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Estimated Glomerular Filtration Rate Decline is Causally Associated with Acute Pulmonary Embolism: A Nested Case–Control and Mendelian Randomization Study

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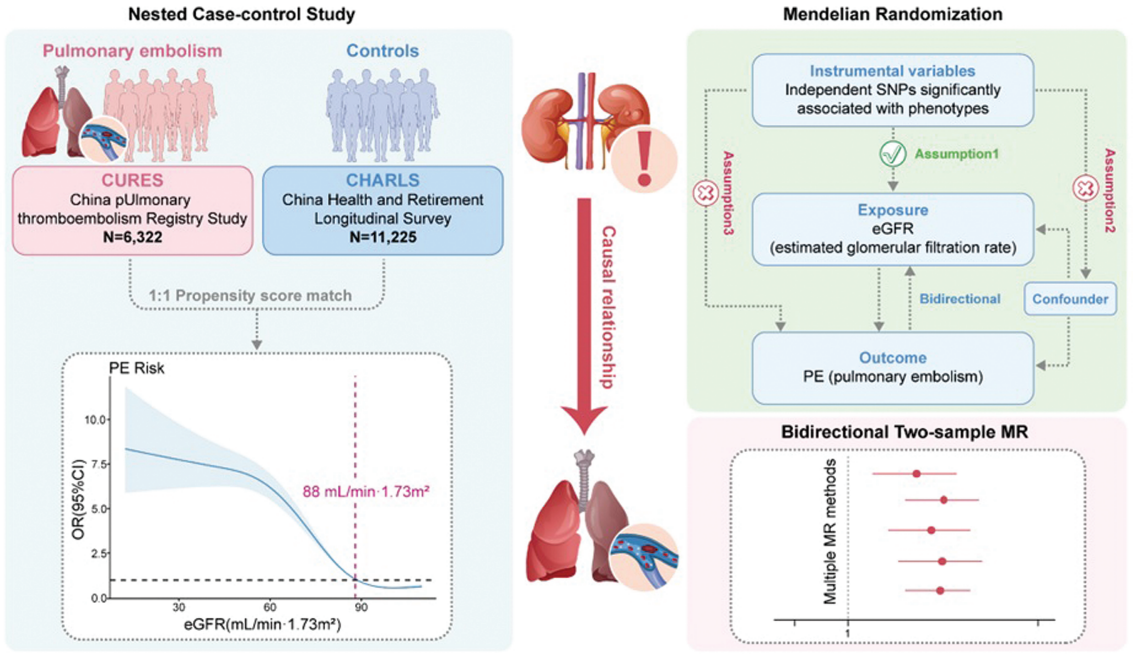

Visual summary. Overall Design of The Study. The current study was composed of two components. First, to characterize the observational association between eGFR and PE, we conducted a nested case–control study from two nationwide cohort studies, namely the China pUlmonary thromboembolism REgistry Study (CURES) and the China Health and Retirement Longitudinal Study (CHARLS). Second, to estimate the causal-effect relationship between eGFR and PE, bidirectional two-sample MR analyses were conducted. Genome-wide association studies (GWASs) summary-level genetic data for eGFR were derived from a meta-analysis of GWASs involving up to 1.2 million individuals. Summary-level genetic data for PE were derived from the FinnGen consortium R10 (10,046 PE cases and 401,128 controls). eGFR, estimated glomerular filtration rate; MR, Mendelian randomization; PE, pulmonary embolism.

Abstract

Background Renal dysfunction is highly prevalent among patients with pulmonary embolism (PE). This study combined population-based study and Mendelian randomization (MR) to observe the relationship between renal function and PE.

Methods A nested case–control study were performed using data of PE patients and controls were from two nationwide cohorts, the China pUlmonary thromboembolism REgistry Study (CURES) and China Health and Retirement Longitudinal Survey (CHARLS). Baseline characteristics were balanced using propensity score matching and inverse probability of treatment weighting. Restricted cubic spline models were applied for the relationship between estimated glomerular filtration rate (eGFR) decline and the risk of PE. Bidirectional two-sample MR analyses were performed using genome-wide association study summary statistics for eGFR involving 1,201,909 individuals and for PE from the FinnGen consortium.

Results The nested case–control study including 17,547 participants (6,322 PE patients) found that eGFR distribution was significantly different between PE patients and controls ($p < 0.001$), PE patients had a higher proportion of eGFR < 60 mL/min/1.73 m^2. eGFR below 88 mL/min/1.73 m^2 was associated with a steep elevation in PE risk. MR analyses indicated a potential causal effect of eGFR decline on PE (odds ratio = 4·26, 95% confidence interval: 2·07–8·79), with no evidence of horizontal pleiotropy and reverse causality.

Conclusion Our findings support the hypothesis that renal function decline contributes to an elevated PE risk. Together with the high prevalence of chronic kidney diseases globally, there arises the necessity for monitoring and modulation of renal function in effective PE prevention.

Keywords

- pulmonary embolism
- glomerular filtration rate
- risk factors
- causal inference
- nested case–control study
- Mendelian randomization analysis

Introduction

Acute pulmonary embolism (PE) refers to a condition in which the pulmonary artery or its branches are obstructed by a thrombus that originated from the deep veins of the pelvis and legs. Together with deep vein thrombosis (DVT), they are commonly known as venous thromboembolism (VTE). With an annual incidence of 39 to 115/100,000 population, PE is the third most prevalent cardiovascular disease worldwide, after ischemic heart disease and stroke and is one of the leading causes of cardiovascular death.[1–3] Nevertheless, in recent years, a steadily increasing global disease burden of PE has been reported, and thus, PE prevention is a priority in global public health.[1] As a multifactorial disease, a series of risk factors for PE have been established, including genetic factors, aging, major trauma and surgery, diabetes mellitus, and a series of noncommunicable diseases.[1,4–8]

The prevalence of renal insufficiency was reported to be high among PE patients in several large PE registries, ranging between 27 and 49%.[9–12] Also, studies have identified that renal impairment was associated with all-cause death, bleeding, and PE recurrence among PE patients.[13–16] Recently, the relationship between impaired renal function and the pulmonary circulation has been observed. Pathophysiological alterations inherent to chronic kidney disease (CKD), such as vascular endothelial damage, play a pivotal role in the pathogenesis PE.[17] However, whether renal function decline is an independent risk factor for PE is still poorly understood. Thus, large-scale population-based studies to examine the association between renal function are needed. However, conventional observational studies can likely be affected by reverse causality and confounding, leading to potentially biased results.

Mendelian randomization (MR) is an important approach to estimating the causal relationship between exposure and outcome, employing genetic variants associated with specific exposure as instruments to compare two genetically defined groups with different average levels of exposure (glossary seen in the ►**Supplementary Table S1**, available in the online version).[18] Since naturally occurring genetic variants associated with phenotypes are distributed randomly in the population at conception, these two genetically defined groups are considered not to be systematically different in terms of confounding variables.

Since these genetic variants are generally not linked to confounders, any differences in the outcome between individuals who carry the variant and those who do not can be attributed to variations in the associated risk factor (detailed description of several statistical methods seen in the ►**Supplementary Table S1**, available in the online version). Thus, MR provides a powerful tool for identifying causal relationships between risk factors and outcome. Previous MR studies have provided evidence on the causal relationship between PE and a series factors like uric acid, smoking.[19,20] However, until now, no MR studies have focused on the bidirectional relationship between renal function and PE.

In this study, we first conducted a nested case–control study from two nationwide cohorts to characterize the observational association between renal function (measured by creatinine-based estimated glomerular filtration rate [eGFR]) and PE, followed by bidirectional MR analyses to estimate the causal relationship between them.

Methods

Data Source and Study Population of Observational Study

PE patient data were collected from the China pUlmonary thromboembolism REgistry Study (CURES), an ongoing nationwide registry that recruited patients aged >18 with acute symptomatic PE from 100 medical centers across China between 2009 and 2015.[21,22] The PE patients were diagnosed by helical computed tomographic pulmonary angiography, ventilation–perfusion lung scintigraphy (V/Q scan), or pulmonary angiography. Meanwhile, data on controls were collected from the China Health and Retirement Longitudinal Survey (CHARLS, Wave 3, 2015), a national survey of Chinese adults over 45 years old.[23] Renal function for both cohorts was defined using creatinine-based eGFR (►**Supplementary Methods**, available in the online version), calculated by the Chronic Kidney Disease Epidemiology Collaboration equation.[24] Definition of comorbidities were shown in the ►**Supplementary Methods** (available in the online version).[22] Then, the eGFR value was converted to categorical variables according to the cutoff value of 30,60,90 mL/min/1.73 m^2.

Propensity Score Matching and Cubic Spline Model Analyses

To balance baseline characteristics of the PE and control populations, propensity score-matching (PSM) was employed, followed by inverse probability of treatment weighting (IPTW). The individual propensity to the presence of PE was estimated using a logistic regression model incorporating confounding variables as covariates, including variables that were significantly different between groups in univariable analyses and were known to be associated with renal function. Then, 1:1 PSM was performed between two groups, followed by IPTW performed as previously described.[25] A restricted cubic spline with four knots to examine the association between eGFR and risk of PE was performed, adjusting for covariates including demographic variables (sex, age, body mass index [BMI]), comorbidities (hypertension, chronic pulmonary diseases, diabetes mellitus, cancer, cardiovascular diseases). *p*-Values were two-tailed, and the significance level was set at p-value <0.05. Statistical analyses were performed using R software (version 4·3·0), and the PSM and IPTW were performed using the R package "*Matching*," cubic spline models were generated using the R package "*rms*."

Genome-Wide Association Study Data of Renal Function

Transethnic genome-wide association study (GWAS) data for eGFR were obtained from the largest meta-analysis on eGFR to date, which pooled data of the Chronic Kidney Disease Genetics Consortium (CKDGen, encompassing European

[$n = 567{,}460$], East Asian [$n = 165{,}726$], African American [$n = 13{,}842$], South Asian [$n = 13{,}359$], and Hispanic ancestry [$n = 4{,}961$] and the UK Biobank [European ancestry, $n = 436{,}581$]), collectively including 1,201,909 participants (►**Supplementary Table S1**, available in the online version).[26] A total of 424 significant (p-value $\leq 5 \times 10^{-8}$) eGFR-associated single nucleotide polymorphisms (SNPs), explaining approximately 10% of eGFR variance, were identified from the dataset and SNPs meeting the selection criteria described below were proposed as primary instrumental variables (IVs) for creatinine-based eGFR (eGFRcrea).[27] Also, eGFRcrea-associated SNPs derived from European ancestry (100% European ancestry from CKDGen and UK Biobank, $n = 1{,}004{,}040$), uncovered by the CKDGen meta-analysis, were employed as supplement IVs to assess the robustness of the primary genetic instruments and minimize population stratification bias.[27] GWASs incorporated in the meta-analyses were adjusted for age, sex, principal components by the developers.[28] Detailed information on the two sets of genetic instruments for eGFR is presented in ►**Supplementary Table S1** (available in the online version). Full GWAS summary statistics were obtained from CKDGen (https://CKDGen.imbi.uni-freiburg.de/).

Genome-Wide Association Study Data of Pulmonary Embolism

We further obtained the PE summary statistics from the FinnGen consortium (https://www.finngen.fi/en/access_results). The FinnGen consortium (R10 release) includes 10,046 PE cases and 401,128 controls. Population of GWAS of PE exhibits no overlap with the participants of the eGFR GWAS. FinnGen excluded subjects who have ambiguous gender, heterozygosity (±4 standard deviation), high genotype missingness (>5%), excess, and non-Finnish ancestry. Also, the SNPs with high missingness (>2%), low Hardy–Weinberg equilibrium p-value ($p < 5 \times 10^{-6}$) and minor allele count, minor allele counts < 3 were excluded. GWASs were adjusted for sex, age, principal components as previously described.[29] More detailed methods, including information on the included study, fine-mapping and analytic codes can be accessed on the Web sites (https://www.finngen.fi/). In the reverse MR, SNPs meeting the selection criteria shown below were retrieved as IVs from the FinnGen summary statistics. Falsification tests were performed to examine the specificity of the study. Dementia and Actinic keratosis, which have not been explicitly reported to be associated with kidney function, were selected to conduct a falsification test and examine the causal relationship between kidney function and these variables. The summary statistics for Dementia (20,338 PE cases and 391,843 controls) and actinic keratosis (12,094 PE cases and 398,605 controls) were obtained from the FinnGen consortium (R10 release).

Selection of Instrumental Variables

MR uses genetic variants, mainly SNPs, as IVs to explore the genetic link between an exposure and an outcome. MR relies on three core assumptions: (1) the genetic variants must be strongly associated with the exposure; (2) the genetic variants must be independent of any confounding factors; (3) the genetic variants must influence the outcome only through their effect on the exposure (the glossary and detailed description of statistical methods seen in the ►**Supplementary Table S1**, available in the online version). These assumptions must be satisfied for the IVs to be considered valid.

A 3-step filtering process was employed to select IVs (►**Supplementary Tables S3–S4,** available in the online version).[30] First, the IV were clumped with 1,000 genomes of European ancestry sample data as a reference to ensure independence between SNP markers (linkage disequilibrium $-$ LD $-$ $R^2 < 0.001$, window size = 1,000 kb). Second, IVs associated with confounders (i.e., risk factors of exposure including cancer, obesity, hypertension, diabetes, inflammatory bowel diseases) were identified by PhenoScanner (http://www.phenoscanner.medschl.cam.ac.uk/) and excluded. Third, the outcome GWAS summary results of the retained IVs were obtained, except if (1) the IV and were not included in the outcome GWAS; (2) the IVs were palindromic and their minimum allele frequency was >0.40, in which case they were defined as directionally ambiguous. Pleiotropy was then examined by MR Pleiotropy RESidual Sum and Outlier (MR-PRESSO), MR-Egger. "Weak instrument" was tested by calculating individual the F statistics for IVs as previously described.[20] An F-statistics exceeding a threshold of 10 was considered as a nonweak instrument.

Bidirectional Two-Sample Mendelian Randomization Analyses

Bidirectional two-sample MR analyses to estimate the causal relationship between eGFR exposure and PE outcome was performed and the random effects of inverse variance weighted (IVW) method was used for the main MR estimate.[31] The STROBE-MR checklist for the reporting of MR studies was used in this study (►**Supplementary Table S2**, available in the online version).

Additional MR estimators, including the weighted median, MR-PRESSO, MR-Egger approaches, were used as complementary analyses to ensure that the causal estimates were robust to heterogeneity and the "no pleiotropy" assumption was not violated[32,33] (►**Supplementary Table S5**, available in the online version). Leave-one-out analyses were performed to assess the reliance of the MR analyses. The I^2 (%) statistic and p-value were generated to examine the heterogeneity among estimates across individual SNPs. Odds ratios (OR) and corresponding confidence intervals (CI) of PE were scaled to 1-unit decrease in log-transformed eGFR. Reverse MR analyses was also conducted to examine the reverse causal effect of PE on eGFR. The R packages "*TwosampleMR*," "*MRPRESSO*" were used to conduct MR analyses with R software (version 4·3·0) and a two-sided p-value < 0.05 was considered statistically significant.

Results

Baseline Characteristics of the Nested Case–Control Study

In total, 17,547 participants available for calculation of eGFR were included in this study, including 6,322 PE patients from

CURES and 11,225 controls from CHARLS. Baseline characteristics were significantly different between these two groups in terms of demographic variables and comorbidities. PE groups were older, with higher BMI, more likely to comorbid cardiovascular diseases, diabetes mellitus, chronic pulmonary diseases, and kidney diseases, (►**Table 1**).

Observational Association of Estimated Glomerular Filtration Rate with Pulmonary Embolism

Demographic variables (sex, age, BMI), comorbidities (hypertension, chronic pulmonary diseases, diabetes mellitus, cancer, cardiovascular diseases, kidney diseases) were used to calculate individual propensity score. After PSM and IPTW, the demographic variables and comorbidities of the two groups were well-balanced (►**Table 1**). The distribution of eGFR was significantly different between PE and controls ($p < 0.001$): more PE patients present in the <30, 30–60, 60–90 quantiles, suggesting that PE was associated with declined renal function. Then, the restricted cubic spline showed that 88 mL/min per 1.73 m^2 was identified as the reference value. Overall, a Z-shape association was observed for PE risk and eGFR (►**Fig. 1**). When the eGFR was lower than 88 mL/min per 1.73 m^2, a marked increase in PE risk as the eGFR decreased, and then the OR of PE reached plateau as eGFR continued to decrease (nonlinear relationship: $p < 0.001$).

Evidence for Causal Effects of Renal Function Decline on Pulmonary Embolism

After IVs selection procedures, 370 independent SNPs reaching genome-wide significance ($p < 5 \times 10^{-8}$) were identified as primary instruments for the dataset of transethnic GWAS of eGFR (►**Supplementary Table S3**, available in the online version). At the same time, 324 independent SNPs derived from the eGFR dataset restricted to the European ancestry were identified as supplementary instruments, to assess the robustness and minimize the population stratification bias (►**Supplementary Table S4**, available in the online version). Importantly, less than 1/3 of the SNPs were overlapping between these two sets of IVs, suggesting that IVs of these two datasets were independent (►**Supplementary Fig. S1**, available in the online version). The strength of the IVs in the two datasets used was evaluated by the F statistics, which were all over 10 (►**Supplementary Tables S3**, **S4,** available in the online version). Funnel plots showed a symmetric distribution of the SNPs from primary and supplementary sets of IVs (►**Supplementary Fig. S2**, available in the online version).

Various methods for MR estimates were employed to assess the causal effect of renal function on PE. The IVW method showed that genetically predicted decline of eGFR was associated with the risk of PE (►**Fig. 2**), suggesting that poorer renal function was probably causally associated with PE (OR = 4·26, 95% CI: 2·07–8·79). Significant heterogeneity was detected across the estimates (Cochrane's Q = 478; $p < 0.001$, ►**Supplementary Table S7**, available in the online version). The MR-Egger intercept indicated the absence of significant pleiotropy ($p = 0.6$, ►**Table 2**). Several outliers were identified by MR-PRESSO, but the distortion test showed that the results were not significantly different before and after removal of the outliers ($p = 0.9$). These together suggested the current results were less likely to be biased by horizontal pleiotropy (►**Table 2**). The scatter plots suggested a positive causal relationship of the SNP effects on eGFR decline against SNP effects on PE (►**Supplementary Fig. S3**, available in the online version). Leave-one-out analyses indicated that the results were robust and not driven by any single SNP (►**Supplementary Figs. S4, S5**, available in the online version). The results of MR analyses using the IVs of genetic data of eGFR restricted in European ancestry were presented in ►**Fig. 2**. Consistently, the associations of genetically predicted decline of eGFR with PE risk based on the random-effect IVW method were significant (OR = 4·69, 95% CI: 2·43–9·08, ►**Fig. 2**), although significant heterogeneity among used SNPs existed (Cochrane's Q = 381; $p = 0.01$, ►**Supplementary Table S7**, available in the online version). Horizontal pleiotropy in MR-Egger regression ($p = 0.17$) and MR-PRESSO was not detected (►**Table 2**). Dataset of two diseases from the FinnGen, Dementia and Actinic keratosis, which have not been explicitly reported to be associated with kidney function, were selected to conduct a falsification test and examine the causal relationship between kidney function and these variables. The results showed no significant causal relationship between eGFR and dementia (P IVW = 0.76), eGFR, and actinic keratosis (P IVW = 0.17), thereby supporting the specificity of our original findings.

No Evidence Suggesting that Pulmonary Embolism has the Potential to be the Cause of Estimated Glomerular Filtration Rate Decline

In the reverse MR, PE was the exposure to examine its causal effect on renal function. Here, none of the methods (IVW, MR-Egger, MR-PRESSO, weighted median) showed significant results, suggesting no evidence that PE could affect creatinine-based eGFR (OR = 1·00, 95% CI: 0.99–1·00, ►**Table 3**). Sensitivity analyses and test for horizonal pleiotropy indicated that the results were robust (►**Supplementary Tables S9**, available in the online version).

Discussion

In this study, we provided the evidence that renal function decline was probably causally associated with PE. The nested case–control study based on two large-scale cohorts suggested that low eGFR was associated with PE prevalence, followed by MR analyses using the largest eGFR GWAS to date, confirmed that genetically predicted eGFR decline was associated with the development of PE. This is the first study combining large-scale observational analyses and MR that reveals the association between declined renal function and the occurrence of PE.

Previously, studies have demonstrated high incidence of VTE in CKD or end-stage renal disease (ESRD) populations confirmed by MR analysis.[34,35] However, these VTE studies did not explore the breakdown of the association between PE and DVT despite significant differences between PE and

Table 1 Characteristics of participants in the nested case–control study before and after propensity score-matching and inverse probability of treatment weighting

	Unmatched			After PSM[a] and IPTW			
	Controls (CHARLS)	Pulmonary embolism (CURES)	*p*-Value	Controls (CHARLS)	Pulmonary embolism (CURES)	*p*-Value	SMD
N	11225	6322		5535·13	5516·77		
Male (%)	5204 (46·4)	3320 (52·5)	<0.001	2935·3 (53·0)	2883·4 (52·3)	0.370	0.015
Age (y ± SD)	61·05 ± 9·69	63·22 ± 14·72	<0.001	62·56 ± 9·50	62·95 ± 15·04	0.086	0.031
BMI (kg/m^2)	23·92 ± 3·92	24·20 ± 3·78	<0.001	24·20 ± 4·05	24·23 ± 3·76	0.659	0.008
Complications							
Hypertension (%)	3641 (32·4)	2284 (36·1)	<0.001	3552·1 (64·2)	3525·7 (63·9)	0.749	0.006
DM (%)	1066 (9·5)	760 (12·0)	<0.001	620.3 (11·2)	628·7 (11·4)	0.730	0.006
Cancer (%)	176 (1·6)	929 (14·7)	<0.001	155·7 (2·8)	148·7 (2·7)	0.621	0.007
Chronic pulmonary diseases (%)	1507 (13·4)	542 (8·6)	<0.001	485·1 (8·8)	500.4 (9·1)	0.501	0.011
CVD (%)	1952 (17·4)	1017 (16·1)	<0.001	899·0 (16·2)	927·7 (16·8)	0.363	0.015
Kidney diseases (%)	1045 (9·3)	132 (2·1)	<0.001	129·8 (2·3)	125·3 (2·3)	0.748	0.005
eGFR category (%)			<0.001			<0.001	0.524
eGFR < 30	49 (0.4)	95 (1·5)		23·2 (0.4)	88·0 (1·6)		
30 ≤ eGFR < 60	460 (4·1)	1084 (17·1)		248·5 (4·5)	959·6 (17·4)		
60 ≤ eGFR < 90	2957 (26·3)	2230 (35·3)		1566·8 (28·3)	1930.7 (35·0)		
eGFR > 90	7759 (69·1)	2913 (46·1)		3696·7 (66·8)	2538·5 (46·0)		

Abbreviations: BMI, body mass index; CHARLS, China Health and Retirement longitudinal Survey; CURES, China Pulmonary Thromboembolism Registry Study; CVD, cardiovascular diseases; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; IPTW, inverse probability of treatment weighting; PSM, propensity score matching; SMD, standardized mean differences.

[a]The individual propensity to the presence of PE was estimated using a logistic regression model using confounding variables as covariates, including demographic information (sex, age, BMI), comorbidities (hypertension, chronic pulmonary diseases, diabetes mellitus, cancer, cardiovascular diseases, kidney diseases).

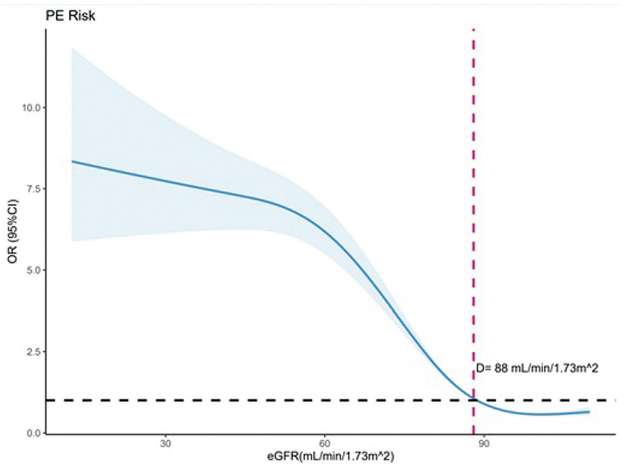

Fig. 1 Association between eGFR values and PE risk. Restricted cubic spline model for risk of developing PE. This figure illustrates the restricted cubic spline model fitted to the relationship between eGFR and PE risk. The *x*-axis represents eGFR in mL/min/1.73 m^2, whereas the *y*-axis depicts the predicted risk of PE. The solid blue line is the estimated odds ratio, and the shaded blue area is the 95% confidence interval, adjusted for covariates including demographic variables (sex, age, BMI), comorbidities (hypertension, chronic pulmonary diseases, diabetes mellitus, cancer, cardiovascular diseases). A total of 88 mL/min per 1.73 m^2 was identified as the reference value. When the eGFR was lower than 88 mL/min per 1.73 m^2, the result showed a marked increase in PE risk as the eGFR decreased, and then the OR of PE reached plateau as eGFR continued to decrease. BMI, body mass index; eGFR, estimated glomerular filtration rate; OR, odds ratio; PE, pulmonary embolism.

DVT in treatment, clinical outcomes, and risk factors.[36] Our study is the first one that focus on the causal association between renal function and PE development. Although PE and DVT have been considered as a same disease with different presentation, recent studies provided evidence that there are differences between the two diseases. Several risk factors, such as pneumonia, chronic obstructive pulmonary disease, and atrial fibrillation are associated with higher risk of PE, but seem to have a much smaller effect on DVT, which may be because some risk factors mainly have an effect on pulmonary vasculature.[36–38] More importantly, a large-scale study comparing PE and DVT patients highlighted that renal insufficiency were more common in PE patients compared with those with DVT, suggesting that renal insufficiency may play a unique role in the pulmonary vasculature, beyond its general effects on the vascular endothelium, and thus, the association of renal function on PE need to be studied separately.[37] Several large PE registries have reported that up to one-third of PE patients were comorbid with renal insufficiency suggesting an association between them, but none of them clearly illustrated the association between renal function and PE risks.[9–12] A study with limited representativeness showed that ESRD patients receiving chronic dialysis were associated with a higher risk of PE, compared with general population, which was consistent with current findings indicating renal function decline could cause PE.[39] Thus, our study provided robust association between renal function and PE, more specifically.

The mechanism under the relationship between renal insufficiency and PE contain several pathways: nephrotic syndrome is the most recognized condition of high risk of VTE, with clear mechanisms of the urinary loss of antithrombin and higher level of platelet activation. Moreover, studies showed endogenous anticoagulants such as antithrombin were lower than general population in patients with nephrotic syndrome. However, inconsistent results were reported by another study using renal impaired population caused by various reasons, suggesting that loss of antithrombin might only exist in patients with damaged glomerular filtration barriers.[40,41] For CKD or renal impairment caused by underlying disease other than nephrotic syndrome, the mechanisms include activation of procoagulant markers, decreased endogenous anticoagulants, enhanced platelet activation and aggregation, and decreased activity of the fibrinolytic system.[35] A series of clinical studies showed coagulating factors including D-dimer, fibrinogen, factor VII, and factor VIII and von Willebrand factor were increased in patients with renal insufficiency.[42,43] Besides, CKD patients were associated with an increased level of plasminogen activator inhibitor-1, suggesting endothelial damage. Furthermore, a study found an inverse correlation between circulating levels of plasmin–antiplasmin complex and creatinine clearance rate, suggesting fibrinolytic activity may be compromised as renal function decreases.[44] Moreover, there were studies showing that patients with nephrotic syndrome had higher levels of P-selectin, suggesting platelet activation in patients with CKDs.[45] Both the above are components of Virchow's triad and could be secondary to CKD.[43,46] PE could be caused by procoagulant status and endothelial damage resulting from renal function decline. However, the pathogenesis likely differs depending on the cause of the kidney disease (nephrotic syndrome, non-nephrotic, and ESRD), but there lacks clear experimental research for further explanation of those mechanisms.

We innovatively quantify the decrease of eGFR that lower than 88 mL/min per 1.73 m^2 would be a cutoff point indicating increasing risk of PE. Consistent with our finding, the risk of different degree of CKD on VTE had also been investigated by other clinical studies and they found that VTE risk increased with worsening CKD stage (the adjusted risk ratio of VTE in Stage 2 and 3/4 CKD was 1.28 and 1.71).[35] Another study showed that the relative risks for developing VTE were gradually increased as renal function decline, from 1·28 for those with mildly decreased renal function to 2·09 for those with eGFR between 15 and 59 mL/min/1.73 m^2.[47] The understanding of the relationship between renal function decline and PE risk could be of great significance in clinical practice. It is reported that the global prevalence of CKD is around 8 to 12%.[48,49] Thus, the findings of a potential causal relationship between renal function decline and PE highlighted the importance of preventing thrombosis in patients with impaired renal function. Thus, preventative measures on thrombosis may be warranted since the study found that PE risk was steeply increased when the eGFR was lower than 88 mL/min per 1.73 m^2. Since renal insufficiency could affect the use of anticoagulants and was associated

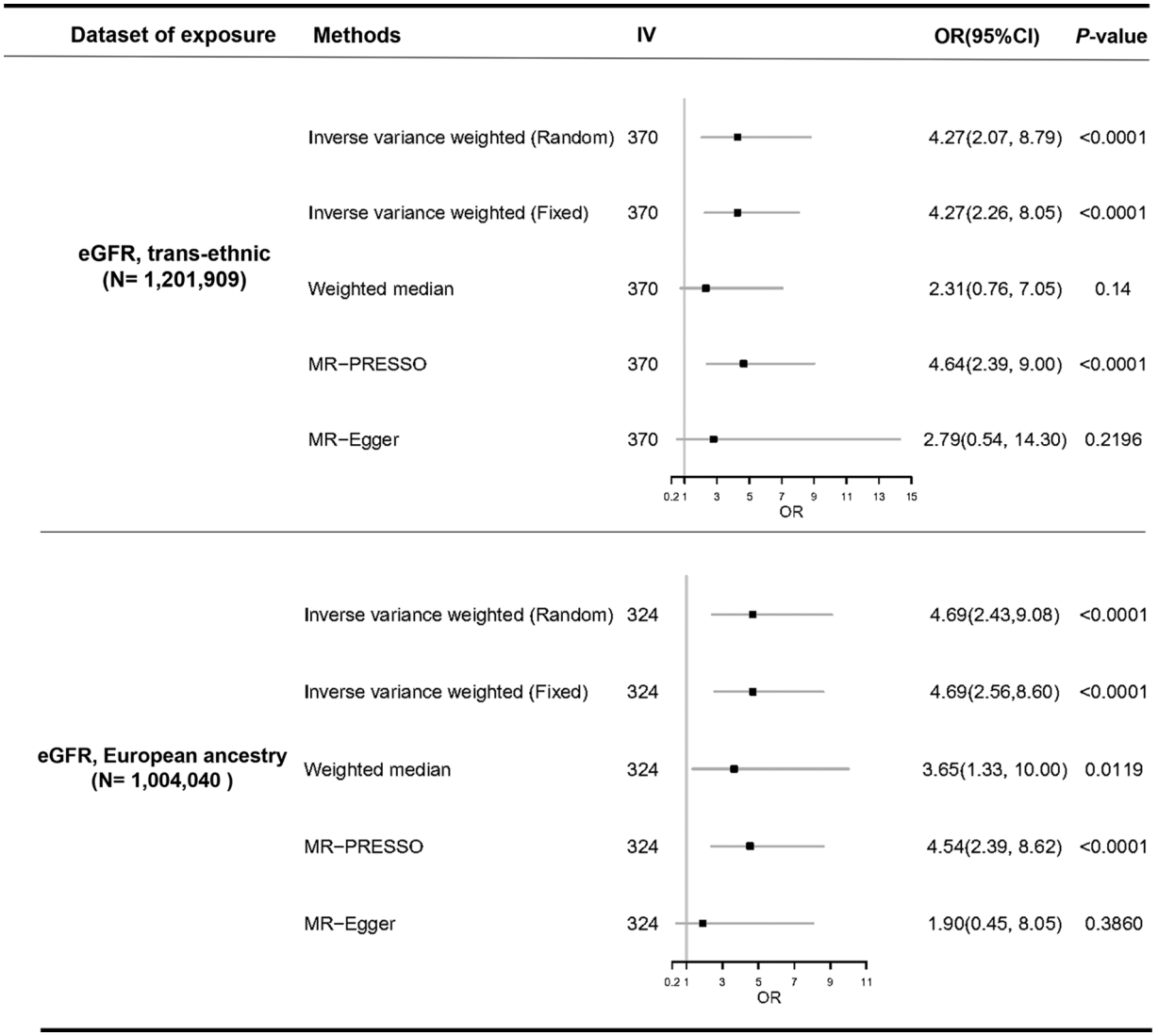

Fig. 2 Two-sample Mendelian randomization revealed that eGFR decline was causally associated with PE. The forest plot illustrated the odd ratios and 95% confidence interval calculated by inverse variance weighted, maximum likelihood, MR-Egger, and MR-PRESSO methods, using primary and supplementary instrumental variables, when eGFR decline was the exposure and PE was the outcome. eGFR, estimated glomerular filtration rate; IVs, instrumental variables; MR, Mendelian randomization; PE, pulmonary embolism.

with poor prognosis of PE, mechanistic and clinical studies to provide evidence of the PE prevention strategies in patients with renal insufficiency were also justified. Furthermore, the modification effects of various renal disease etiologies on the association between renal function decline and PE risk warrants further investigation. Lastly, the findings of the current observational study indicated modulation of renal function could be an effective measure to reduce the incidence of PE and in turn the interventional studies to validate the findings are warranted.

The primary strength of the current study is combining the nested case–control study and MR study with large

Table 2 Egger regression and MR-PRESSO revealed no evidence of horizontal pleiotropy in the forward Mendelian randomization

Exposure	Outcome	Egger-intercept	Egger-SE	Egger-*p*-Value	MR-PRESSO distortion test
eGFR, Trans-ethnic	Pulmonary Embolism	0.001	0.002	0.57	0.9
eGFR European ancestry	Pulmonary Embolism	0.003	0.002	0.17	No significant outliers

Abbreviations: eGFR, estimated glomerular filtration rate; MR, Mendelian randomization; PE, pulmonary embolism.
Note: Egger regression and MR-PRESSO test results for horizontal pleiotropy of Mendelian randomization analyses using primary and supplementary instrumental variables, with eGFR as exposure and PE as outcome.

Table 3 Reverse Mendelian randomization indicated no causal effect of pulmonary embolism on estimated glomerular filtration rate decline

Exposure	Outcome	Methods	IVs	OR	95% CI	*p*-Value
PE	eGFR, Transethnic	Inverse variance weighted (random)	15	1.00	0.99, 1.00	0.58
		Inverse variance weighted (fixed)	15	1.00	0.99, 1.00	0.15
		Weighted median	15	1.00	0.99, 1.00	0.20
		MR-PRESSO	15	1.00	0.99, 1.01	0.17
		MR-Egger	15	1.00	0.99, 1.00	0.25
PE	eGFR, European ancestry	Inverse variance weighted (random)	15	1.00	0.99, 1.00	0.75
		Inverse variance weighted (fixed)	15	1.00	0.99, 1.00	0.48
		Weighted median	15	1.00	0.99, 1.00	0.17
		MR-PRESSO	15	1.00	0.99, 1.00	0.71
		MR-Egger	15	1.00	0.99, 1.00	0.25

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; IV, instrumental variable; MR, Mendelian randomization; OR, odds ratio; PE, pulmonary embolism.
Note: The table illustrated the odd ratios and 95% CI calculated by inverse variance weighted, maximum likelihood, MR-Egger, and MR-PRESSO methods, using primary and supplementary instrumental variables, when PE was the exposure and eGFR decline was the outcome.

population, which minimized bias from confounding and reverse causality. Moreover, unlike previous studies focusing on VTE, the research for the first time uncovered the potential causal relationship between renal function and PE. Furthermore, the MR analyses employed genetic instruments of eGFR from the most recent and largest GWAS studies, and findings were reinforced by the consistent results observed using two independent sets of IVs and several analytical approaches for MR estimates. However, several limitations of the current study are necessary to be discussed. First, a major limitation of the MR design is horizontal pleiotropy. However, in this study, biases induced by pleiotropic effects are likely minimal. There was no indications of horizontal pleiotropy in the MR-Egger test and consistent results were drawn from several sensitivity analyses. Second, the results of the nested case–control study could be potentially biased since cases and controls came from two cohorts employing different technical specifications. Nevertheless, both cohorts employed the same and standardized test for serum creatinine (►**Supplementary Methods**, available in the online version). Also, unmeasured or unknown confounders may influence the observed associations. Atrial fibrillation, although discussed as a potential factor associated with PE, could not be included as a covariate in the propensity score matching due to the absence of relevant data in the database. Lastly, the result of eGFR or renal function could be affected by different measurement or formulas, and proteinuria, inferred by studies that was associated with VTE, was not included in our study.[50]

Conclusion

This study provided compelling evidence from a large population supporting eGFR decline is an independent risk factor for PE, and the risk of PE significantly increased when kidney function declines to the threshold right below the normal level (88 mL/min per 1.73 m^2). These findings indicated that modulation of renal function could be an effective measure for PE prevention; also, given the high global prevalence of CKD and high mortality of PE, there arises the necessity for monitoring the risk of thrombosis and the implementation of preventive strategies concerning PE, in CKD patients.

What is known about this topic?

- Existing studies revealed a high prevalence of renal impairment among pulmonary embolism (PE) patients and the prognosis of PE patients with renal insufficiency.
- Few population-based studies have explored the relationship between renal function decline and PE and the direction.

What does this paper add?

- PE patients were associated with a higher prevalence of low eGFR compared with the general population and eGFR levels below 88 mL/min/1.73 m^2 were associated with a steep increase in PE risk. MR analyses found that renal function decline has the potential to be causally associated with PE, with no evidence of horizontal pleiotropy and reverse causality.
- These findings uncovered the connection between the lung and kidneys and provided multidisciplinary strategies for patient care. The study indicated that monitoring and modulation of renal function could be important and effective measures for reducing PE incidence. This also enhances our understanding of complications arising from CKD and underscores the necessity for monitoring the risk of thrombosis and implementing preventive strategies against PE in patients with CKD to prevent serious complications.

Authors' Contribution

D.W., P.Y., Z.Zhai conceived and designed the study. Y.L., H.L., X.Z., Y.C. collected data. Y.L., H.L., G.F., H.Z., Z.H., H.W., H.H., X.L. analyzed and interpreted data. Y.L. and H.L. replicated the results of this article back-to-back. Y.L., H.L., D.W. and X.L. drafted the manuscript. Y.Z., F.X. contributed to the design and building of the CURES. X.L. provided profession of nephrology. X.L., P.Y., Z.Zhai, C.W. revised the manuscript. D.W. were the lead corresponding authors. All authors participated in the proofreading of the manuscript and provided final approval of the version to be published.

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Conflict of Interest

None declared.

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