

Renal Insufficiency and Short-Term Outcomes of Acute Pulmonary Embolism: A Systemic Review and Meta-Analysis

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Abstract

Background This article evaluates the association between renal insufficiency and short-term outcomes among patients with acute pulmonary embolism.

Methods The literature search was completed on December 31, 2019 and data were contracted from 13 cohort studies. Diagnosis of renal insufficiency was based on estimated glomerular filtration rate (eGFR), serum creatinine level, or self-report. The primary outcome was all-cause mortality of 30 days or during hospitalization. The pooled risk ratios (RRs), pooled mortality rates, and between-study heterogeneity were estimated by random-effect models. All the statistical analyses were performed using STATA/SE software.

Results We included 13 studies ($N = 35,662$) in the meta-analysis, including two focused on acute kidney injury (AKI). Early all-cause mortality in patients with versus without renal insufficiency were 15% (95% confidence interval [CI] 9–22%) and 5% (95% CI 3–8%), respectively (RR 1.76, 95% CI 1.61–1.92). For patients with $eGFR < 30$ mL/min·1.73m⁻², rates were 30% (95% CI 11–75%) versus 10% (95% CI 5–14%) (RR 3.32, 95% CI 1.53–6.70). For patients with AKI during hospitalization, rates were 32% (95% CI 11–75%) versus 13% (95% CI 4–29%) (RR 2.69, 95% CI 1.24–5.84). Pulmonary embolism (PE)-related death and fatal bleeding were significantly higher in patients with renal insufficiency.

Conclusion Renal insufficiency, especially AKI and severe renal insufficiency, was associated with early mortality in acute PE patients. Our results may escalate vigilance in risk stratification and management of PE patients with renal insufficiency in clinical practice.

Keywords

- ▶ pulmonary embolism
- ▶ venous thromboembolism
- ▶ renal insufficiency
- ▶ acute kidney injury
- ▶ mortality

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Introduction

Acute pulmonary embolism (PE) contributes to the global burden in terms of morbidity mortality, and financial impact on health care systems.¹ A reliable risk classification and prediction model of PE is important for identifying patients with higher risk of short- or long-term adverse outcomes, thus affects clinical decision-making. Pulmonary Embolism Severity Index (PESI) or simplified PESI (sPESI)¹ are recently reliable in assessments of 30-day outcome of patients with acute PE and have been widely validated.^{2–4} sPESI score focused on 6 equally weighed variables—age > 80 years, cancer, chronic heart failure or chronic pulmonary disease, systolic blood pressure < 100 mm Hg, and arterial oxyhemoglobin saturation < 90%.⁵ Whereas several studies suggested that the clinical severity scores alone might be insufficient to accurately stratify the full spectrum of disease, biomarkers are beneficial for further identification of patients in different risk of outcomes.^{6,7}

Renal dysfunction is one of the generally accepted indications of an increased mortality in various cardiovascular diseases. Several large registries have demonstrated the impact of renal function in both short- and long-term prognosis of acute PE. In the International Cooperative Pulmonary Embolism Registry study, renal dysfunction (defined as creatinine level > 2.0 mg/dL) was an independent predictor of mortality (hazard ratio [HR] 2.0; 95% confidence interval [CI] 1.4–3.0).⁸ In Registro Informatizado de Enfermedad TromboEmbólica (RIETE) study, creatinine clearance (CrCl) < 30 mL/min was independently associated with an increased risk for fatal PE (odds ratio [OR] 5.2; 95% CI 3.4–7.8) and fatal bleeding (OR 5.0; 95% CI 2.0–12) within 15 days of diagnosis.⁹

Due to the different expression of renal function (e.g., creatinine level, CrCl, or estimated glomerular filtration rate [eGFR] calculated by different formula) in separate studies, the association between renal insufficiency and the prognosis of acute PE is inconsistent. Therefore, we conducted the present meta-analysis to determine the prognostic relevance of renal insufficiency in patients with acute PE.

Methods

Literature Search and Study Selection

The literatures published in Pubmed, Web of Science, or EMBASE in the past 12 years from January 1, 2008, to December 31, 2019, was searched. The search terms included: kidney disease, kidney failure, kidney insufficiency, kidney function, kidney dysfunction, renal disease, renal failure, renal insufficiency, renal dysfunction, pulmonary embolism, pulmonary thromboembolism, thromboembolism, and venous thromboembolism (VTE). If appropriate, medical leading terms were used, such as MeSH and Emtree words.

We performed an additional manual search of potentially eligible studies within references of the included studies, international guidelines, relevant (systematic) reviews, and derivation/validation studies of prognostic scores.

Search results were screened independently by two reviewers for the relevance of titles/abstracts and full-texts of the studies fulfilling the inclusion criteria. Potential disagreements were solved by a third reviewer.

The present work was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline.¹⁰

Inclusion Criteria

Studies were considered eligible if they fulfilled all the following criteria: (1) Patients should be included through objectively confirmed acute PE. (2) Data on renal function status at baseline or acute kidney injury (AKI) are available. (3) At least one of the outcomes of interest was assessed during short-term (in-hospital or less than 30 days) follow-up. (4) Publications must be in English language.

Renal Function Measurement and Definition

Renal function was estimated by the either of the following definitions:

eGFR by Modification of Diet in Renal Disease (MDRD):

$$\text{GFR} = 186 \times \text{Scr}^{-1.154} \times \text{age}^{-0.203} \times 1.212 \text{ (if black)} \times 0.742 \text{ (if female)}$$

or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation:

$$\text{GFR} = 141 \times \min(\text{Scr}/\kappa, 1)^\alpha \times \max(\text{Scr}/\kappa, 1)^{-1.209} \times 0.993^{\text{age}} \times 1.018 \text{ (if female)} \times 1.159 \text{ (if black)}$$

The classification of renal dysfunction was based on the cutoffs reported in the selected studies.

AKI was determined according to the “Kidney Disease: Improving Global Outcomes” definition.¹¹

Renal insufficiency was defined as self-reported “renal dysfunction,” or creatinine elevation (according to particular studies), or eGFR < 60 mL/min·1.73m⁻². Severe renal insufficiency was defined as eGFR < 30 or 35 mL/min·1.73m⁻².

Data Extraction and Quality Assessment

Two researchers (D.W. and X.L.) independently extracted the following information from each study: lead author, publication year, country of origin, participant characteristics, measurement of renal function, classification of renal function, outcomes, and follow-up duration. The quality of studies was assessed in accordance with the Newcastle-Ottawa Scale for cohort studies.¹²

Outcomes

We defined short-term all-cause mortality (death during the hospital stay or within the first 30 days following diagnosis of PE) as the primary outcome of our meta-analysis. The secondary outcomes were PE-related death, bleeding events (including major bleeding and fatal bleeding¹³), and adverse

outcomes (defined as death, cardiopulmonary resuscitation or cardiogenic shock, use of vasopressors, thrombolysis, mechanical ventilation, etc.).

Statistical Analysis

We estimated pooled relative risk (RR) and 95% CI and weighed rates between groups of patients with and without renal dysfunction using a random-effect model. We assessed statistical heterogeneity of exposure effects by calculating the inconsistency index I^2 statistic (ranging from 0 to 100%) on the basis of the Cochrane Q test, which summarizes the amount of variance among studies beyond chance. Heterogeneity was defined as low ($I^2 < 25\%$), moderate ($I^2 = 25\text{--}75\%$), or high ($I^2 > 75\%$). The presence of publication bias was evaluated by visually inspecting funnel plots. Meanwhile, the Egger's test, a weighted regression test helping justify the asymmetry of funnel plots, was performed to assess the statistical evidence of publication bias, with a significance level defined as $p < 0.1$.

We performed predefined subgroup analyses investigating the prognostic value of different cutoffs, stratifications, and study designs. STATA software (StataCorp, Texas, United States, version 14.0 for Windows) was served for data analysis.

Results

The literature search identified 1,849 records in Pubmed, 1,876 in Web of Science, and 5,641 in EMBASE, leaving 2,732 records after duplicate removing. ► **Fig. 1** shows the selection flowchart of the meta-analysis. Eventually, we include 13 studies in the meta-analysis with a total of 35,662 patients diagnosed with acute PE (► **Table 1**), 2 of them were conference abstracts and the others were published articles. Of these studies, baseline renal function stratification was available in 11 studies (7 measured by eGFR,^{14–21} 2 by serum creatinine level,^{22,23} and 2 by self-report^{24,25}), and data on AKI occurrence after hospitalization was available in 2 studies.^{26,27}

Short-Term Mortality

The analysis of renal insufficiency was reported from 7 studies in 1,761 of 5,364 patients (32.8%). Short-term all-cause mortality among those patients were 15% (95% CI 9–22%) and 5% (95% CI 3–8%), respectively (RR 1.76, 95% CI 1.61–1.92; I^2 0%). Subgroup analysis of short-term all-cause mortality showed patients with creatinine elevation had a pooled RR of 2.18 (95% CI 1.41–3.36), patients with eGFR < 60 mL/min \cdot 1.73m $^{-2}$ had a pooled RR of 1.72 (95% CI 1.56–1.89) (► **Table 2**, ► **Fig. 2**).

Severe renal insufficiency was reported in 2 studies with 206 out of 3,508 patients (5.9%). Short-term all-cause mortality among those patients were 30% (95% CI 2–59%) and 10% (95% CI 5–14%), respectively (RR 3.32, 95% CI 1.53–6.70; I^2 80.7%) (► **Fig. 3**).

AKI after hospitalization was reported from 2 studies in 6,594 out of 28,719 patients (23.0%). Short-term all-cause mortality among those patients were 32% (95% CI 11–75%)

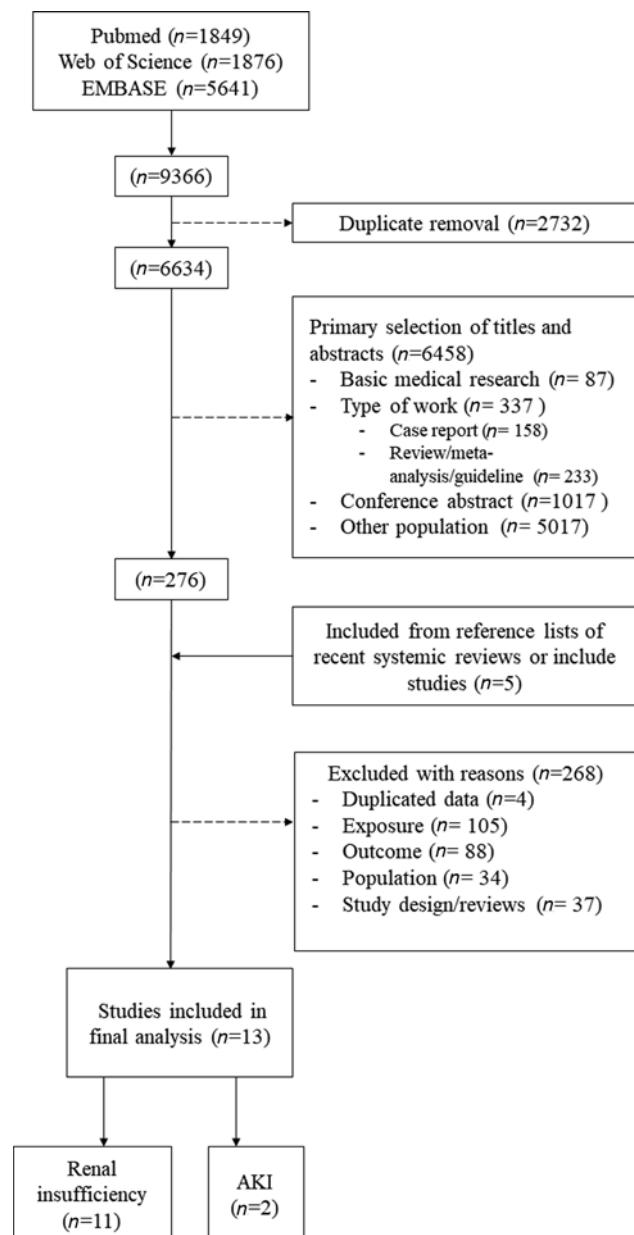


Fig. 1 Flowchart of study selection. AKI, acute kidney injury.

and 13% (95% CI 4–29%), respectively (RR 2.69, 95% CI 1.24–5.84; I^2 98.2%) (► **Fig. 4A**).

Secondary Outcomes

PE-related mortality was higher in patients with renal insufficiency (12% vs. 4%, RR 1.72, 95% CI 1.55–1.91; I^2 0%) (► **Fig. 5A**).

Fatal bleeding was available as a secondary outcome in two studies. Patients with renal insufficiency had higher risk of fatal bleeding (RR 1.43, 95% CI 1.22–1.67; I^2 0%) (► **Fig. 5B**).

Adverse outcomes were available as a combined endpoint in three studies. Patients with renal insufficiency had higher incidence but the risk ratio was not statistically significant (22% vs. 12%, RR 2.64, 95% CI 0.80–8.58).

Major bleeding was described in the two studies focused on AKI. The risk of major bleeding among AKI patients was not significantly higher than those without AKI (► **Fig. 3B**).

Table 1 Characteristics of enrolled studies

Author	Year	Country	Study type	Follow-up days	Risk level	RI definition (formula)	Sample size	RI number (%)	Male (%)	Age (SD)	All-cause death (RI/non-RI)	NOS score
Renal insufficiency												
1 Agrawal et al ¹⁵	2014	India	Prospective cohort	In-hospital	All	Self-Reported	200	77 (39%)	123 (62%)	43.8	24/12	6
2 Verschuuren et al ²⁵	2013	Europe	Prospective cohort	30 d	All	Self-Reported	549	25 (4.5%)	262 (48%)	69	NA	6
3 Jo et al ²²	2013	Korea	Retrospective cohort	30 d	All	Creatinine > 1.3 mg/dL	667	96 (14%)	NA	NA	17/40	7
4 Keller et al ²³	2017	Germany	Retrospective cohort	In-hospital	All	Creatinine > 1.3 mg/dL in men, > 1.1 mg/dL in women	182	40 (22%)	70 (39%)	68.5 (15.3)	1/4	6
5 Kostubiec et al ¹⁴	2019	Europe	Prospective cohort	30 d	All	eGFR < 60 mL/min·1.73 m ⁻² (MDRD)	2,845	1,023 (36%)	1,424 (50%)	66 (17)	123/100	7
6 Trimaille et al ⁹	2019	France	Retrospective cohort	30 d	All	eGFR < 60 mL/min·1.73 m ⁻² (MDRD)	678	183 (27%)	294 (43%)	NA	10/9	7
7 Almeida et al ¹⁰	2015	Portugal	Retrospective cohort	In-hospital	All	eGFR < 60 mL/min·1.73 m ⁻² (MDRD)	129	59 (46%)	46 (36%)	66.95	12/4	NA
8 Salinger-Martinovic et al ¹⁷	2019	Serbia	Prospective cohort	In-hospital	All	eGFR < 60 mL/min·1.73 m ⁻² (MDRD)	663	283 (43%)	NA	NA	70/30	NA
9 Berghaus et al ¹⁹	2012	Germany	Retrospective cohort	In-hospital	All	eGFR < 60 mL/min·1.73 m ⁻² (MDRD)	329	161 (49%)	52 (32%)	65 (16.7)	NA	7
10 Altinsoy et al ²⁰	2017	Turkey	Retrospective cohort	30 d	Normotensive	eGFR < 60 mL/min·1.73 m ⁻² (MDRD)	99	38 (38%)	55 (56%)	68	NA	7
11 Kresoja et al ²¹	2019	Germany	Prospective cohort	In-hospital	Without patients treated with thrombolysis	eGFR < 60 mL/min·1.73 m ⁻²	602	160 (27%)	262 (48%)	69	NA	7
Severe renal insufficiency												
5 Kostubiec et al ¹⁴	2019	Europe	Prospective cohort	30 d	All	eGFR ≤ 30 mL/min·1.73 m ⁻² (MDRD)	2,845	145 (5%)	1424 (50%)	66 (17)	24/199	7
8 Salinger-Martinovic et al ¹⁷	2019	Serbia	Prospective cohort	In-hospital	All	eGFR < 30 mL/min·1.73 m ⁻² (MDRD)	663	61 (9%)			28/72	NA
AKI												
12 Murgier et al ²⁶	2019	RIETE registry	Prospective cohort	30 d	All	KDIGO definition	21,131	6,222 (29%)	10,118 (48%)		634/602	7
13 Chang et al ²⁷	2017	Taiwan	Retrospective cohort	In-hospital	All	NA	7,588	372 (5%)	3,677 (48%)	65.8 (16.9)	201/1515	6

Abbreviations: AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; MDRD, Modification of Diet in Renal Disease; NA, not available; NOS, Newcastle-Ottawa Scale; RI, renal insufficiency; RIETE, Registro Informatizado de Enfermedad TromboEmbólica; SD, standard deviation.

Table 2 Pooled rates and RRs of short-term outcomes of patients with/without renal insufficiency

	With renal insufficiency/ rate (95% CI)	Without renal insufficiency/ rate (95% CI)	RR (95% CI)
All-cause mortality			
Self-reported renal disease	31% (21%, 42%)	10% (5%, 15%)	2.06 (1.50, 2.84)
Creatinine elevation	10% (5%, 25%)	5% (1%, 9%)	2.18 (1.41, 3.36)
eGFR < 60 mL/min·1.73 m ⁻²	15% (8%, 22%)	5% (2%, 8%)	1.72 (1.56, 1.89)
Severe renal insufficiency	30% (2%, 59%)	10% (5%, 14%)	3.32 (1.53, 6.70)
AKI	32% (11%, 75%)	13% (4%, 29%)	2.69 (1.24, 5.84)
PE-related death			
eGFR < 60 ml/min·1.73 m ⁻²	12% (6%, 18%)	4% (2%, 5%)	1.72 (1.55, 1.91)
Fatal bleeding			
Self-reported renal disease	NA	NA	NA
Creatinine elevation	NA	NA	NA
eGFR < 60 mL/min·1.73 m ⁻²	7% (0, 21%)	0 (0, 1%)	1.43 (1.22, 1.67)
AKI	5% (1%, 9%)	4% (0, 10%)	1.30 (0.79, 2.14)
Adverse outcomes			
eGFR < 60 ml/min·1.73 m ⁻²	22% (12%, 32%)	12% (0%, 26%)	2.64 (0.80, 8.68)

Abbreviations: AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; NA, not available; RR, risk ratio; 95% CI, 95% confidence interval.

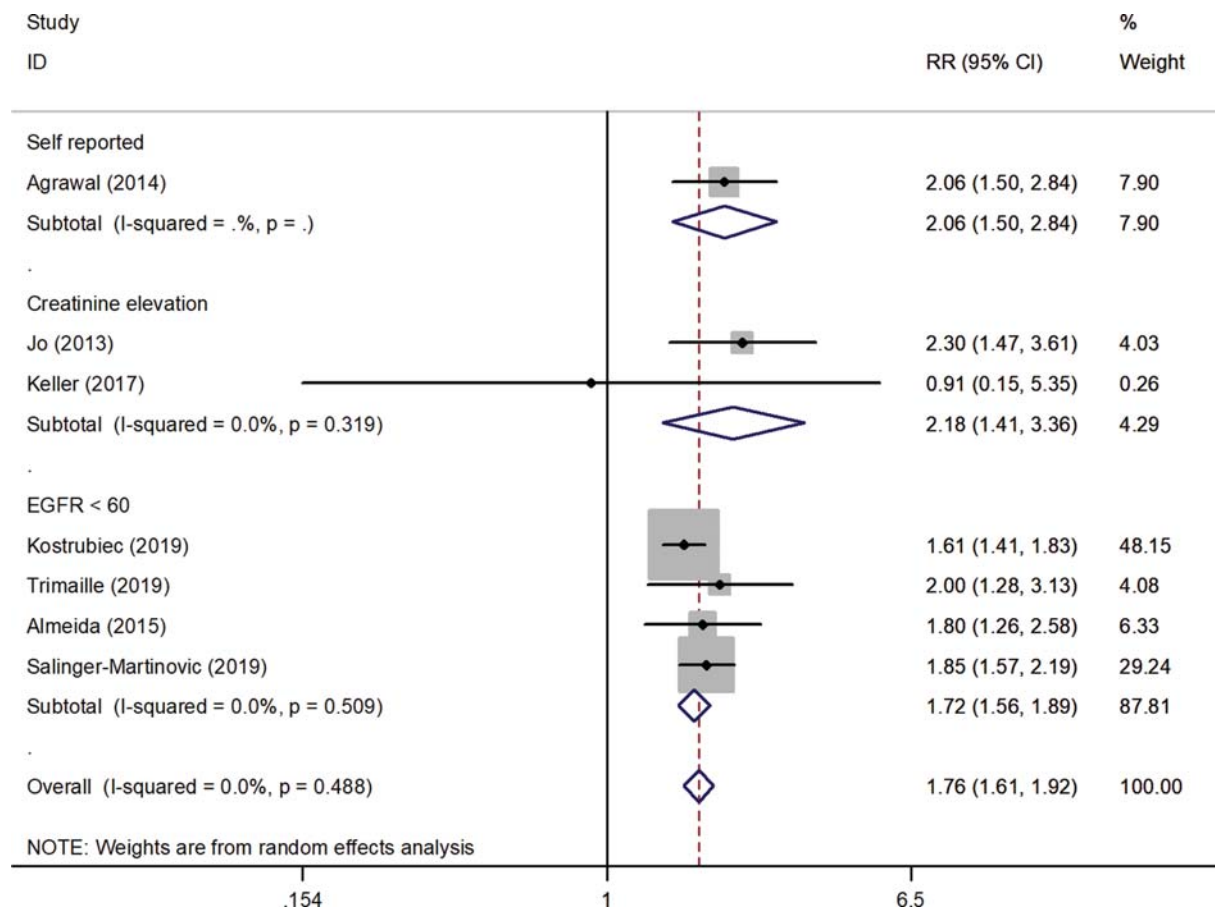


Fig. 2 Overall forest plot of renal insufficiency and all-cause death in pulmonary embolism (PE) patients. 95% CI, 95% confidence interval; eGFR, estimated glomerular filtration rate; RR, risk ratio.

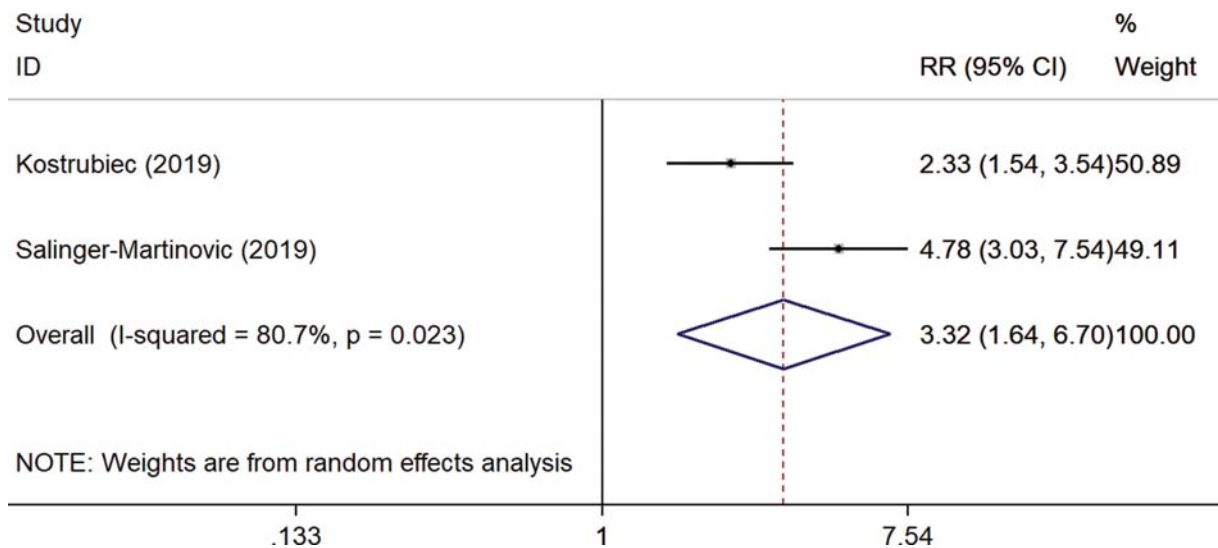


Fig. 3 Forest plot of all-cause death in pulmonary embolism (PE) patients with severe renal insufficiency.

Outcomes of Normotensive Patients

Three studies focused on normotensive or patients without thrombolysis. The outcomes are listed in ▶ **Table 3**. All-cause death, major bleeding, and adverse outcomes were higher in patients with renal insufficiency. Pooled RRs were not able to be calculated as the outcomes differed in each study.

Publication Bias

According to the funnel plot (▶ **Fig. 6**) and the asymmetry statistic of Egger's regression, the probability of publication bias was low (Egger's test $p = 0.583$).

Discussion

The results of the present meta-analysis indicate that renal insufficiency was a common comorbidity (nearly one-third) among acute PE patients. Renal insufficiency and AKI may have a significant impact on the early negative prognosis of acute PE patients. PE patients with renal insufficiency also had higher risk in PE-related death and fatal bleeding. Patients with severe renal insufficiency had significantly high risk (over threefold) for short-term all-cause mortality. Our results may have implications for the acute-phase management of PE patients who appear to have CKD and also calls for more attention to the dynamic changes of kidney function during management, in addition to the guideline-suggested risk stratification.

The prevalence of renal insufficiency, severe renal insufficiency, and AKI in different studies were around 14 to 46%, 5 to 9%, and 5 to 29%, respectively, indicating a high proportion of renal disease among PE patients. Several studies investigated an increasing risk for CKD patients to develop VTE.^{28,29} CKD patients are at risk of clot formation and risk of thrombosis. The mechanism includes increased level of procoagulant factors, decreased endogenous anticoagulants, and fibrinolytic activity.³⁰ Impaired kidney function may reflect not only chronic renal disease but also deterioration secondary to hemodynamic disturbances. Renal function is not only closely associ-

ated with preexisting renal pathology but also with hemodynamic alterations. However, it is difficult to distinguish between preexisting renal insufficiency and secondary kidney injury.³¹ Study from RIETE revealed that AKI was found almost in one-third of patients with PE and being more frequent and severe in patients with high-risk PE.²⁶ Right ventricular dysfunction in PE patients causes central venous pressure increase, results in venous congestion, and leads to renal congestion then injury.³²

Renal insufficiency has been reported to be a predictor of both early and long-term increased mortality in patients with VTE. Studies also demonstrated a long-term impact of renal failure in VTE patients. A study from RIETE showed that $\text{CrCl} < 50 \text{ mL/min}$ was an independent risk factor for 3-month all-cause death in VTE patients (adjusted HR 1.83).³³ Two of the studies included in our meta-analysis showed that patients with renal insufficiency had a HR of 2.31 (95% CI 2.13–2.48) for 6-month all-cause mortality in PE patients.¹⁴ Other studies that focus on VTE patients demonstrated similar results. In GARFILED-VTE study, over 12-month follow-up, patients with moderate- to-severe CKD were at an increased risk of all-cause mortality, major bleeding, and recurrent VTE.³⁴

The balance between bleeding and thrombosis in CKD patients receiving anticoagulant drugs is particularly complicated. Drug dosage should be adjusted according to patients' renal function. It has been reported that long-term risk of mortality and bleeding increased in CKD patients on warfarin therapy.³⁵ Ageno et al found that among 6,122 VTE patients, 38.1% were with moderate renal impairment and those patients were prescribed more nonvitamin K antagonist oral anticoagulants than those with normal renal function.³⁶ CKD has been considered as exclusion criteria in most of the randomized clinical trials. Thus, the high proportion of PE/VTE patients with CKD calls for more attention in routine clinical practice.

Our study indicated that renal function was associated with short-term PE outcome despite its different

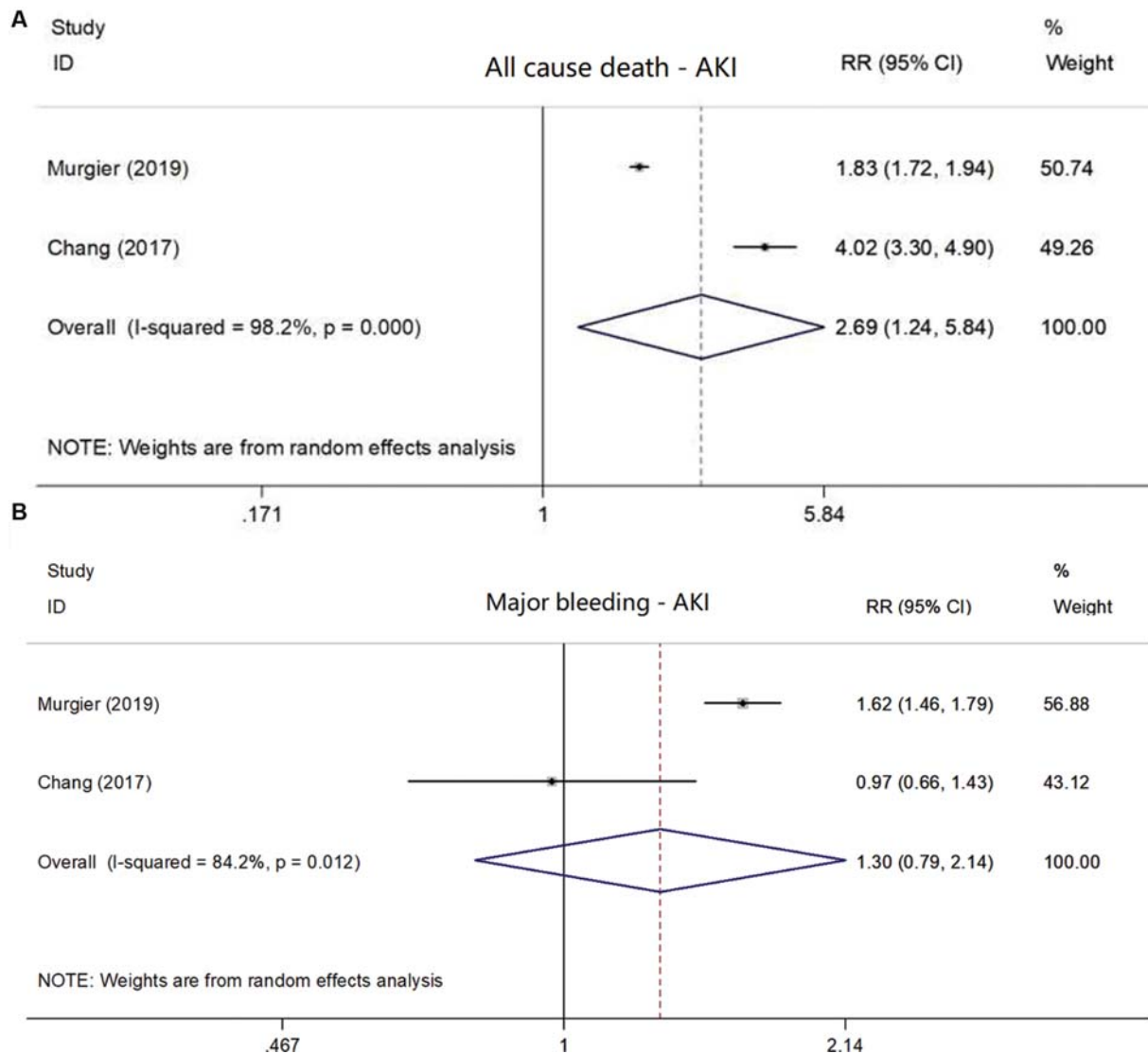


Fig. 4 Forest plots of all-cause death (A) and major bleeding (B) in pulmonary embolism (PE) patients with AKI. AKI, acute kidney injury; 95% CI, 95% confidence interval; RR, risk ratio.

stratifications of involved studies. GFR is routinely used as an indicator of renal function. The most popular method for GFR estimation is the simplified MDRD equation, which takes into account serum creatinine levels, age, race, and gender.³⁷ However, the CKD-EPI equation has been developed and reported to be more accurate than the MDRD formula.³⁸ The studies recruited in our analysis used MDRD or CrCl to estimate the renal function status; even one study defined chronic renal diseases according to patients' self-report. All the three measurements-defined renal insufficiency showed significant influence to short-term adverse outcome in PE patients. Altinsoy et al suggested that the CKD-EPI formula had higher value in predicting adverse outcome in PE patients than MDRD formula, by comparing the two equations among a same cluster of patients.²⁰ Some studies used serum creatinine level or the International Classification of Disease, 9th Revision, Clinical Modification to estimate renal function or define CKD and demonstrated no relationship between renal insufficiency and PE outcome,^{2,39} and some

results were paradoxical.²⁹ Thus, unified and accurate method to assess renal function in PE patients should be suggested.

To our knowledge, this is the first meta-analysis that focuses on renal function and short-term outcomes of acute PE. The recruited studies covered Europe, North America, and Asia. Our results call for attention to renal function, as well as its dynamic change during hospitalization of acute PE patients. Adding renal function to existing clinical severity score for acute PE is suggested. Meanwhile, the reason of the increased risk of death and bleeding should be further explained by investigating the correlation between treatment strategy and outcomes.

Limitations

Our meta-analysis has several limitations that need to be discussed. First, only 10 articles were included in the final analysis. Although there have been several ongoing large

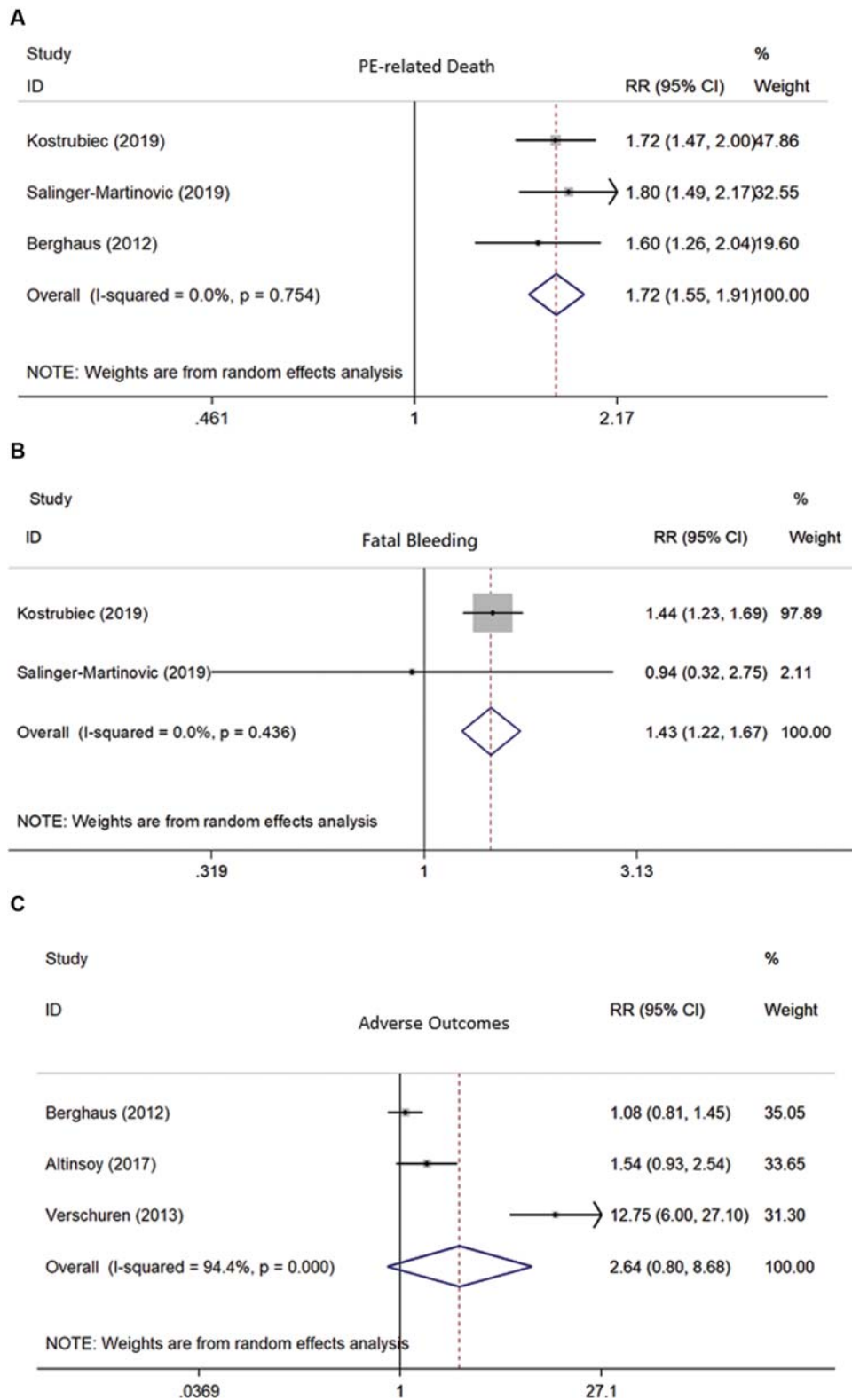


Fig. 5 Forest plots of pulmonary embolism (PE)-related death (A), fatal bleeding (B), and adverse outcomes (C) in pulmonary embolism (PE) patients with renal insufficiency. 95% CI, 95% confidence interval; RR, risk ratio.

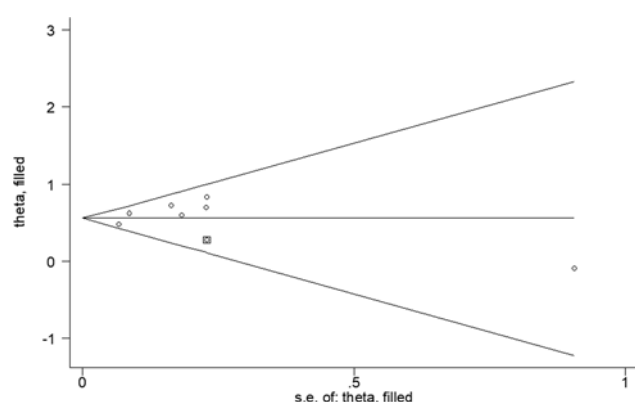
multicenter registries, accurate renal function classification is not available for all the studies and studies without clear definitions of renal insufficiency were excluded from analysis. Second, stratifications of renal function were different in the selected studies and are impossible to transform, which

may result in heterogeneity. Third, only normotensive patients were included in fatal bleeding analysis of severe renal insufficiency, which might be another source of heterogeneity. Finally, our study only included articles published in English language, which would increase the

Table 3 Short-term clinical outcomes of normotensive PE patients

No.	Author	Risk level	RI classification	RI number (%)	Outcome					
					All-cause death		Major bleeding		Adverse outcomes	
					With RI (%)	Without RI (%)	With RI (%)	Without RI (%)	With RI (%)	Without RI (%)
1	Kostrubiec et al	Low/intermediate	eGFR ≤ 60 mL/min·1.73 m ⁻²	924 (34.7%)	95 (10.3%)	89 (5.1%)	–	–	–	–
2	Kostrubiec et al	Low/intermediate	eGFR ≤ 30 mL/min·1.73 m ⁻²	116 (4.4%)	16 (13.8%)	168 (6.6%)	–	–	–	–
3	Altinsoy et al	Normotensive	eGFR < 60 mL/min·1.73m ⁻²	38 (38.4%)	–	–	9 (23.7%)	7 (11.5%)	–	–
4	Kresoja et al	All but without thrombolysis	eGFR < 60 mL/min·1.73m ⁻²	160 (26.6%)	–	–	–	–	13 (8.1%)	9 (2.0%)

Abbreviations: eGFR, estimated glomerular filtration rate; NA, not available; PE, pulmonary embolism; RI, renal insufficiency.

**Fig. 6** Filled funnel plot with pseudo-95% confidence limits.

publication bias. Subgroup analysis of normotensive PE patients could not be conducted due to the heterogeneity of studies. Further consideration of these patients should be focused as their characteristics and outcomes were different from high-risk PE.

Conclusion

Renal insufficiency is a predictor of short-term all-cause mortality in patients with acute PE. AKI and severe renal insufficiency had high risk for adverse short-term outcome in these patients. Our results may raise the attention in risk stratification and management of these patients in clinical practice.

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Conflict of Interest

None declared.

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