

World Journal of *Nephrology*

World J Nephrol 2021 July 25; 10(4): 37-75



MINIREVIEWS

- 37 Lower urinary tract dysfunction in pediatrics progress to kidney disease in adolescents: Toward precision medicine in treatment

Wishahi M

ORIGINAL ARTICLE**Retrospective Cohort Study**

- 47 Should pediatric idiopathic hypercalciuria be treated with hypocalciuric agents?

Penido MGG, Tavares MS

SYSTEMATIC REVIEWS

- 59 Prediction of mortality among patients with chronic kidney disease: A systematic review

Hansrivijit P, Chen YJ, Lnu K, Trongtorsak A, Puthenpura MM, Thongprayoon C, Bathini T, Mao MA, Cheungpasitporn W

ABOUT COVER

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Prediction of mortality among patients with chronic kidney disease: A systematic review

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Abstract

BACKGROUND

Chronic kidney disease (CKD) is a common medical condition that is increasing in prevalence. Existing published evidence has revealed through regression analyses that several clinical characteristics are associated with mortality in CKD patients. However, the predictive accuracies of these risk factors for mortality have not been clearly demonstrated.

AIM

To demonstrate the accuracy of mortality predictive factors in CKD patients by utilizing the area under the receiver operating characteristic (ROC) curve (AUC) analysis.

METHODS

We searched Ovid MEDLINE, EMBASE, and the Cochrane Library for eligible articles through January 2021. Studies were included based on the following

according to the PRISMA 2009 Checklist.

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criteria: (1) Study nature was observational or conference abstract; (2) Study populations involved patients with non-transplant CKD at any CKD stage severity; and (3) Predictive factors for mortality were presented with AUC analysis and its associated 95% confidence interval (CI). AUC of 0.70-0.79 is considered acceptable, 0.80-0.89 is considered excellent, and more than 0.90 is considered outstanding.

RESULTS

Of 1759 citations, a total of 18 studies ($n = 14579$) were included in this systematic review. Eight hundred thirty two patients had non-dialysis CKD, and 13747 patients had dialysis-dependent CKD (2160 patients on hemodialysis, 370 patients on peritoneal dialysis, and 11217 patients on non-differentiated dialysis modality). Of 24 mortality predictive factors, none were deemed outstanding for mortality prediction. A total of seven predictive factors [N-terminal pro-brain natriuretic peptide (NT-proBNP), BNP, soluble urokinase plasminogen activator receptor (suPAR), augmentation index, left atrial reservoir strain, C-reactive protein, and systolic pulmonary artery pressure] were identified as excellent. Seventeen predictive factors were in the acceptable range, which we classified into the following subgroups: predictors for the non-dialysis population, echocardiographic factors, comorbidities, and miscellaneous.

CONCLUSION

Several factors were found to predict mortality in CKD patients. Echocardiography is an important tool for mortality prognostication in CKD patients by evaluating left atrial reservoir strain, systolic pulmonary artery pressure, diastolic function, and left ventricular mass index.

Key Words: Chronic kidney disease; End stage kidney disease; End stage renal disease; Dialysis; Mortality; Death; Predictors

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Core Tip: Although the current evidence has shown that several clinical factors are associated with mortality in chronic kidney disease (CKD), the accuracy of mortality prediction has not been clearly demonstrated. Our systematic review of studies that reported prognostic mortality factors using area under the receiver operating characteristic curve analysis in CKD patients provides an accuracy measurement. A total of 18 studies were identified. Eight hundred thirty two patients had non-dialysis CKD, and 13747 patients had end-stage kidney disease. Of 24 predictive factors, none were considered outstanding for mortality prediction. A total of seven predictive factors were identified as excellent. Our review summarizes the current accuracy of prognostic factors for CKD mortality.

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INTRODUCTION

Chronic kidney disease (CKD) is defined by the presence of kidney damage (such as hematuria or structural abnormalities), an estimated glomerular filtration rate (eGFR) of less than 60 mL/min per 1.73 m², or albuminuria of greater than 30 mg in 24 h with duration of more than 3 mo[1]. The prevalence of CKD ranges from 8% to 16% of the population worldwide[2,3]. CKD is more prevalent in low- and middle-income countries compared with high-income countries[4]. With the increasing prevalence of hypertension and diabetes, it is projected that CKD prevalence in adults over 30-years-old will increase from 14.4% in 2020 to 16.7% in 2030[5]. Moreover, in the general

population of the United States, the average GFR decline rate is approximately 1 mL/min per 1.73 m² per year[6,7] with a lifetime risk of developing CKD (as defined by eGFR less than 60 mL/min per 1.73 m²) of more than 50%[8].

Progression of CKD has been associated with significantly increased adverse clinical outcomes, such as end-stage kidney disease (ESKD), dialysis dependence, cardiovascular events, and all-cause mortality[9,10]. Tonelli *et al*[11] conducted a meta-analysis of 38 studies that included over 1.3 million participants. They showed that the absolute risk for death increased exponentially with decreasing kidney function[11]. Several risk factors have been identified to predict mortality in CKD patients. One meta-analysis demonstrated that age, diabetes, previous cardiovascular disease, adiponectin, and C-reactive protein are all risk factors for mortality in dialysis patients [12]. Alternatively, an analysis of the Cleveland Clinic CKD Registry of 621 CKD patients with age > 65 years showed that increasing age, congestive heart failure, absence of arteriovenous fistula, and lack of nephrology care prior to dialysis initiation were significant risk factors for increased 1-year mortality after dialysis initiation[13]. However, data on mortality risk factors for non-dialysis dependent CKD patients are limited.

Nearly all of the available evidence has reported their findings using regression analysis. Thus, the accuracy of mortality prediction has not been clearly demonstrated. In this study, we conducted a systematic review of studies that utilized associated area under the receiver operating characteristic (ROC) curve (AUC) analysis to report predictive factors for mortality in CKD patients. This method allows the reader to assess the predictive accuracy of distributional models in comparison with regression analyses[14]. Our findings would help guide the future design of an accurate mortality risk calculator for CKD patients.

MATERIALS AND METHODS

Search strategy

This manuscript follows the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis)[15] statement as well as MOOSE (Meta-analysis of Observational Studies in Epidemiology)[16] guidelines. A systematic search was conducted through Ovid MEDLINE, EMBASE, and the Cochrane Library from each respective database inception to January 2021. The domain for the systematic search on Cochrane Library included PubMed, EMBASE, ClinicalTrials.gov, and International Clinical Trial Registry Platform (ICTRP). The following search terms were used: (“chronic kidney disease” OR “CKD” OR “end-stage kidney disease” OR “ESKD” OR “end-stage renal disease” OR “ESRD”) AND (“mortality” OR “death” OR “survival”) AND (“area under curve” OR “AUC”). The detailed search strategy for each database is summarized in [Supplementary material](#), Appendix 1. No language restrictions were applied during the systematic search.

Inclusion criteria

The eligibility of each study was determined by the following inclusion criteria: (1) The study nature was observational or conference abstract; (2) Study populations involved patients with non-transplant CKD at any CKD stage severity; and (3) Predictive factors for mortality were presented with AUC analysis and its associated 95% confidence interval (CI). Case reports, case series, review articles, or articles concerning pediatric patients were excluded. Study eligibility was independently evaluated by two investigators (Hansrivijit P and Chen YJ). Disagreements were resolved by mutual consensus among all authors. The quality of each study was appraised using the Newcastle-Ottawa quality scale which assesses six components: (1) representativeness of the subjects, (2) ascertainment of the exposure, (3) demonstration of the outcome of interest was not present at the start of study, (4) assessment of outcome, (5) follow-up duration period was long enough for the outcome to occur, and (6) adequate follow-up duration.

Review process and data extraction

The titles and abstracts of all references were screened (Hansrivijit P and Chen YJ) prior to proceeding with full-text review. The full-text of the selected screened articles were then reviewed to determine their eligibility for inclusion into the systematic review. A standardized data collection form was invented to extract the following information from included study: first author's name, year of publication, country of origin, study design, subject(s), sample size, age, male sex, AUC and its 95%CI, and

follow-up duration. Full articles or conference abstracts that reported the AUC without 95%CI were excluded. An AUC of 1.0 represents the ideal predictor with a 100% sensitivity and 0% false positive rate. Thus, in this mortality model, factors with AUC closer to 1.0 represented a better predictor for mortality, with AUC of 0.70-0.79 considered acceptable, 0.80-0.89 considered excellent, and more than 0.90 considered outstanding[17,18].

RESULTS

Study characteristics

A total of 1759 citations underwent three passes of article screening. After duplicates were removed, another 1665 irrelevant articles were excluded after the title and abstract were screened. The methods and results of the remaining 94 articles were then evaluated for eligibility in accordance with the inclusion criteria. Only 31 articles passed this stage to undergo full-text review. A final total of 18 studies from 2004 to 2021 consisting of 14579 subjects were included in this systematic review. **Figure 1** provides a flowchart of the literature search and study selection. All studies were observational in nature (retrospective in 33.3% and prospective in 66.7%). The median age was 62.0 (\pm 4.1) years, and 57.3% were male. The median duration of follow-up was 2.0 (\pm 1.1) years. **Table 1** describes the included study characteristics and results. The risk of bias assessment is shown in **Supplementary Table 1**.

Study population

Of 14579 patients from 18 studies, 832 patients had non-dialysis CKD, and 13,747 patients had dialysis-dependent CKD. Among studies that included dialysis-dependent CKD patients, 2160 patients required hemodialysis (HD) and 370 patients required peritoneal dialysis (PD). The remaining 11217 patients (from four studies) had been composed of a non-differentiated mixed population of HD and PD patients. **Figure 2** illustrates the study population classification.

Predictive factors for mortality

A total of 24 predictive factors for mortality were identified. We classified these factors into three categories depending on their AUCs. None had an AUC greater than 0.90, which is considered outstanding for mortality prediction. The majority ($n = 17$) were in the acceptable range (AUCs 0.70-0.79). A total of seven predictive factors were identified as excellent (AUCs 0.80-0.89). **Table 2** shows the predictive factors for mortality based on the population studied.

DISCUSSION

Excellent predictors (AUC 0.80-0.89)

N-terminal pro-brain natriuretic peptide (NT-proBNP) and brain natriuretic peptide (BNP) were found to be excellent predictors of mortality in dialysis patients[22,24]. In the general population, numerous factors such as age, female sex, and obesity can influence NT-proBNP level separate from heart failure[37]. BNP is eliminated by three main mechanisms: enzymatic metabolism, clearance through receptors, and urinary excretion[22]. Both BNP and NT-proBNP can be elevated in dialysis patients due to poor renal clearance, concomitant heart disease, heart failure, and volume expansion [38,39]. The mechanisms underlying the link between elevated BNP and NT-proBNP with increased mortality have not been fully established. One study suggested that chronic HD induces recurrent transient episodes of myocardial ischemia that result in myocardial stunning, hibernation, and remodeling[40]. Burton *et al*[40] described in this study that the decline in cardiac function and cardiac stunning were correlated with increasing BNP levels. These myocardial changes likely have a causative pathophysiologic role in the high cardiovascular complication rates and deaths in HD patients.

Soluble urokinase plasminogen activator receptor (suPAR) and C-reactive protein (CRP) were also excellent predictors for mortality in dialysis patients[29,36]. SuPAR is a proteolytic cleavage product of the glycosyl-phosphatidylinositol anchor of the urokinase plasminogen activator receptor expressed on immune and endothelial cells [41]. The concentration of suPAR is low in healthy individuals, but it becomes elevated in the presence of infection or inflammatory diseases[41]. Observational studies of

Table 1 Study characteristics

Ref.	Country	Study type	n	Subject	Age, yr	Male, %	AUC for mortality (95%CI)	Follow-up
Dara <i>et al</i> [19], 2004	United States	Retrospective	476	HD patients	66	58	APACHE III on hospital mortality 0.76 (0.66-0.84) and 30-d mortality 0.78 (0.68-0.86); SOFA score on hospital mortality 0.65 (0.55-0.75) and 30-d mortality 0.66 (0.55-0.76)	-
Miskulin <i>et al</i> [20], 2004	United States	Prospective	1779	Outpatient dialysis patients	62	53	ICED 0.72 (0.69-0.75); CCI 0.67 (0.65-0.70); Wright- Khan indices 0.68 (0.65-0.70); Davies indices 0.68 (0.65-0.70)	1 yr
Wang <i>et al</i> [21], 2007	Hong Kong	Prospective	238	ESRD on continuous PD	55.7	51.3	cTnT 0.774 (0.706-0.841); High sensitivity CRP 0.691 (0.614-0.768)	3 yr
Sun <i>et al</i> [22], 2008	China	Prospective	217	HD patients	65.4	62.2	BNP on CV events 0.61 (0.57-0.70); NT-proBNP on CV events 0.83 (0.75-0.91)	2 yr
Selim <i>et al</i> [23], 2010	Macedonia	Prospective	125	HD patients	48.8	-	BNP > 1200 pg/mL on CV mortality 0.612 (0.473-0.750); NT-proBNP > 10000 pg/mL on CV mortality 0.747 (0.677-0.816)	2 yr
Breidthardt <i>et al</i> [24], 2011	Switzerland	Retrospective	113	HD patients	67.9	60	BNP: all-cause mortality 0.70 (0.60-0.81); BNP: CV mortality 0.82 (0.73-0.90)	735 d
Tomaszuk-Kazberuk <i>et al</i> [25], 2011	Poland	Prospective	39	HD patients	59	63.8	Perfusion defects on MCE for death 0.752 (0.582-0.878)	3 yr
Chiang <i>et al</i> [26], 2016	Taiwan	Prospective	132	ESRD patients on PD	53.7	47.0	Short-term detrended fluctuation analysis (DFA α 1) < 0.95-0.761 (0.617-0.905)	34 mo
Sato <i>et al</i> [27], 2017	Japan	Retrospective	302	HD patients	63.4	65.4	Neutrophil-lymphocyte ratio for 1-yr mortality 0.791 (0.602-0.980)	1 yr
Wang <i>et al</i> [28], 2018	China	Prospective	300	CKD 3-5	60	53.6	UPCR for mortality 0.78 (0.72-0.84); eGFR for mortality 0.75 (0.69-0.81); Mitral E/E' ratio for mortality 0.74 (0.67-0.80); LV mass index for mortality 0.72 (0.65-0.79); LVEF for mortality 0.50 (0.42-0.58)	68 mo
Wlazeł <i>et al</i> [29], 2018	Poland	Prospective	64	HD patients	66	66	SuPAR 0.84 (0.7-0.94)	3 yr
Danial <i>et al</i> [30], 2019	Malaysia	Retrospective	160	CKD 3-5 with adverse drug reaction	-	57.5	Mortality risk score model 0.789 (0.700-0.878)	Few weeks (until end date of ADRs)
Jagadeswaran <i>et al</i> [31], 2019	India	Prospective	129	Pre-dialysis CKD 3-5	50.6	51.2	Malnutrition inflammation score for mortality 0.709 (0.604-0.815)	36 mo
Mukai <i>et al</i> [32], 2019	Sweden	Prospective	261	CKD 5 (both dialysis and non-dialysis)	56	66	Skin autofluorescence for all-cause mortality 0.78 (0.71-0.86); Augmentation index for all-cause mortality 0.81 (0.75-0.87)	25 mo
Pladys <i>et al</i> [33], 2020	France	Retrospective	9052	ESRD on dialysis	68.4	-	Rennes score model 1(REIN and SNDS data) 0.789 (0.761-0.816); Model 2 (REIN data only) 0.794 (0.768-0.821); Wright classification 0.631 (0.621-0.639); Modified CCI 0.703 (0.689-0.716)	1 yr
Shahidi <i>et al</i> [34], 2020	Iran	Retrospective	824	HD patients	57.9	61.8	Hemoglobin change on mortality 0.61 (0.56-0.65)	24.08 mo
Gan <i>et al</i> [35], 2021	Australia	Prospective	243	CKD 3-4	65.6	62.6	Left atrial reservoir strain for CV death 0.84 (0.76-0.90)	3.9 yr
Rroji <i>et al</i> [36], 2021	Albania	Prospective	125	ESRD on dialysis	52.4	60.0	CRP on CV mortality 0.80 (0.73-0.92); Left ventricular mass index on CV mortality 0.76 (0.65-0.88); Ratio of early mitral inflow velocity/annular diastolic velocity	2 yr

(E/E') on CV mortality 0.75 (0.64-0.86); Systolic pulmonary artery pressure on CV mortality 0.80 (0.68-0.92); Pulse pressure on CV mortality 0.72 (0.60-0.84)

APACHE: Acute physiology and chronic health evaluation; AUC: Area under receiver operating characteristic curve; BMI: Body mass index; BNP: Brain natriuretic peptide; CAPD: Continuous ambulatory peritoneal dialysis; CCI: Charlson Comorbidity Index; CKD: Chronic kidney disease; CRP: C-reactive protein; CI: Confidence interval; cTnT: Cardiac troponin T; CV: Cardiovascular; E/E': Ratio of early inflow velocity/annular diastolic velocity; eGFR: Estimated glomerular filtration rate; ESRD: End-stage renal disease; HD: Hemodialysis; ICED: Index of coexisting disease; LV: Left ventricular; MCE: Myocardial contrast echocardiography; ND: Non-dialysis; NT-proBNP: N-terminal pro-brain natriuretic peptide; PAP: Pulmonary artery pressure; PD: Peritoneal dialysis; REIN: Renal epidemiology and information network; SOFA: Sequential organ failure assessment; SNDS: French national health insurance information system; SuPAR: Soluble urokinase plasminogen activator receptor; UPCR: Urine protein creatinine ratio.

dialysis patients have shown that higher suPAR levels are detected in patients that have severe angiographic coronary artery disease[29,42] or after cardiovascular events, both of which are associated with significantly increased cardiovascular death[43]. Increased suPAR levels are also associated with end-organ fibrosis, such as cirrhosis [44,45] and focal segmental glomerulosclerosis[46]. Similarly, CRP is a nonspecific acute phase reactant that can be elevated in the setting of infection or inflammatory processes[47]. Higher CRP levels are associated with pulmonary hypertension, which could represent crosstalk between inflammatory cells and pulmonary wall components[36,48,49]. Moreover, a population-based study demonstrated that CRP is independently associated with elevated parathyroid hormone levels (PTH) and increased mortality[50]. Elevated PTH in CKD patients can lead to renal osteodystrophy and accelerated vascular calcification. The associations between suPAR, CRP, and increased death suggest that these markers show promise for use as standard CKD mortality predictors in the future.

Echocardiography has been shown as a useful tool in the assessment of mortality risk in CKD patients. Gan *et al*[35] have demonstrated that impaired left atrial reservoir strain (LASr) is the best predictor of adverse cardiovascular outcomes in CKD stage 3-4 patients. In this assessment, the left atrium is divided into a total of 12 segments: six segments each from the apical four- and two-chamber views. LASr is measured from the average peak systolic strain from the 12 segments[35]. Impaired LASr is defined as $\leq 23\%$, based on a previously reported lower limit of reference value[51]. A few hypotheses have been postulated to link impaired LASr and mortality in the CKD population. First, the left atrium may be more predictive for mortality because it is a thin-walled chamber and may exhibit earlier alterations before the left ventricle[51]. Second, alterations of LASr irrespective of left ventricular (LV) function have been noted in heart failure with preserved ejection fraction[52], further highlighting it as a more sensitive marker. The underlying mechanisms for reduced LASr are believed to be a consequence of atrial fibrosis, which could be accelerated in the setting of CKD due to the attendant high systemic inflammatory state[53,54]. These potential pathophysiologic mechanisms may explain the significance of reduced LASr as an early indicator for poor outcomes in non-dialysis CKD patients.

Rroji *et al*[36] added that systolic pulmonary artery pressure (PAP) is predictive for mortality in dialysis patients. Other studies have concordantly shown that pulmonary hypertension (PH) confers a significant mortality risk in dialysis patients[55,56]. The prevalence of PH increases with CKD severity[55], and several studies have proposed mechanisms for the association between PH and CKD for both non-dialysis and dialysis patients. Arteriovenous fistulas for dialysis access and exposure to bio-incompatible dialysis membranes are a few of these factors that could increase the risk for PH in CKD patients[48,57]. The latter causes neutrophil activation that subsequently migrates to the lungs, resulting in increased pulmonary inflammation and vascular resistance[57]. For non-dialysis CKD patients, CKD itself can pathophysiologically directly incite pulmonary circulatory dysfunction and remodeling through uremic toxins, systemic inflammation, altered vasoregulation and endothelial dysfunction[48]. Altogether, prompt detection of PH *via* measurement of the systolic PAP could result in earlier intervention in order to prevent excess mortality in CKD patients.

Augmentation index (AIx) was predictive of mortality in CKD patients[32]. AIx was derived from the arterial pulse wave analysis using a tonometry-based SphygmoCor device[32]. Augmentation pressure (AP) is defined as the maximum systolic pressure subtracted from the inflection point pressure (the merging of incident and the reflected wave). AIx is defined as AP divided by pulse pressure (PP), presented as a percentage.

Table 2 Predictive factors for mortality in chronic kidney disease patients

AUC range	Interpretation	Predictive factors (AUC)	Subjects	Ref.
≥ 0.90	Outstanding	-	-	-
0.80-0.89	Excellent	NT-proBNP (0.83)	HD	Sun <i>et al</i> [22]
		BNP (0.82)	HD	Breidthardt <i>et al</i> [24]
		SuPAR (0.84)	HD	Wlazel <i>et al</i> [29]
		Augmentation index (0.81)	ND, HD, PD	Mukai <i>et al</i> [32]
		Left atrial reservoir strain (0.84)	ND	Gan <i>et al</i> [35]
		CRP (0.80)	HD, PD	Rroji <i>et al</i> [36]
		Systolic PAP (0.80)	HD, PD	Rroji <i>et al</i> [36]
0.70-0.79	Acceptable	APACHE III (0.76)	HD	Dara <i>et al</i> [19]
		ICED (0.72)	HD, PD	Miskulin <i>et al</i> [20]
		cTnT (0.77)	PD	Wang <i>et al</i> [21],
		NT-proBNP > 10000 pg/mL (0.75)	HD	Sun <i>et al</i> [22]
		MCE perfusion defect (0.75)	HD	Tomaszuk-Kazberuk <i>et al</i> [25]
		DFA1 < 0.95 (0.76)	PD	Chiang <i>et al</i> [26]
		Neutrophil/lymphocyte ratio (0.79)	HD	Sato <i>et al</i> [27]
		UPCR (0.78)	ND	Wang <i>et al</i> [28]
		eGFR (0.75)	ND	Wang <i>et al</i> [28]
		Mitral E/E' ratio (0.74, 0.75)	ND, HD, PD	Wang <i>et al</i> [28] and Rroji <i>et al</i> [36]
		LV mass index (0.72, 0.76)	ND, HD, PD	Wang <i>et al</i> [28] and Rroji <i>et al</i> [36]
		Mortality risk score (0.79)	ND	Danial <i>et al</i> [30]
		Malnutrition inflammation score (0.71)	ND	Jagadeswaran <i>et al</i> [31]
		Skin autofluorescence (0.78)	ND, HD, PD	Mukai <i>et al</i> [32]
		Rennes score (0.79)	HD, PD	Pladys <i>et al</i> [33]
		Modified CCI (0.70)	HD, PD	Pladys <i>et al</i> [33]
Pulse pressure (0.72)	HD, PD	Rroji <i>et al</i> [36]		

APACHE: Acute physiology and chronic health evaluation; AUC: Area under receiver operating characteristic curve; BMI: Body mass index; BNP: Brain natriuretic peptide; CAPD: Continuous ambulatory peritoneal dialysis; CCI: Charlson Comorbidity Index; CKD: Chronic kidney disease; CRP: C-reactive protein; CI: Confidence interval; cTnT: Cardiac troponin T; CV: Cardiovascular; E/E': Ratio of early inflow velocity/annular diastolic velocity; eGFR: Estimated glomerular filtration rate; ESRD: End-stage renal disease; HD: Hemodialysis; ICED: Index of coexisting disease; LV: Left ventricular; MCE: Myocardial contrast echocardiography; ND: Non-dialysis; NT-proBNP: N-terminal pro-brain natriuretic peptide; PAP: Pulmonary artery pressure; PD: Peritoneal dialysis; REIN: Renal epidemiology and information network; SOFA: Sequential organ failure assessment; SNDS: French national health insurance information system; SuPAR: Soluble urokinase plasminogen activator receptor; UPCR: Urine protein creatinine ratio.

This index represents arterial stiffness, which could be a result of various patho-physiologic mechanisms. For example, fibrosis, disruption of elastin fibers, calcification, or diffusion of macromolecules within arterial walls are potential contributors [32]. Although AIx is useful in predicting mortality in CKD patients, given the invasive nature of this procedure, the clinical use of this parameter to monitor and prognosticate outcomes in the ambulatory setting is limited.

Acceptable predictors (AUC 0.70-0.79)

Non-dialysis population: Several predictive factors for mortality have been identified among non-dialysis CKD participants. Urine protein creatinine ratio (UPCR), eGFR, mortality risk score and malnutrition inflammation score (MIS) have been demonstrated to be predictive of mortality in this patient population[28,30,31]. It is thus not surprising that Wang *et al*[21] reported that UPCR and eGFR are predictive of

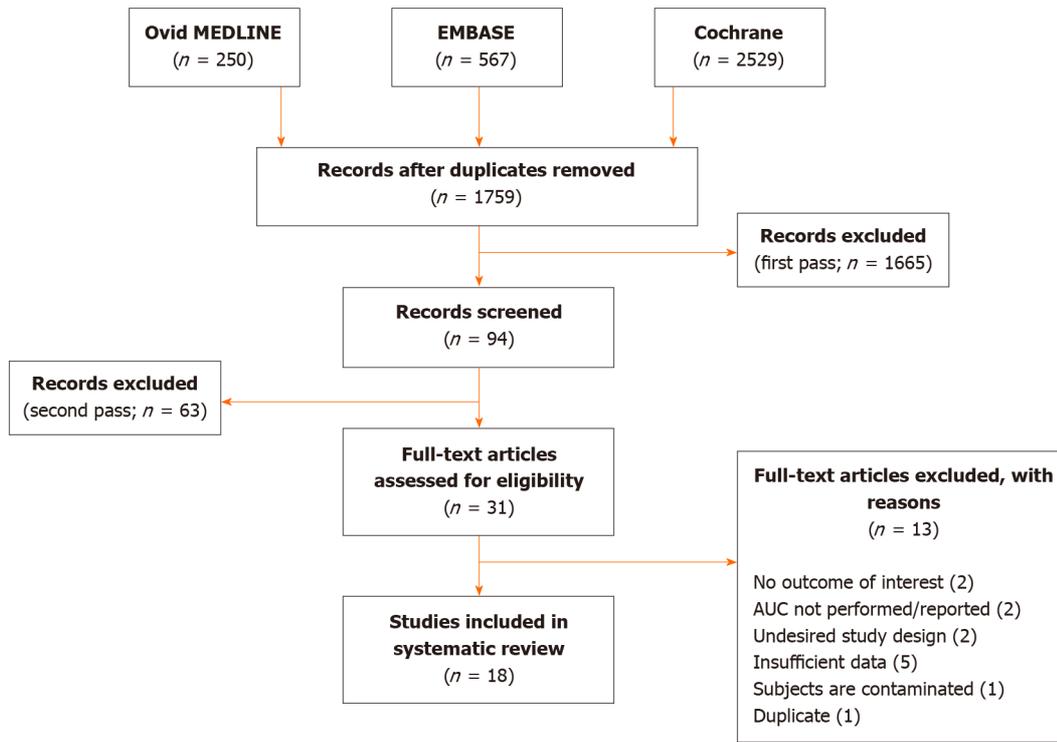


Figure 1 Flowchart of the literature search and study selection. “Undesired study design” includes non-human studies ($n = 2$); “Insufficient data” includes conference abstracts that reported only area under the receiver operating characteristic curve (AUC) without 95% confidence interval ($n = 5$); “Subjects are contaminated” refers to a study that has mixed chronic kidney disease (CKD) and non-CKD subjects ($n = 1$).

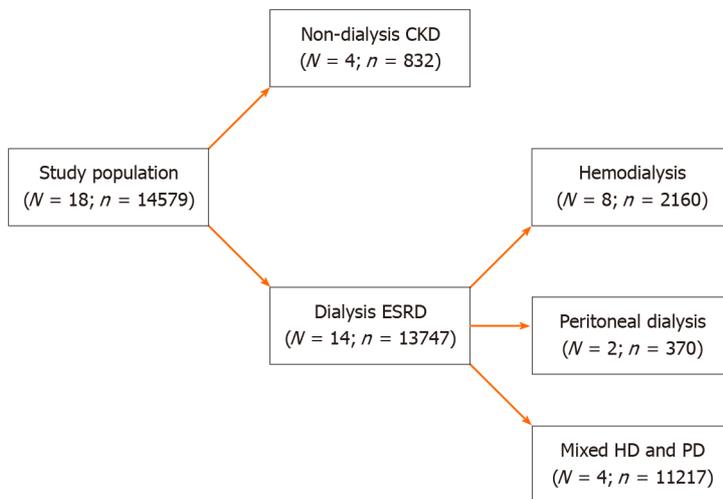


Figure 2 Algorithm of study population classification. CKD: Chronic kidney disease; ESRD: End-stage renal disease; HD: Hemodialysis; N: Number of population classification; PD: Peritoneal dialysis.

mortality among CKD patients. The presence of proteinuria in CKD patients has been widely associated with an increased risk of CKD progression and death[58]. Similarly, eGFR decline represents progression of CKD severity, which independently confers a significantly increased mortality risk[59,60]. Renal interstitial fibrosis/scarring and tubular atrophy are consistent with GFR decline and degree of proteinuria[58]. Along with these changes, the tubular epithelial cells are stimulated to synthesize reactive oxygen species, which further attracts inflammatory cells and interstitial myofibroblasts, leading to more fibrosis and scarring[58]. These interstitial changes are associated with CKD progression, which could indirectly increase mortality[58]. Thus, early interventions aiming to prevent proteinuria and CKD progression are essential for reducing mortality in CKD patients.

In 2019, Danial *et al*[30] developed a mortality risk score for CKD patients. In this study, the authors investigated mortality from adverse drug reactions (ADRs) that specifically occurred in CKD patients. The mortality risk prediction model included the following variables: (1) History of heart disease; (2) Dyslipidemia; (3) Electrolyte imbalance; (4) Psychotic agents; (5) Creatine kinase; (6) Total number of medications; and (7) Conservative management (how the treatment was provided to subjects with ADR)[30]. The authors noted that these clinical factors are easily obtained in clinical practice, and this score allowed preemptive identification of CKD patients at risk of ADR-associated mortality. These patients may thus have a significant benefit with early clinical intervention and medication adjustment. However, this model has not been proven to be predictive of mortality outside the scope of ADR, and consequently, its applicability in general CKD patients may be limited.

MIS is another mortality risk predictor tool for both pre-dialysis and dialysis-dependent CKD patients. The MIS consists of ten elements obtained from the past medical history, physical examination, body mass index, and laboratory indices[61]. In 2001, Kalantar-Zadeh *et al*[61] demonstrated that the MIS correlated with morbidity and mortality in maintenance HD patients. Later, Jagadeswaran *et al*[31] applied MIS to a pre-dialysis Indian population and found that MIS had a 56.5% sensitivity and 81% specificity (AUC 0.709; 95%CI: 0.604-0.815) for mortality prediction during a 36-month follow-up. The mortality risk increased by 13.7% for each additional point in the MIS. These studies demonstrate the importance of malnutrition prevention for both pre-dialysis and dialysis-dependent CKD patients.

Echocardiographic factors: The ratios of early inflow velocity/annular diastolic velocity (E/E') through the mitral valve and the LV mass index are predictive of mortality in CKD patients, regardless of dialysis status[28,36]. Mitral E/E' ratio may be a marker of LV diastolic dysfunction[62] or a predictor of pulmonary hypertension [36]. Diastolic dysfunction has been associated with increased mortality in various CKD and non-CKD patient populations[63-65]. Similarly, an increased LV mass index represents LV hypertrophy, a well-established predictor for heart failure and death in CKD patients[66]. The 2013 European Society of Hypertension/European Society of Cardiology guidelines recommend performing echocardiography to refine cardiovascular risk assessment in hypertensive patients[67]. However, there are no recommendations specifically for CKD patients, despite studies showing an increased prevalence of LV hypertrophy with advancing CKD[68]. Our study further adds to the available evidence supporting echocardiography for mortality risk stratification in CKD patients. It should be highlighted that a combination of echocardiographic findings should be utilized to predict mortality in CKD patients, rather than isolated findings. This concept is supported by Tripepi *et al*[69] where the measurement of LV mass index in isolation does not provide significant prognostic value for CKD patients.

Real-time myocardial contrast echocardiography (MCE) is a non-invasive tool for assessment of myocardial ischemia in HD patients[70]. During this procedure, intravenous contrast is utilized to assess myocardial perfusion adequacy, which is defined as homogenous enhancement in > 50% of myocardial wall thickness for each segment[25]. One study showed that MCE and coronary angiography resulted in equal accuracy for anticipating combined cardiovascular endpoints and death[25]. The authors concluded that MCE is a safe and uncomplicated test that can aid in the selection of candidates for coronary revascularization. However, this data was limited to only HD patients. The utility of MCE should be confirmed in large multi-center studies of non-dialysis CKD patients.

Comorbidities: Comorbidities may serve as significant predictors for mortality in dialysis patients. Miskulin *et al*[20] investigated the index of coexisting disease (ICED) as an accurate mortality predictor in dialysis patients. In this study, ICED had greater discriminatory ability than other instruments. ICED is comprised of 19 medical conditions and 11 physical impairments; these are classified into four and three severity levels, respectively[20]. Another unique feature of ICED is the assessment of physical limitations, which has been shown as a strong prognostic factor in dialysis patients[71].

The Rennes comorbidity score and modified Charlson Comorbidity Index (CCI) have also been demonstrated to be predictive for mortality among dialysis patients [33]. The Rennes comorbidity score consists of seven components: Age, albumin level, cardiac, respiratory, and hepatic diseases, active malignancy, and walking disability [33]. Similarly, the modified CCI consists of 16 matrices composed of a wide range of medical comorbidities found in the original CCI plus patient's age[33]. Pladys *et al*[33] found that the original CCI (without including patient's age) had a low ability to

predict 1-year mortality. Surprisingly, the Rennes score resulted in a very impressive ability to predict 1-year mortality among dialysis patients despite its inclusion of only seven variables[33]. Altogether, we conclude that specific comorbidities are crucial in determining mortality risk among dialysis patients. Not unexpectedly, accuracy is improved by the consideration of several high-yield comorbidities rather than relying solely on one particular comorbidity.

Miscellaneous: Acute physiologic assessment and chronic health evaluation (APACHE) III is an acceptable predictor for hospital, and 30-d mortality among HD patients admitted to the intensive care unit (ICU)[19]. The APACHE III prognostic system was invented in 1991 and has been validated in several patient populations [72]. The APACHE III is calculated from clinical data obtained during the first 24 h of ICU admission. It consists of several components, including the primary reason for ICU admission, age, sex, race, preexisting comorbidities, and location prior to ICU admission[72]. Although several modifications have been made to the original APACHE score, only APACHE III has confirmed accuracy for mortality prediction in critically ill HD patients. Dara *et al*[19] compared the performance of APACHE III with the SOFA score. They found that APACHE III outperformed SOFA score for mortality prediction in critically ill HD patients. In our systematic review, this was the only study that focused on ICU patients.

The prognostic value of serological biomarkers, such as cardiac troponin T (cTnT) and NT-proBNP, for mortality in dialysis patients has been shown in observational studies[21,22]. As noted earlier, these biomarkers highlight the association between cardiac remodeling and death in dialysis patients. cTnT has been shown to predict mortality in PD patients independent of inflammation, residual renal function, and cardiac hypertrophy[21]. This was supported by the recent Netherland Cooperative Study on the Adequacy of Dialysis report, where the predictive power of cTnT for mortality is superior to other risk factors in a mixed population of HD and PD patients [73]. We suggest the use of cTnT for its prognostic value in at least PD patients due to its ease of testing.

Pre-dialysis neutrophil-lymphocyte ratio (NLR) is a novel and strong short-term predictor for all-cause mortality in HD patients[27]. NLR has been shown to have predictive utility in numerous disease states, including acute myocardial infarction and autoimmune disease[74,75]. NLR represents systemic inflammation, nutritional status, and atherosclerosis, which are all prevalent in CKD patients[76,77]. One single-center Japanese cohort revealed that NLR is superior to other generic biomarkers for 1-year survival among patients with ESKD due to diabetic nephropathy[27]. Although the usefulness of NLR has been widely studied in CKD patients, more data on its accuracy in diverse CKD patients are needed.

Skin autofluorescence (SAF) has been studied in healthy and uremic individuals[78-80]. SAF is predictive of microvascular disease progression, cardiovascular events, and nonspecific adverse clinical outcomes in diabetic and CKD patients regardless of dialysis status[79,81-84]. SAF is measured by illuminating approximately 1 cm² of skin surface with a 300-420 nm light source. SAF is calculated as the ratio between the emission light and reflected excitation light, multiplied by 100[32]. It is speculated that SAF represents the accumulation of advanced glycation end-products that cause collagen and elastin cross-linking, which can translate into increased arterial stiffness [85-87]. In 2019, Mukai *et al*[32] found that SAF in CKD patients is predictive of adverse clinical outcomes, including death. This study supports the association between SAF, arterial stiffness, and increased mortality in CKD patients.

PP is the difference between systolic and diastolic blood pressure. Rroji *et al*[36] demonstrated that PP has a significant impact on dialysis patient survival. In their study, patients with pulmonary hypertension had significantly higher PP compared with patients without pulmonary hypertension. The underlying mechanism between increased PP and death in CKD is not fully understood. However, we postulate that increased PP, either from a reduction of diastolic blood pressure or increase of systolic pressure, could increase morbidity and mortality due to reduced coronary perfusion pressure, elevated systemic vascular resistance, or decreased vascular compliance[88]. However, the predictive value of PP in CKD patients needs to be demonstrated in a larger study.

Detrended fluctuation analysis (DFA) of heart rate dynamics is another prognostic marker for PD patients. In recent years, heart rate variability derived from beat-to-beat heart rate dynamic monitors has been used as a surrogate marker of autonomic modulation in an effort to predict patient outcomes[89-91]. DFA is a scaling analysis method to represent the correlation properties of a signal[92]. This form of analysis permits the detection of long-range correlation embedded in non-stationary time series

[93]. To date, a few studies have demonstrated that DFA provides significant information on risk of cardiovascular events in heart failure and acute coronary syndrome patients[94,95]. In 2016, Chiang and colleagues showed that lower short-term DFA was predictive of total mortality in PD patients (median follow-up duration of 34 mo)[26]. They were the first study to measure and associate autonomic dysregulation with clinical outcomes in ESRD patients. Subsequent studies have shown consistent data obtained from the general population, where reduced DFA was associated with increased mortality *via* sudden cardiac death[96]. DFA shows potential promise in CKD patients since ESRD is associated with an overactive sympathetic nervous system[97]. This dysregulation results in an amplification of intracellular cyclic AMP (cAMP), which leads to an increase of the action potentials in the sinoatrial node[98]. These pathophysiological changes can be detected in the altered beat-to-beat variability[99]. However, DFA is a relatively new method of clinical analysis, and its application in other patient populations such as HD and non-dialysis CKD remains to be elucidated.

Limitations

Our study has several limitations that should be considered. First, the predictive factors reported in each study were not homogenous. They varied from each study due to study design and patient population. Because of this limitation, a meta-analysis, subgroup analysis, and test of homogeneity could not be performed. Second, all included studies were observational in nature, making them susceptible to selection bias. However, we minimized this bias by conducting the risk of bias assessment. Third, the pooled sample size for PD patients remained relatively small compared to non-dialysis CKD and HD patients. Generalization of our research findings to the PD population should be cautiously performed. Nonetheless, the findings from our research could be applied towards the design of future prospective studies with the goal of developing a prognostication scoring system for mortality in CKD patients. To date, the outstanding factors (defined by $AUC \geq 0.90$) for mortality prediction in CKD patients have yet to be discovered.

CONCLUSION

Several factors were identified to provide accurate predictions of mortality in CKD patients. Echocardiography is an important tool for mortality prognostication in CKD patients by evaluating LASr, systolic PAP, mitral E/E' ratio, and LV mass index. NT-proBNP, BNP, suPAR, CRP, and AIx are excellent factors in mortality prediction among CKD patients.

ARTICLE HIGHLIGHTS

Research background

Chronic kidney disease (CKD) is a common medical condition that is increasing in prevalence. Understanding the accuracy of mortality risk factors in CKD patients could mitigate death.

Research motivation

Evidence has shown that several clinical factors are associated with mortality in CKD patients using regression analyses. However, the accuracy of these mortality predictive factors has not been clearly demonstrated.

Research objectives

To establish the accuracy of mortality predictive factors among CKD patients by utilizing the area under the receiver operating characteristic curve (AUC) analysis.

Research methods

Ovid MEDLINE, EMBASE, and the Cochrane Library were searched for eligible articles through January 2021. Only studies that reported their mortality predictive factors with AUC and 95% confidence interval were included. These factors were classified as acceptable, excellent, or outstanding based on their AUC.

Research results

Of 1759 citations, a total of 18 studies ($n = 14579$) were included in the systematic review. Eight hundred thirty two patients had non-dialysis CKD, and 13747 patients had dialysis-dependent CKD (2160 hemodialysis, 370 peritoneal dialysis, and 11217 undifferentiated modalities of dialysis). Of 24 predictive factors, none were considered outstanding for mortality prediction. A total of seven predictive factors (N-terminal pro-brain natriuretic peptide, brain natriuretic peptide, soluble urokinase plasminogen activator receptor, augmentation index, left atrial reservoir strain, C-reactive protein, and systolic pulmonary artery pressure) were identified as excellent. Seventeen predictive factors were in the acceptable range, which we classified into the following subgroups: predictors for the non-dialysis population, echocardiographic factors, comorbidities, and miscellaneous.

Research conclusions

This study determined several mortality risk factors for CKD patients that were deemed acceptable or excellent. Echocardiography is an important tool for mortality prognostication in CKD patients.

Research perspectives

The results of this study provide a preliminary perspective on the importance of identifying better prognostic factors for mortality in CKD patients. There is a lack of predictive risk factors with an AUC greater than 0.90. Currently identified mortality risk factors can be combined to create a risk calculator for CKD patients, which could be subsequently validated in future research.

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