retrospective cohort study. Thus, some information may be missed, like no assessment of renal anatomic abnormalities before pregnancy or when the patient was diagnosed with severe PE, as it is not a standard procedure for initial examination before pregnancy or at the time of diagnosis in our hospital. The high mobility of the population makes this research even more challenging. Since most of the patients in this study were seasonal residents who moved frequently, it was difficult to ascertain their whereabouts, reducing the number of participating patients. However, these limitations do not invalidate our conclusion that EOP is associated with a higher risk of CKD than LOP.

Conclusion

In women with a history of PE, the outcome of persistent hypertension and/or proteinuria may have renal repercussions. The systolic and diastolic blood pressures were found to be substantially associated with prior history of PE, which influences future renal consequences in both the EOP and LOP groups. In a five-year follow-up, women with severe PE had a higher risk of developing CKD than normotensive women. In addition, women with a history of EOP are more likely to develop persistent hypertension and CKD than women with prior LOP history. Further comprehensive prospective studies with well-designed and longer follow-ups are required to confirm the findings of this study.

Abbreviations

EOP
Early-onset preeclampsia
LOP

late-onset preeclampsia
PE
Pre-eclampsia
GH
gestational Hipertension
CKD
chronic kidney disease
ESKD
end-stage kidney disease
ESRD
end-stage renal disease
KDIGO
Kidney Disease Improvement Global Outcome
GFR
glomerular filtration rate
eGFR
estimated glomerular filtration rate
ISSHP
International Society for the Study of Hypertension in Pregnancy
IDMS
isotope dilution mass spectrometry
IUGR
intrauterine growth restriction
SD
standard deviation
IQR
interquartile range
CI
confidence intervals
BMI
body mass index.

Declarations

Ethics approval and consent to participate

The study was approved by the Human Research and Ethics Committee for Basic Science and Clinical Research of Dr. Soetomo General Academic Hospital approved the research protocol (Ref. No: 0842/KEPK/XII/2018). Informed consent was obtained from all participants before the initiation of the study.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

ERN, ADM: conceived research idea, supervised, designed questionnaire, data collection, manuscript draft and review. MIA, EGD: co-supervised, manuscript review. ERN, KML, ASL: designed questionnaire, data collection, manuscript draft. KML, SNR: data analysis, manuscript draft and review. ERN, KML,ADW, ADM: design of research, data collection, data analysis. All authors read and approved the manuscript.

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Figures

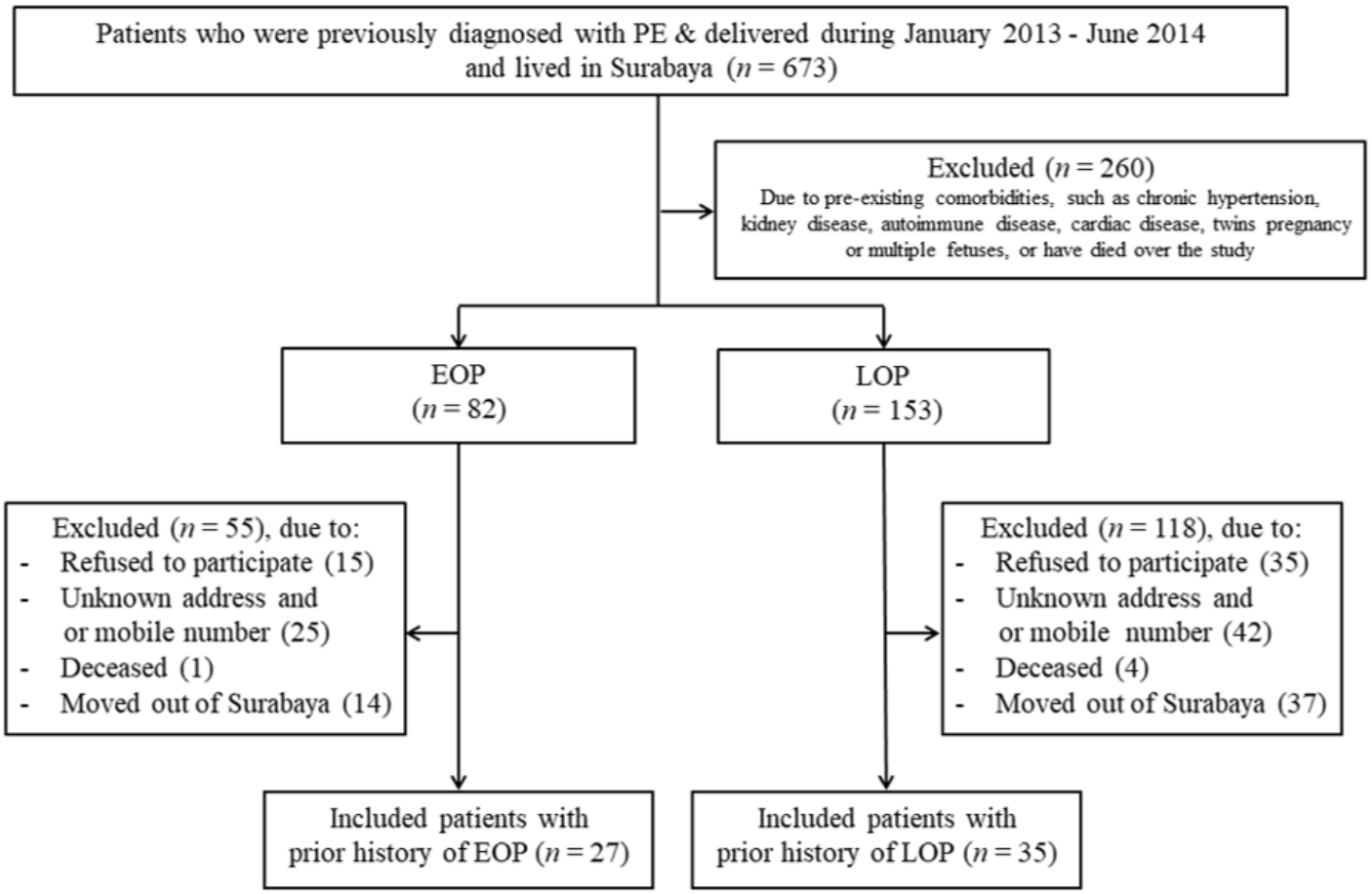

Figure 1

Study Flowchart. PE, pre-eclampsia; EOP, early-onset pre-eclampsia; LOP, late-onset pre-eclampsia