The Impact of Chronic Kidney Disease on Outcomes in the Intensive Care Unit: Epidemiology and Performance of Common Predictive Scoring Systems

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PREFACE

Hajar El wadia was the primary author of this thesis. This research was conducted with approval of the project proposal submitted in June 2024 to the School of Epidemiology and Public Health at the University of Ottawa.

This thesis comprises two manuscripts primarily authored by the student (Hajar El wadia). Contributions were provided by student's supervisor, Dr. Gregory L. Hundemer; co-supervisor, Dr. Gregory A. Knoll; and thesis advisory committee members, Dr. Edward G. Clark, Dr. Shane W. English, and Dr. Ron Wald. Additional co-authors include Dr. Ayub Akbari, Dr. Samuel A. Silver, Nickolas Beauregard, and Deena Fremont.

The student was responsible for the conception of the research, literature review, screening and data extraction for the systematic review, co-design of the study methodologies, data analyses, interpretation of results, and drafting the manuscripts and thesis. The supervisor, co-supervisor, advisory committee members, and additional co-authors provided methodological and analytical guidance, as well as feedback throughout the planning, execution and writing of the manuscripts. All co-authors reviewed and approved the final versions of the manuscripts.

No research ethics board approval was necessary to conduct this project.

Manuscript 1

Title: Performance of ICU Scoring Systems in Patients with Pre-Existing Kidney Disease: A Systematic Review and Meta-Analysis

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Manuscript 2

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Finally, I thank my friends for their support and companionship throughout this journey. I am also grateful to my clinical manager, Kim, for her understanding and flexibility, which allowed me to balance full-time studies and my professional responsibilities.

ABSTRACT

Purpose: This thesis investigated outcomes of chronic kidney disease (CKD) patients in the intensive care unit (ICU).

Methodology: A systematic review evaluated ICU scoring systems performance in CKD patients, and a cohort study assessed associations between CKD stages and outcomes.

Results: The systematic review identified 12 heterogeneous studies. APACHE II/III, SAPS II, and SOFA showed good discrimination in end-stage kidney disease (ESKD) patients on dialysis but consistently overestimated mortality and performed poorly among kidney transplant recipients. The cohort study of 531,090 ICU admissions revealed one quarter had pre-existing CKD. Increasing CKD severity was independently associated with higher mortality and greater risk of kidney replacement therapy (KRT). Dialysis dependent stage 5 CKD showed lower mortality compared to non-dialysis dependent stage 5 CKD.

Conclusion: CKD is highly prevalent among ICU patients and strongly associated with mortality and KRT dependence. The scoring systems overestimate mortality risk in this population, highlighting the need for CKD stratification specific studies.

150/150 words

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CHAPTER 1. INTRODUCTION

1 BACKGROUND

1.1 Chronic Kidney Disease and Acute Care

Chronic kidney disease (CKD) is a common and progressive condition associated with high risks of progression to kidney failure, cardiovascular events, and mortality.[1–4] It is defined by sustained impairment of kidney function and diagnosed when abnormalities persist for at least 90 days.[1,2,5–7] This impairment is defined as a reduced estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2, albuminuria greater than 3 mg/mmol, or any evidence of structural kidney damage.[1,2,5,7,8] CKD represents a substantial global health burden, affecting approximately 14 percent of the world's population and causing over one million deaths annually.[1,3,9] This burden is driven largely by diabetes and hypertension.[1,3,9] In Canada, the impact is similarly significant, with CKD affecting one in ten adults; the age-standardized mortality rate increased from about 7.9 deaths per 100,000 population per year in 2017 to approximately 18 deaths per 100,000 population per year in 2023.[3,9] Although only a small proportion of individuals with CKD progress to kidney failure requiring dialysis, the high prevalence of CKD further contributes to the overall burden of cardiovascular events, acute kidney injury, and infection-related mortality long before kidney failure occurs.[10–12] Progression to end-stage kidney disease (ESKD) marks the advanced stage of CKD, where the eGFR falls below 15 mL/min/1.73 m^2. At this stage, long-term survival without dialysis is limited.

Dialysis-dependent ESKD patients place a significant burden on the Canadian healthcare system. Annual health expenditures for dialysis patients constitute approximately 1.1% of total national health spending.[13,14] In 2016, a Canadian cohort study reported more than 112,000 hospitalizations among dialysis patients, with 11.5% attributable to dialysis-related infections.[14] The vulnerability of these patients is most evident during the first year of dialysis initiation, where hospitalization rates reach 110 to 140 per 100 patient-year, compared with only 7 hospitalizations per 100 patient-year in the general Canadian population.[14,15] Moreover, dialysis-dependent ESKD patients account for three to four percent of ICU admissions in Canada, a proportion vastly exceeding their representation in the general population.[16–23] These patients have higher mortality and resource use than those without kidney disease.[16–22] This complexity is further reflected in Ontario, where hemodialysis patients have nearly five times as many emergency department visits and more than seven times as many hospital admissions when compared to matched controls from the general population.[14,17] This population level pattern highlights the high risk of CKD, and especially ESKD patients, and its association with higher acute health care utilization.[12,17]

1.2 Kidney Transplant Patients and Acute Care

Kidney transplant is the preferred treatment option for ESKD patients offering an improved survival and quality of life compared to dialysis treatments.[24–26] Yet, the transition from dialysis to transplantation does not eliminate vulnerability. Immunosuppression, cardiovascular disease, infections, and graft-related complications contribute to elevated morbidity when compared to the general population.[27,28] Even

when transplant-related complications are excluded as reasons for hospital admission, kidney transplant patients continue to have higher hospitalization rates than individuals without kidney disease.[27]

Despite these risks, transplant outcomes have improved substantially, with 5-yeat graft survival rates of 90% for living donor and 82% for deceased donor kidney transplants in younger adults.[29,30] In Canada, graft survival remains high at 90% and 79% at 5 years for living and deceased donor transplants, respectively.[31] However, kidney transplant recipients remain vulnerable to critical illness, with approximately 10% requiring ICU admission, most commonly for sepsis or cardiovascular complications.[32,33] Hence, kidney transplant recipients form a distinct subgroup whose acute care needs differ from, yet overlap with, individuals receiving dialysis.

1.3 The Intensive Care Unit

The demand for critical care continues to rise as the population ages and as individuals live longer with increasingly complex chronic diseases.[34–37] This implies persistent challenges for ICU capacity, with Canada maintaining roughly 13 adult ICU beds per 100,000 individuals.[16,38] Notably, about 85% of ICU admissions are unplanned and arise from acute clinical deterioration that necessitates urgent and expensive care.[16]

ICU admission and treatment decisions are inherently complex. They involve weighing clinical prognosis, potential benefits, multidisciplinary input, and operational constraints.[39] To support decision making in the ICU, several predictive scoring systems have been developed and validated to quantify organ dysfunction and estimate mortality.[39,40]

Commonly adopted models include Acute Physiology and Chronic Health Evaluation (APACHE) II and III, Simplified Acute Physiology Score (SAPS) II and III, and Mortality Probability Model (MPM). Scoring systems such as the Sequential Organ Failure Assessment (SOFA) and the MultiOrgan Dysfunction Score (MODS) focus on the degree of organ dysfunction. Most of these models are now used to support benchmarking, standardized mortality ratios, and health systems planning, in addition to informing triage and research practices.[41–43] However, these scoring systems were largely developed using the general ICU populations and do not perform equivalently in specific patient populations, including those with chronic obstructive pulmonary disease, cancer, HIV, and post-cardiac arrest patients.[44–47]

1.4 Performance of the ICU Predictive Scoring Systems in Pre-Existing Kidney Disease Patients

Some validation studies have highlighted important limitations of commonly used ICU scoring systems for individuals with CKD. [2,22,48–50] For instance, APACHE II and SAPS II interpret chronically elevated serum creatinine or reduced urine output, which is typical in ESKD individuals, as an acute physiologic change leading to potential overestimation of the mortality risk.[22,48] Similarly, the SOFA score quantifies kidney dysfunction exclusively using serum creatinine and urine output measured during ICU admission, an approach that may inadequately distinguish acute kidney injury from chronic baseline dysfunction in patients with pre-existing CKD or ESKD. Static ICU admission-based scores may therefore misclassify chronic organ dysfunction as acute injury and misestimate mortality.

In a related context, *Sanghavi et al.* cautioned that commonly used ICU scoring systems may overestimate mortality risk in patients with chronic comorbidities, thereby biasing both clinical decisions and hospital benchmarking.[51] Yet, evidence supporting the adaptation or validation of standard ICU scoring systems, specifically for patients with CKD or ESKD, remains limited.

1.5 Summary of Rationale

Patients with CKD, ESKD and kidney transplant recipients are clinically complex high-risk population with high rates of morbidity and mortality. Yet, despite the growing ICU burden of ESKD and kidney transplant patients, there are very few studies evaluating how well common ICU severity scoring systems predict mortality outcomes in these high-risk groups.

At the same time, understanding the ICU outcomes across the spectrum of CKD severity remains poorly studied. The current evidence tends to treat CKD as a binary condition (Yes/No) or focus mainly on ESKD patients, which offers little to no insights into how these outcomes vary among patients with earlier stages of CKD. There remains limited evidence describing ICU outcomes across the spectrum of CKD severity.

Herein, this thesis aims to evaluate the performance of commonly used ICU severity scoring systems in patients with impaired kidney function and to describe ICU outcomes across the CKD stages to help in understanding how baseline renal function shapes critical illness treatment in the ICU. Addressing both aims will help inform and strengthen prognostication and support more accurate clinical decision making in the ICU.

2 THESIS OBJECTIVES

The aim of this thesis was to evaluate the performance of the commonly used ICU predictive scoring systems in patients with pre-existing kidney disease and to examine the impact of CKD severity by stage in both short- and long-term outcomes following ICU admission. These objectives were achieved through two complementary components:

(1) Systematic review and meta-analysis: Synthesized existing evidence on the performance metrics of commonly used ICU predictive scoring systems in adult patients with pre-existing kidney disease and compared their performance across kidney disease subgroups to identify any gaps or methodological limitations in the current literature.

(2) Retrospective analysis: Assessed the short-term and long-term outcomes among adults with pre-existing CKD admitted to the ICU, stratified by CKD stages. This analysis examined the association between CKD severity stages and mortality risk, as well as kidney replacement therapy outcomes, after adjusting for demographics, comorbidities, and markers of acute illness severity.

3 THESIS STRUCTURE

This thesis consists of a systematic review and a population-based cohort study using administrative health data. This is structured in a thesis-by-manuscript format. The chapters are organized as follows:

- **Chapter 1**: provides an overview of the evidence on the ICU outcomes among patients with pre-existing kidney disease and summarizes the

performance of the commonly used ICU predictive scoring systems in this high-risk patient population. It also introduces conceptual framework relevant to evaluating healthcare services, describes the databases used in the quantitative cohort study, and outlines the rationale and objectives of the thesis.

- **Chapter 2**: this is a systematic review and meta-analysis manuscript ("Performance of ICU Scoring Systems in Patients with Pre-Existing Kidney Disease: A Systematic Review and Meta-Analysis"). This chapter synthesizes existing evidence on the discriminatory power and calibration performance of ICU predictive scoring systems in adults with pre-existing kidney disease.
- **Chapter 3**: addresses the second objective of the thesis through a quantitative analysis ("Severity of Chronic Kidney Disease and Outcomes Following Admission to the Intensive Care Unit") using available data in the ICES (formerly, Institute for Clinical Evaluative Sciences) database. This chapter evaluates ICU and post-ICU outcomes among CKD adult patients stratified according to CKD severity stages, using population-based cohort from November 2008 to February 2021.
- Finally, **Chapter 4**: provides an integrative discussion synthesizing findings across the two manuscripts, highlining their implications for future research and applications in clinical practice for CKD patients and their health care needs.

4 METHODOLOGY AND FRAMEWORKS

Assessing the extent to which healthcare systems meet their intended goals requires robust conceptual models and methodological frameworks to evaluate the critical relationships involved. The conceptual foundation for this thesis is informed by the Donabedian Structure, Process, and Outcome (SPO) model, a well-established framework in healthcare research that provides an insight into the evaluation of the organizational setting, the process of care delivery, and the resulting health outcomes.[52] This model emphasizes that the assessment of health care quality should not rely exclusively on outcomes but must also include the process encompassing all interactions of patients with the health care system, including justification of diagnosis and therapy.[52] It underlines the importance of the structure, in the assessment of health care quality.[52] In the context of CKD and ESKD patients admitted to the ICU, the structural elements include ICU settings and their resources, while processes include the use of the scoring systems in clinical decision-making and life support interventions (e.g., ventilation, vasopressors). Outcomes such as mortality reflect the culmination of these dynamic components.

A Directed Acyclic Graph (DAG) was developed to illustrate the hypothesized causal pathways linking CKD to ICU outcomes (**Figure 1**). In line with the Donabedian model, the DAG lists the structural elements, care processes in the ICU, and the outcomes by organizing the covariates that influence these relationships. According to this DAG, patient demographics, comorbidities, severity of illness on ICU admission, and prior health services utilization are treated as confounders because they shape both the organizational settings under which patients are admitted to the ICU and the trajectory

of care they subsequently receive. Therefore, the DAG operationalizes the Donabedian model by clarifying how structural and process related factors interact to influence mortality and kidney outcomes. It also identifies the appropriate adjustments needed to obtain valid estimates of the association between CKD status and ICU outcomes.

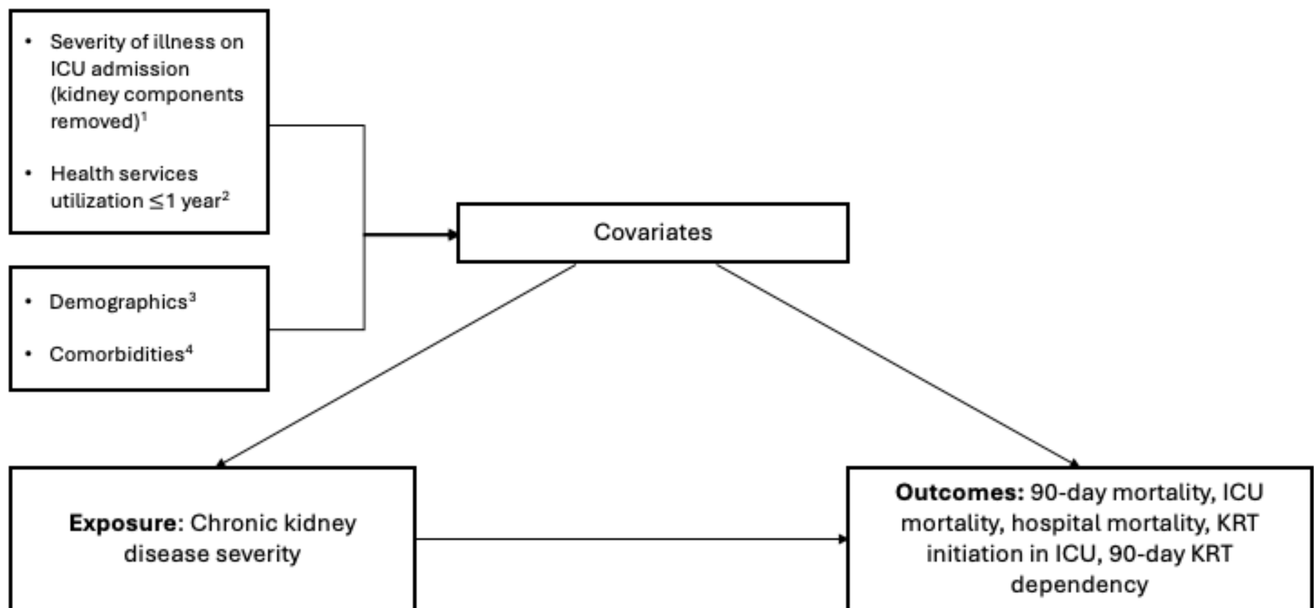

Figure 1: Directed acyclic graph depicting the hypothesized causal relationship between chronic kidney disease and ICU outcomes.

Covariates were defined based on prior clinical knowledge, literature, and availability within ICES as confounder variables affecting both chronic kidney disease (CKD) severity and ICU outcomes.

[1] Including the use of vasopressors on ICU admission, use of mechanical ventilation on ICU admission, and severity of illness according to the Multiple Organ Dysfunction Score (MODS) on ICU admission subtracting the contribution of the *MODS renal component* (i.e., serum creatinine).

[2] Nephrologist consults, Emergency room visits and hospitalizations

[3] Age, sex, rural residence, neighbourhood income quintile

[4] coronary artery disease, myocardial infarction, diabetes mellitus, hypertension, congestive heart failure, arrhythmia, stroke, chronic liver disease, chronic obstructive pulmonary disease, HIV infection, cancer, and alcoholism

4.1 Data Sources, Access, and Linkage

To address the second objective of the thesis, we obtained data from ICES, an independent research organization with legislative authority to access Ontario's health data for research and health system evaluation purposes.[53] ICES houses a large repository of routinely collected, linkable administrative and clinical datasets covering health services use, outcomes, demographics, and disease surveillance for Ontario residents.[53] The datasets were linked via unique identifiers set as ICES Key Numbers (IKNs) based on each resident's encrypted health card number. Below, we provide brief descriptions of the datasets used in cohort definition.

Critical Care Information System (CCIS)

The CCIS is Ontario's health registry for Level 2 and Level 3 critical care units to support standardized data collection, analysis, and reporting.[54] As part of the Ministry of Health's Critical Care Strategy, CCIS enables evidence-based decision making by capturing real-time information on patient admissions, interventions, outcomes, and resource use, this system supports capacity planning, performance improvement and coordinated patient care across hospitals.[54] It captures a comprehensive set of clinical and operational data elements, including patient demographics, ICU admission details, Influenza-like Illness (ILI) indicators, daily Life Support Interventions (LSI/NEMS), antimicrobial therapy indicators, and outcomes such as central line infections, ventilator-associated pneumonia, and unplanned extubations. CCIS also records Multiple Organ Dysfunction Score (MODS) values on admission and tracks bed availability, transfers, and discharge information, providing a complete picture of critical care across Ontario.[54]

For the second objective of this thesis, CCIS was used to define study population and collect ICU and MODS-specific information.

Canadian Organ Replacement Registry (CORR)

The CORR tool is a national clinical registry that collects information on patients receiving chronic dialysis or kidney transplantation in Canada.[55] The registry captures patient demographics, treatment modality, transplant status, and clinical outcomes. It also supports surveillance, health system planning and research related to ESKD.[55] In the cohort study, the CORR tool was used to get serum creatinine during 1-year lookback window.

Discharge Abstract Database (DAD)

The DAD contains patient-level administrative, clinical, and demographical information for all acute care hospitalization in Ontario.[56] It includes diagnostic and procedural data coded using standardized classification systems, International Classification of Diseases, 10th Revision (ICD-10) and interventional codes from Canadian Classification of Health Interventions (CCI), respectively.[56] In this project's cohort study, DAD was used to identify hospitalizations before and after ICU admission and capture diagnostic and procedural information from all hospitalizations, as well as identifying comorbid conditions.

ICES-Derived HIV Cohort

The %HSPN_mmb macro in ICES was used to capture most comorbidities included in the population-based cohort study of this project, except HIV. The HIV data set in ICES is a cumulative dataset that contains all Ontario HIV positive patients identified since

1992. For the purpose of our study, individuals were flagged positive for HIV if they had a diagnosis date before index date.

National Ambulatory Care Reporting System (NACRS)

The NACRS tool captures data on all-hospital based and community-based ambulatory care visits in Ontario, including emergency department encounters, same-day surgeries, and outpatient clinics.[57] For this project, NACRS was used to identify emergency department visits and ambulatory care utilization prior to ICU admission, which serves as an indicator of baseline health status, disease severity, and patterns of healthcare access among CKD patients. It was also used to capture comorbid conditions.

Ontario Drug Benefit Claims (ODB) and Drugs List (DIN)

The ODB database contains information on Ontario Drug Benefit program claims, including recipient, payment, dispensing pharmacy, and practitioner details for prescription drugs dispensed under the ODB program.[58] It reflects records of drugs reimbursed through the publicly funded drug benefit system for eligible Ontario residents.[58] The ODB database also includes Drug Identification Numbers (DINs) for dispensed prescriptions, which can be linked to the DIN reference database to identify and classify drug products appearing in ODB records. [58,59] In this thesis, medication classes were used as proxies for selected comorbid conditions (e.g., anti-diabetic drugs to identify patients with diabetes).

Ontario Health Insurance Plan (OHIP)

The OHIP database comprises records of claims for physician insured health services paid for by the provincial government.[60] This database captures information on outpatient and inpatient physician encounters, diagnostic services, and procedural

care.[60] In this project, OHIP data was used to assess prior healthcare utilization, identify comorbid conditions, and characterize patterns of physician contact before ICU admission. OHIP claims complement hospital-based data by providing insights into care delivered in outpatient and community settings.

Ontario Laboratories Information System (OLIS)

The OLIS database houses the laboratory results from hospitals and in the community across Ontario.[61] It provides detailed information on test type, result values, units, and collection dates.[61] This this project, OLIS was used to obtain laboratory measurements relevant to kidney function, including serum creatinine, and urine albumin/creatinine ratio. These data support the identification and classification of CKD status and allow for more precise clinical characterization of the study population.

Registered Persons Database (RPDB)

The RPDB database includes demographic information on all individuals who ever received an Ontario health card number.[62] It includes age, sex, residential postal code, dates of health insurance eligibility, and vital status, including date of death. This database serves as the foundational linkage file for cohort creation and follow-up.[62] In this study, RPDB is used to ascertain OHIP eligibility at index capture demographics, enable linkage across datasets, and ascertain mortality outcomes.

Same Day Surgery (SDS)

The SDS dataset is an administrative health database, derived from the NACRS tool, that captures information on surgical procedures performed in Ontario hospitals where patients are admitted and discharged on the same day.[63] The SDS database includes patient demographics, diagnostic and procedure codes, and details of the surgical

encounters.[63] The SDS dataset was used to capture comorbid conditions for the cohort study.

4.2 Time Frame for the Cohort Study

To address the second objective of the thesis, the retrospective cohort design spanned November 2008 to February 2021 (**Figure 2**). The index event date was defined as the date of ICU admission. To establish baseline characteristics and comorbidities, a 1-year lookback window prior to the index ICU admission was utilized. Following the index event, patients were followed for 90 days to assess kidney function recovery and health outcomes. The 90-day follow-up timepoint was selected based on KDIGO and ADQI consensus recommendations, which define this interval as the critical threshold distinguishing acute kidney disease from CKD.[64,65] The 1-year lookback window enabled comprehensive ascertainment of pre-existing comorbidities and baseline kidney function, consistent with established methodologies for risk adjustment in acute care research.[66]

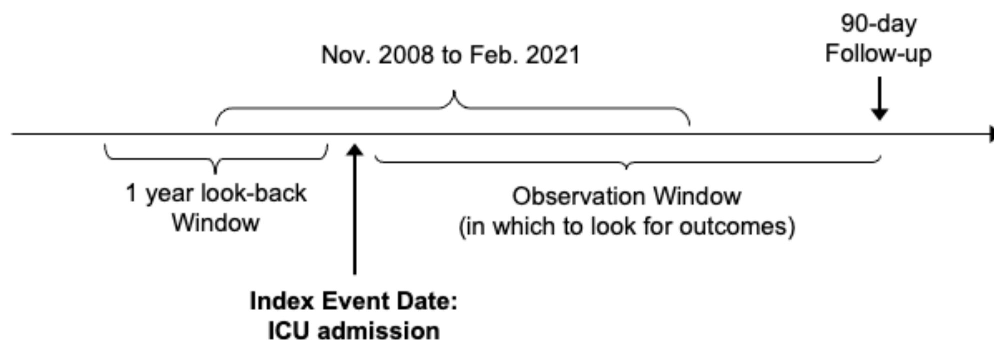

Figure 2. Cohort Study Timeline

Study Timeline illustrating the 1-year look-back period prior to index ICU admission to capture baseline characteristics. Study outcomes were assessed during the observation window from November 2008 to February 2021, followed by a 90-day post ICU admission follow-up.

Chapter 2. Performance of ICU Scoring Systems in Patients with Pre-Existing Kidney Disease: A Systematic Review and Meta-Analysis

PREFACE

The manuscript of this systematic review and meta-analysis evaluates the performance of commonly used ICU scoring systems in patients with pre-existing kidney disease, admitted to the ICU. The study was led by Hajar El wadia, who co-conceived the idea, drafted the research proposal, co-developed and implemented the search strategy and study eligibility criteria, screened citations and extracted data with four other screeners, conducted the meta-analysis, verified and analyzed the extracted data, prepared the initial drafts of all tables and figures, and prepared the initial draft of this manuscript. Drs Hundemer and Clark co-supervised this study, co-conceived the idea, provided methodological and clinical advice as the study progressed, interpreted the findings, and critically reviewed the manuscript. Drs Akbari, Knoll, English, and Wald, provided methodological and clinical advice as the study progressed, and critically reviewed the manuscript. Risa Shorr co-developed and implemented the search strategy. Marisha Karim, Amos Buh, Abdulghani O. Kabli, Nandini Biyani, and Inok Lee screened citations, extracted data, and reviewed the manuscript. All authors read, provided feedback on, and approved the final version of this manuscript.

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ABSTRACT

Background: Several scoring systems are used to predict mortality among patients admitted to the intensive care unit (ICU) but do not account for baseline kidney function. This systematic review and meta-analysis evaluate the performance of commonly used ICU scoring systems in patients with non-dialysis chronic kidney disease (CKD), end-stage kidney disease (ESKD) on maintenance dialysis, and kidney transplant recipients.

Methods: We searched Ovid Medline, Embase, and Scopus from database inception through October 10, 2024, to identify observational studies reporting mortality prediction performance of ICU scoring systems in patients with pre-existing kidney disease, analyzed independently or compared with a general ICU population.

Results: Twelve studies involving 578,027 patients met inclusion criteria, evaluating five ICU scoring systems (SOFA, APACHE II/III, SAPS II/III). Most studies involved patients with ESKD on maintenance dialysis and kidney transplant recipients; data on patients with non-dialysis CKD were very limited. For ESKD on maintenance dialysis, the area under the receiver operating characteristic curve (AUROC) showed excellent discrimination for all ICU scoring systems. However, discrimination was consistently lower in ESKD when compared with general ICU population, and calibration metrics showed consistent overestimation of mortality risk in ESKD. Among kidney transplant recipients, scoring systems displayed consistently poor discrimination, for both SAPS III and SOFA, with variable calibration metrics.

Conclusions: Common ICU scoring systems frequently overestimate mortality risk among patients with ESKD on dialysis and kidney transplantation. These findings highlight the need to develop or recalibrate scoring systems for patients with pre-existing kidney disease.

KEYWORDS

Intensive care unit, ICU,

APACHE

SAPS

SOFA

Chronic kidney disease, CKD

End-stage kidney disease, ESKD

BACKGROUND

Several predictive scoring systems have been developed to measure severity of illness and predict outcomes for patients admitted to the intensive care unit (ICU). Commonly used and validated scoring systems include Acute Physiologic and Chronic Health Evaluation (APACHE) [1–8], Simplified Acute Physiologic Score (SAPS) [1,9], and Sequential Organ Failure Assessment (SOFA) [10]. These scoring systems utilize information including comorbidities, admission diagnosis, physiologic data, and laboratory measurements to provide a numerical severity of illness score that predicts mortality, as well as length of stay in some instances. In addition to predicting mortality, they play important roles in clinical trial design by ensuring comparable baseline risks between groups [11], healthcare system assessment of quality care benchmarks [12], and allocation of limited hospital resources [13].

While these commonly used ICU predictive scoring systems were developed for general ICU populations, their performance may differ in specific patient populations including ethnic minorities [14] and in different clinical scenarios including cardiac surgery [15–17], acute myocardial infarction [18], post-cardiac arrest [19], solid organ transplant [20], cancer [21], HIV [22], COVID-19 [23], and pregnancy [24]. As a result, specialized ICU scoring systems have been designed for some of these specialized patient populations [25,26]. However, there is limited data on patients with pre-existing kidney disease, including non-dialysis chronic kidney disease (CKD), end-stage kidney disease (ESKD) on maintenance dialysis, and kidney transplantation. Notably, patients with pre-existing kidney disease are at increased risk for ICU admission with ESKD patients having an estimated 25- to

30-fold higher risk of ICU admission relative to the general ICU population [27]. Most of these scoring systems incorporate some measure of kidney function, usually by assessing serum creatinine or urine output on arrival to the ICU. However, they generally do not consider baseline kidney function, or they use a simple dichotomous yes/no label indicating the presence of baseline CKD/ESKD. Therefore, these scoring systems do not fully account for whether reduced kidney function in the ICU is a manifestation of severity of acute illness (i.e., acute kidney injury [AKI]) or simply a reflection of poor baseline kidney function, which may limit their performance in populations with pre-existing kidney disease. Specifically, by not incorporating the change in kidney function from baseline, these scoring systems may be prone to overestimation of mortality risk for such individuals. This systematic review and meta-analysis aims to evaluate the performance of commonly used ICU predictive scoring systems among individuals with pre-existing kidney disease following current critical appraisal guidelines [28].

METHODS

Protocol

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines (28, 29) (see **Supplementary Table 1** for the PRISMA checklist). The protocol was registered *a priori* on the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42024611547) and was previously published [29]. Deviations from the protocol along with explanations are provided in **Supplementary Table 2.**

Data Sources and Searches

We searched Ovid MEDLINE, EMBASE, and Scopus from database inception to October 10, 2024 using a search strategy developed with the assistance of an information specialist and medical librarian (RS). The search strategy incorporated a combination of medical subject headings (MeSH) and keywords related to the ICU scoring systems, such as "*APACHE*", "*SAPS*", "*SOFA*", "*mortality prediction*", "*Intensive Care Unit*", "*Organ Dysfunction*", "*Critical Care*", and more. A complete description of the search strategy is provided in **Supplementary Table 3**.

Eligibility Criteria

This review assessed observational studies involving adult patients (≥18 years) with pre-existing kidney disease (non-dialysis CKD, ESKD on maintenance dialysis, or kidney transplantation) admitted to the ICU. Eligible studies evaluated the predictive

performance of commonly used ICU severity of illness scoring systems in estimating mortality outcomes, including but not limited to APACHE, SAPS, and SOFA. Eligible studies were required to report performance metrics of mortality prediction systems in patients with pre-existing kidney disease either analyzed independently or compared with ICU patients without pre-existing kidney disease. Only peer-reviewed articles published in English were considered. Studies were excluded if they did not report data separately for ICU patients with pre-existing kidney disease, if they focused exclusively on AKI with or without pre-existing CKD, if severity of illness scoring systems were applied outside of ICU settings, or if materials were grey literature or conference abstracts.

Study Selection

All retrieved articles were imported to Covidence for duplicate removal and screening. Five reviewers (HE, MK, AOK, NB, and IL) independently screened all titles and abstracts in duplicate. Any disagreements at this stage resulted in the inclusion of the article to full-text screening. Full-text articles were then screened in duplicate, with discrepancies resolved through consensus or arbitration by a third reviewer (AB). The reasons for exclusion were recorded after full-text screening. Reviewers were not blinded to the authors or journals when screening articles.

Data Extraction and Quality Assessment

A standardized data extraction form was developed in Microsoft Excel and piloted by reviewers. Data were independently extracted, in duplicate, from full-text studies by five reviewers (HE, MK, AOK, NB, and IL). The extracted data included (1) first author, year,

and country, (2) study design and sample size, (3) description of baseline kidney disease (CKD [by stage], ESKD, kidney transplant), (4) list of scoring systems evaluated, (5) ICU and hospital mortality, and (6) reported performance metrics.

The methodological quality of the included studies was assessed using a standard critical appraisal tool from the Joanna Briggs Institute (JBI) [30]. Risk of bias for each study was assessed using the Prediction model Risk Of Bias ASsessment Tool (PROBAST), which includes four domains (participants, predictors, outcomes, and analysis) relevant to prognostic model studies [31,32]. Quality scores were summarized and certainty of the evidence for each outcome was rated according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework as recommended by the most current guidelines for prognostic models' assessment.

Data Synthesis and Statistical Analysis

Data were synthesized on the performance of ICU scoring systems in predicting mortality among patients with pre-existing kidney disease. The primary metrics of interest were discrimination and calibration. Discrimination refers to the accuracy of a given prediction (i.e., the ability to distinguish between survivors and non-survivors). Commonly reported discrimination metrics include the area under the receiver operating characteristic curve (AUROC), and c-statistics. Calibration describes how a prediction model performs over a wide spectrum of predicted mortalities (i.e., the agreement between the numbers of expected and observed outcome events across all outcome probabilities). Therefore, calibration provides insight about whether a given model

underestimates or overestimates risk for a given population. Commonly reported calibration metrics include calibration slope/intercept, standardized mortality ratio (SMR), and the Hosmer-Lemeshow goodness-of-fit test.

Meta-analysis

The meta-analysis of AUROC values was conducted using random effects model and refined by conducting the pooling of estimates on the logit-transformed AUROC scale to improve statistical stability[32–35]. Random effects models were estimated using restricted maximum likelihood (REML) as implemented in the *meta version 8.2-0* package in R (4.3.3) within RStudio (version 2025.05.1+513). The pooled estimates were subsequently back-transformed to the AUROC scale for interpretation. For each study, the standard error (SE) were derived from the reported 95% confidence interval (CI) using a normal approximation and included in the random effects model. Statistical heterogeneity was assessed using the I^2, with conventional threshold values $\geq$ 50% considered indicative of substantial heterogeneity[36], and by computing 95% prediction intervals to reflect the expected range of AUROC values in new settings[32]. Meta-analysis of calibration was not feasible as studies varied in whether calibration was reported and in statistical methods used when reported (e.g., SMR, Hosmer-Lemeshow, calibration plots). The analysis code used in this study is publicly available on GitHub https://github.com/HajarEl24/R-Program/commit/fd6fa0fb870365e91aaf3b4a8f663e783edfc10d

RESULTS

Literature Search

A total of 30,433 results were identified utilizing the databases search strategy (**Figure 1**). After the removal of duplicate results (n = 12,603), 17,830 unique citations underwent title and abstract screening. A total of 563 articles were then retrieved for full-text review. The most common reason for exclusion at this stage was ineligible patient population (n = 434), followed by wrong outcomes (n = 34), abstract-only publications (n = 32), and non-eligible study designs (n = 29). A full listing of excluded studies and the reasons for exclusion are provided in **Supplementary Table 4**. Ultimately, 12 studies met all eligibility criteria and were included in this systematic review.

Study Characteristics

Table 1 summarizes key characteristics of the included studies. A total of 578,027 patients admitted to ICU were assessed using the selected studies. This included 7,368 ESKD patients on maintenance dialysis and 1,112 kidney transplant recipients. Notably, there was very little information available on severity of illness score performance specifically among patients with non-dialysis CKD with assessment in only 51 such patients. Individual study sample sizes ranged from 73 to 128,134 patients. The included studies were conducted worldwide across Australia (n = 1), Brazil (n = 2), China (n = 1), France (n = 1), India (n = 2), Japan (n = 1), Pakistan (n = 1), Turkey (n = 1), and the United States (n = 2). Study populations included ESKD patients on maintenance dialysis only (n = 3) [37–39], a mix of non-dialysis CKD and ESKD patients (n = 2) (41),

kidney transplant recipients only (n = 2) [42,43], a mix of all solid organ transplant recipients (n = 1) [20], and general ICU populations (n = 4) [44–47].

Across the 12 studies, five common ICU severity scoring systems were evaluated: SOFA (n = 6), APACHE II (n = 7), SAPS II (n = 5), APACHE III (n = 3), and SAPS III (n = 2). All models incorporated kidney function indicators including creatinine, urine output, or blood urea nitrogen (BUN), although the timing and type of measurement varied. APACHE II, APACHE III, SAPS II, and SOFA scores are all calculated using the worst values recorded within the first 24 hours of ICU admission [9,48–50], while SAPS III is the only model utilizing the worst value within the first hour of ICU admission for score calculation [51]. Of these systems, only APACHE II incorporated chronic dialysis status as a dichotomous variable (Yes/No) under the chronic health component [49]. However, none of the predictive models assessed in this review included baseline creatinine or eGFR values. A detailed summary of each scoring system components is presented in **Supplementary Table 5**.

Performance of ICU Scoring Systems in Chronic Kidney Disease and End-Stage Kidney Disease

Table 2 displays a summary of the nine studies focused on ICU patients with ESKD on maintenance dialysis [37–41,44–47]. Five of the studies included both maintenance hemodialysis and peritoneal dialysis under the definition of ESKD, while four studies included only maintenance hemodialysis [37,40,46,47]. Although Rana *et al.* and Clermont *et al.* did not report discrimination metrics, Rana *et al.* evaluated SAPS II in 189 ESKD

patients and found it was not a statistically significant factor in a multivariate analysis of mortality prediction [37], while Clermont *et al.* reported calibration metrics only [47].

Discrimination

Discriminatory performance was evaluated using AUROC. Among the prospective studies, Goswami *et al.* looked at 94 ESKD and six stage-4 CKD patients and reported excellent discrimination for APACHE II (0.96), SAPS II (0.99), and SOFA (0.95) [40]. However, confidence intervals were not provided [40]. Juneja *et al.* assessed 73 ESKD patients though no control (general ICU population) group was included for comparison [38]. The authors reported excellent discrimination (APACHE II [0.87, 95% CI: 0.78-0.95], and SOFA [0.92, 95% CI: 0.86-0.98]), with APACHE II overestimating mortality among ESKD patients [predicted 56.9%; observed 41.1%]) [38]. Similarly, Manhes *et al*. evaluated the performance of SAPS II in 92 ESKD patients and reported excellent discrimination (0.86, 95% CI: 0.82-0.90) without comparison to non-ESKD patients [45]. Akbas *et al.* assessed APACHE II predictive performance in 101 ESKD patients and reported acceptable discrimination (0.78, 95% CI 0.55–0.89) [41]. Among the selected studies, Shimada *et al.* conducted the largest comparative analysis where four scoring systems were evaluated in ESKD and non-ESKD individuals [44]. For ESKD patients, discrimination was consistently lower (APACHE II [0.81, 95% CI 0.80-0.83], APACHE III [0.83, 95% CI: 0.82-0.85], SAPS II [0.81, 95% CI 0.80– 0.83], and SOFA [0.79, 95% CI 0.77-0.80]), compared to non-ESKD patients (APACHE II [0.89, 95% CI 0.88-0.89], APACHE III [0.90, 95% CI 0.89-0.90], and SOFA [0.85,95% CI 0.84-0.85]) [44]. By comparison, Dara *et al.* evaluated 93 ESKD patients and reported the performance of

APACHE III (0.78, [95% CI 0.68–0.86]) and SOFA (0.66, [95% CI 0.55–0.76]) [46]. In a matched cohort study, Uchino *et al.* reported discriminatory performance of APACHE II (0.82, 95% CI 0.65–0.92) and SAPS II (0.85, 95% CI: 0.68–0.95) in 38 ESKD patients[52].

Calibration

Clermont *et al.* assessed APACHE III in 57 patients with ESKD[47]. Although the discrimination metrics were not reported , calibration showed overestimation in ESKD (SMR 0.52)[47]. Manhes *et al*. reported acceptable calibration (Hosmer-Lemeshow test [H = 4.78, df = 5, p = 0.44]) and higher ICU (28% versus 22%) and hospital (38% versus 28%) mortality in ESKD compared with non-ESKD patients, suggesting a mild overestimation of mortality risk [45]. Moreover, Shimada *et al.* reported that calibration slopes in ESKD (APACHE II [0.884], APACHE III [0.982], SAPS II [0.939], and SOFA [1.005]) were lower compared to non-ESKD patients (APACHE II [1.081], APACHE III [1.001], SAPS II [1.003], and SOFA [1.012]), indicating overestimation of mortality risks in ESKD patients [44]. Uchino *et al.* reported calibration metrics for APACHE II and SAPS II, using the SMR, indicating a slight overestimation of mortality in ESKD patients (SMR = 0.92 for both scoring systems).

Performance of ICU Scoring Systems in Kidney Transplant Recipients

Table 3 provides a summary of three studies assessing the predictive performance of ICU severity of illness scoring systems among kidney transplant recipients [20,42,43].

Discrimination

Zhang *et al.* conducted a retrospective study where SOFA scores were calculated daily for the first three days of ICU admission [42]. The AUROC values suggested poor discriminatory performance though with some improvement over time, increasing from 0.52 (95% CI: 0.44-0.61) on day one, to 0.65 (95% CI: 0.56-0.75) on day two, and reaching 0.73 (95% CI: 0.63-0.83) on day three. Calibration metrics were not reported. Freitas *et al.* conducted another retrospective study involving 413 kidney transplant recipients and reported poor discrimination (APACHE II, 0.69 [95% CI 0.62-0.76]), SAPS III, 0.73 [95% CI 0.67-0.80]), and SOFA 0.71, [95% CI: 0.65-0.78]) [43]. Oliveira *et al.* conducted a prospective study of solid organ transplant recipients, which included 271 kidney transplant recipients [20]. The reported AUROC values were 0.55 for APACHE II and 0.46 for SAPS III in kidney transplant recipients, indicating poor discrimination.

Calibration

Freitas *et al.* assessed the calibration metrics for APACHE II and SAPS III using the SMR, indicating overestimation of mortality in kidney transplant recipients (SMR <1 for both scoring systems). Likewise, Oliveira *et al.* evaluated calibration using the SMR suggesting overestimation of mortality for APACHE II (SMR<1) and underestimation of mortality for SAPS III (SMR >1) in kidney transplant recipients [20].

Meta-Analysis

Overall, nine of the included studies reported AUROC values for at least one severity of illness scoring system [20,38,39,41–46]. However, three studies were excluded from the meta-

analysis: two did not report AUROC metrics [37,47] and another reported AUROC values without the corresponding 95% CI [40].

Among patients with ESKD on maintenance dialysis, the pooled estimates demonstrated that all evaluated scoring systems achieved excellent discriminatory accuracy (**Figures 2A-D**). The pooled AUROC for APACHE II, based on four studies, was 0.81 (95% CI: 0.80-0.83), with minimal between-study heterogeneity, reflected by low I^2 and narrow prediction intervals (0.80 - 0.83). [38,41,44,52] The pooled AUROC for APACHE III from two studies was 0.82 (95% CI: 0.79-0.85). [44,46] SAPS II, pooled from three studies, had an AUROC of 0.83 (95% CI: 0.79-0.87). [44,45,52] Both APACHE III and SAPS II had some heterogeneity as evidenced by the moderate I^2 and wide prediction intervals (APACHE III [0.77-0.86], SAPS II [0.76-0.89]). In contrast, the SOFA score with three studies demonstrated greater variability, with a pooled AUROC estimate of 0.80 (95% CI: 0.62-0.91) and significant heterogeneity (I^2 = 82.9%), supported by wide prediction intervals (0.42-0.96). [38,44,46] Certainty of evidence according to GRADE criteria for the pooled estimates was rated as low for APACHE II, APACHE III, and SAPS II, and very low for SOFA, largely due to the significant heterogeneity and inconsistency (**Supplementary Table 6**).

Among kidney transplant recipients, the discriminatory performance was consistently poor (**Figures 3A–B**). The pooled AUROC for SAPS III across two studies was 0.63 (95% CI: 0.36–0.84; I^2 = 77.1%), reflecting poor discriminatory accuracy with high heterogeneity [43,53]. Similarly, SOFA had poor discriminatory accuracy with a pooled

AUROC of 0.62 (95% CI: 0.42–0.78; I^2 = 91.3%) and substantial heterogeneity [42,43]. Both models indicated significant variability across studies with wide prediction intervals (SAPS III [0.22-0.91], SOFA [0.30-0.86]). For kidney transplant recipients, the certainty of evidence utilizing GRADE was rated very low for both models due to serious concerns with heterogeneity, inconsistency, and imprecision (**Supplementary Table 6**).

Meta-analysis was not performed among non-dialysis CKD patients due to a lack of studies assessing ICU predictive scoring systems specifically among this population. Furthermore, meta-analysis of model calibration was not performed because studies varied substantially in whether calibration was assessed and, when it was, the metrics used were highly heterogeneous (see **Table 2** and **Table 3** for how calibration metrics where reported, if any, by study).

Risk of Bias

The methodological quality of the included studies, according to JBI appraisal scores, ranges from 62% to 90% suggesting moderate to high risk of bias (**Supplementary Table 7**). Complementing the JBI appraisal tool, PROBAST identified high risk of bias in most studies due to limitations in the analysis domain, specifically small sample sizes (<100 outcome events), limited handling of missing data, and inconsistent reporting of calibration metrics (**Supplementary Table 8**). **Supplementary Figure 1** provides a visual summary of these findings, highlighting overall high risk of bias in statistical analysis domain across the included studies.

DISCUSSION

This systematic review and meta-analysis of the literature for observational studies evaluating the performance of commonly used ICU predictive scoring systems among individuals with pre-existing kidney disease identified 12 eligible studies for inclusion. These studies primarily focused on patients with ESKD on maintenance dialysis and kidney transplant recipients with few focused on the much larger non-dialysis CKD population. Across studies, we found that ICU scoring systems (APACHE, SAPS, and SOFA) consistently overestimated mortality risk in patients with ESKD, despite maintaining adequate discriminatory performance in most cohorts [38–41,44,45]. Among kidney transplant recipients, these scoring systems displayed consistently poor discriminatory performance along with variable calibration metrics [20,42,43]. These findings indicate that commonly used ICU scoring systems substantially misrepresent mortality risk prognosis among individuals with pre-existing kidney disease.

A central finding of this review is the lack of available data on the prognostic accuracy of ICU severity scores among patients with pre-existing kidney disease. This is highly relevant, as these patients comprise a substantial proportion of the ICU population. Prior studies have demonstrated that approximately 20% of patients admitted to the ICU have non-dialysis CKD [54] while 1-9% have ESKD [55]. Despite this, we identified only 12 studies assessing the performance of these commonly used ICU scoring systems among patients with pre-existing kidney disease, many of which had relatively small sample sizes. Strikingly, there is a severe lack of data within the non-dialysis CKD population which is, by far, the largest pre-existing kidney disease population in both the

ICU and the population in general. We only identified two studies that specifically assessed the non-dialysis CKD population – one study of six patients with stage 4 CKD which were pooled together with a larger population of ESKD patients and a second study of 45 patients [40,41] with stages 2-5 CKD for which data on model performance was not provided. Therefore, a knowledge gap remains regarding the performance of these commonly used ICU scoring systems in the non-dialysis CKD population and, more specifically, by CKD stage, which should be addressed by future research.

The tendency towards mortality risk overestimation in populations with pre-existing kidney disease may be best explained by the way kidney function is incorporated into these scoring systems. Most scores calculate risk using a single creatinine value or urine output measurements within the first 24 hours of ICU admission [9,48–51]. Among patients with normal baseline kidney function, this may provide an accurate assessment of severity of illness which parallels the severity of AKI. However, for those with pre-existing kidney disease, this may not hold true. Such severity scores may incorrectly presume the presence and/or severity of AKI leading to an overestimation of risk among CKD and ESKD populations. While certain scoring systems such as APACHE II [49] do incorporate a dichotomous yes/no variable about maintenance dialysis, this still fails to capture the wide spectrum of CKD. In kidney transplant recipients, this problem is further compounded by the influence of immunosuppression (e.g., calcineurin inhibitors) and fluctuating graft function, which is not captured in traditional ICU scoring systems. Hence, the reliance on a single worst kidney function value on ICU admission rather

than changes from baseline values to ICU admission predisposes to systematic inflation of mortality risk among these populations.

These findings have important implications. The consistent overestimation of mortality risk may contribute to an overly pessimistic approach to care of patients with pre-existing kidney disease, leading to premature limitation of therapy, the inappropriate denial of scarce life-saving therapies during a crisis, or misinforming families about prognosis. Moreover, benchmarking ICU outcomes using these scoring systems could introduce bias for hospitals that care for a higher proportion of CKD, ESKD, or kidney transplant patients, as the high predicted mortality rates may reflect model miscalibration rather than true hospital performance.

It is important to remember that the ICU scoring systems evaluated in this study (APACHE, SAPS, SOFA) were derived from general ICU populations which represent a wide mix of patients based on demographics, social factors, and comorbidities. The original studies describing these scoring systems reported excellent discriminatory accuracy and acceptable calibration for their overall performance [9,48]. Yet, subsequent evaluations of the original scoring systems demonstrated a deterioration in performance, especially calibration, when applied to new settings or special populations in the ICU [56,57]. For instance, traditional scoring systems have shown reduced performance among cardiac surgery patients, spurring the development of cardiac-

specific predictive models, such as the Cardiac Surgery Score (CASUS) [58], which show improved performance in this subgroup.

These findings beg the question of whether new or recalibrated ICU scoring systems may provide more accurate risk estimations for patients with pre-existing kidney disease. Such models could be designed in a way as to more reliably account for baseline kidney function in a standardized fashion (e.g., based on outpatient serum creatinine values when available) such that the change in kidney function from baseline to ICU admission is captured. In turn, this may result in a number of downstream benefits including more accurate mortality risk estimation leading to more informed goals of care discussions, better resource allocation, and enhanced quality care benchmarking.

Our study is strengthened by a sensitive and comprehensive search strategy that covered several databases. We also acknowledge several limitations. First, several included studies were likely designed to address different research needs. Therefore, they did not comprehensively report on model performance metrics by specific pre-existing kidney disease populations, and many did not provide a non-kidney disease population as a comparator. Second, performance metrics specifically for calibration were highly heterogeneous, therefore leaving us unable to meta-analyze the calibration metrics. Third, there were only two studies which included a very limited number of non-dialysis CKD patients. In turn, we were not able to draw any substantial conclusions

about how traditional ICU scoring systems perform in the broad non-dialysis CKD population (or by CKD stage). This remains a major knowledge gap to be addressed in the future.

In summary, traditional ICU scoring systems show important limitations when applied to patients with pre-existing kidney disease. This includes a consistent overestimation of mortality risk among patients with ESKD on maintenance dialysis and overall poor discrimination and calibration among kidney transplant recipients. Moreover, there is little to no data on how these scoring systems perform in the non-dialysis CKD population. Future work should include large multi-center external validation of ICU scoring systems across the complete spectrum of CKD and consideration for the development of novel or recalibrated scoring systems specifically designed for patients with pre-existing kidney disease.

LIST OF ABBREVIATIONS

AKI	Acute Kidney Injury
APACHE II/III	Acute Physiology and Chronic Health Evaluation II/III
AUROC	Area Under the Receiver Operating Characteristic Curve
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CKD	Chronic Kidney Disease
COVID19	Coronavirus Disease 2019
eGFR	Estimated Glomerular Filtration Rate
ESKD	End-Stage Kidney Disease
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HIV	Human Immunodeficiency Virus
ICU	Intensive Care Unit
JBI	Joanna Briggs Institute
JBI-MAStARI	Joanna Briggs Institute Meta-Analysis of Statistical Assessment and Review Instrument
KTx	Kidney Transplant Recipients
MeSH	Medical Subject Headings
MV	Mechanical Ventilation
NKF	Normal Kidney Function
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROBAST	Prediction model Risk Of Bias Assessment Tool
PROSPERO	International Prospective Register of Systematic Reviews
SAPS II/III	Simplified Acute Physiology Score II/III
SMR	Standardized Mortality Ratio
SOFA	Sequential Organ Failure Assessment

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Ethics Approval and Consent to Participate

Not Applicable

Consent for Publication

Not applicable

Data Sharing Statement

All data generated or analysed during this study are included in this article and its supplementary information files

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Authors’ Contributions

HE, EGC, and GLH conceived the systematic review and contributed to the development of the study eligibility criteria, data extraction criteria, and the quality and risk of bias assessment strategy. HE, EGC, GLH, and RS developed the search strategy. HE, MK, AB, AOK, NB, IL, and DF made substantial contributions to data acquisition. HE conducted statistical analysis. HE, EGC, and GLH drafted the manuscript. RW, SWE, SAS, AA, and GAK participated in the study design and revised the manuscript. All authors read, provided feedback on, and approved the final manuscript.

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FIGURES

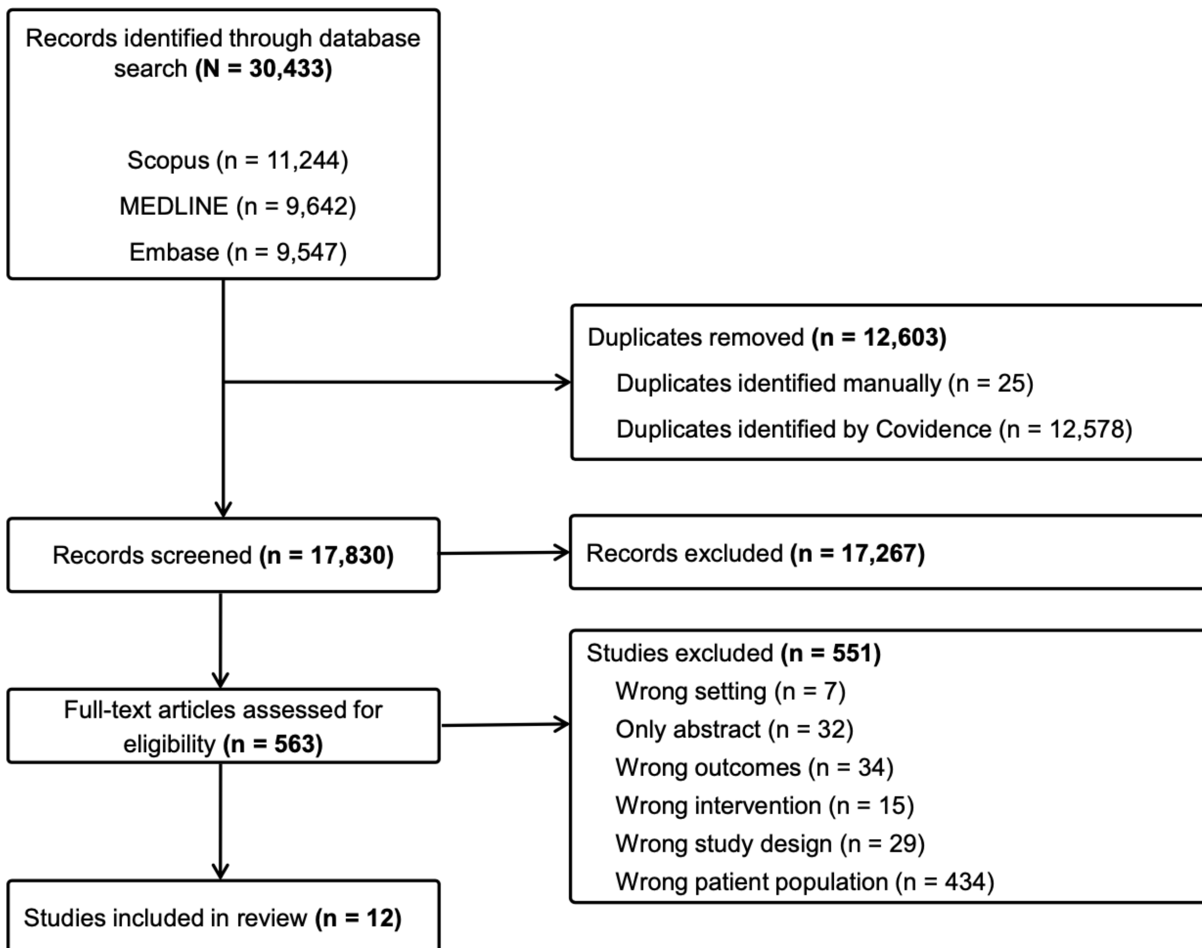
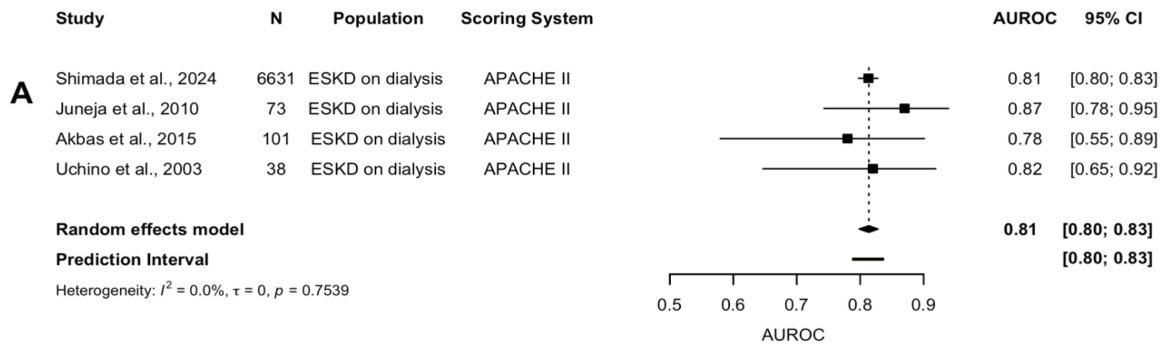
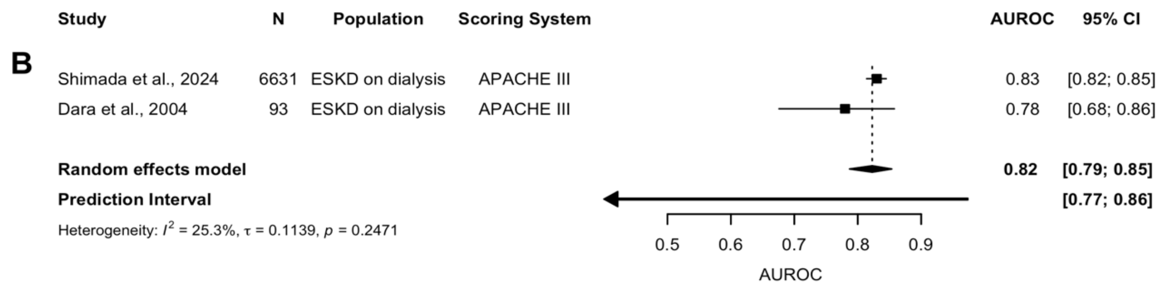
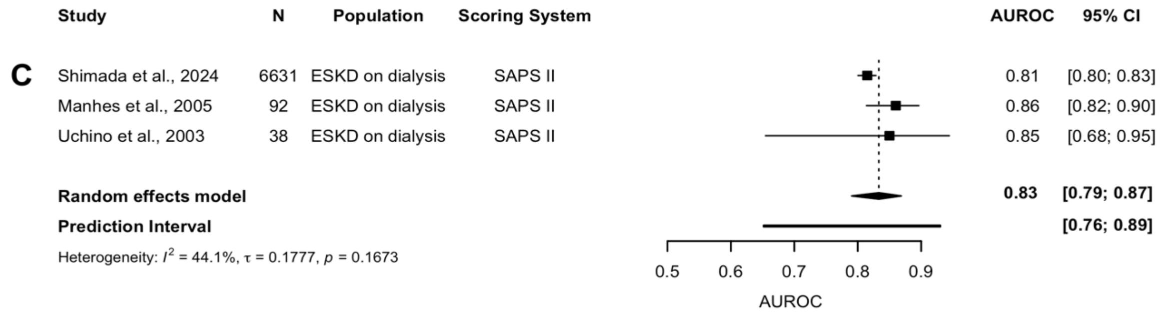


Figure 1. PRISMA flow diagram detailing the study selection process.







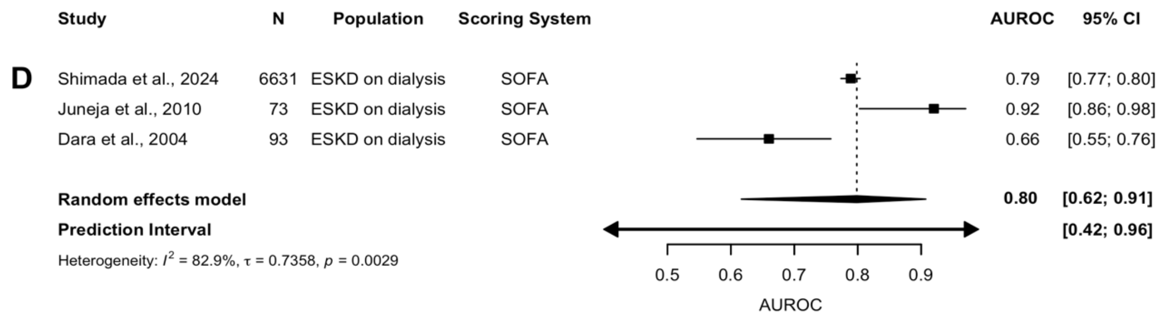
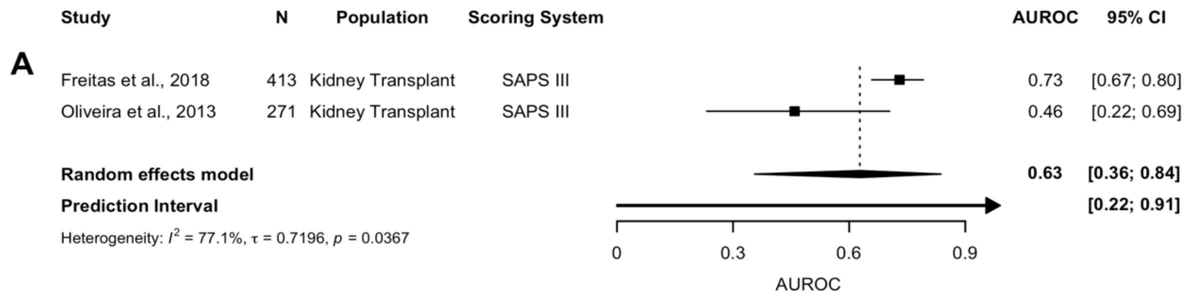


Figure 2. AUROC estimates for discriminatory performance in patients with ESKD on maintenance dialysis admitted to the ICU.

Each forest plot has black boxes representing each study and its contribution to the overall estimate; horizontal lines represent the 95% CI; the diamonds represent the pooled estimates for each scoring systems as follows: A. APACHE II, B. APACHE III, C. SAPS II, D. SOFA.

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; AUROC, area under the receiver operating characteristic curve; CI, confidence interval; ESKD, end-stage kidney disease; ICU, intensive care unit; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment.



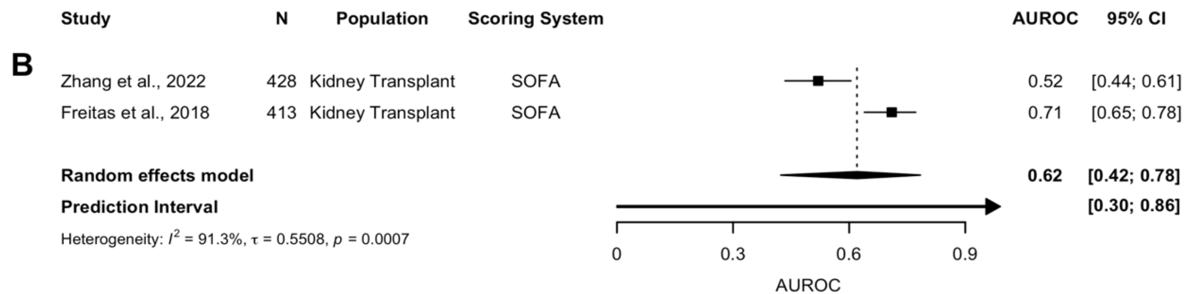


Figure 3. AUROC estimates for discriminatory performance in kidney transplant recipients admitted to the ICU.

Forest plots representing each study with its reported discriminatory performance in kidney transplant recipients admitted to the ICU; horizontal lines represent the 95% CI for the following scoring systems: A. SAPS III, B. SOFA.

Abbreviations: AUROC, area under the receiver operating characteristic curve; CI, confidence interval; ICU, intensive care unit; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment.

TABLES

Table 1. Study Characteristics.

Study (Publication Year)	Country	Cohort Study Design	ICU Study Population	Sample Size, N	Sub-group sample size (n)	% Male	Mean (SD)/ Median [IQR] age	Study Period	ICU Mortality (%)	Hospital Mortality (%)	Scoring System(s)	Primary Outcome	Secondary Outcomes
Rana et al. (2024)	Pakistan	Prospective	ESKD	189	ESKD n= 189	51	61 (13)	Jan 2021 – Dec 2022	12.6	NA	SAPS II	ICU mortality	Number of organ system failure, MV duration
Shimada et al. (2024)	Japan	Retrospective	All	128,134	ESKD n = 6,631 * Non-ESKD n= 121	62	71 [60–78]	Apr 2018-Mar 2021	All = 4 ESKD = 7.2 Non-ESKD = 3.8	All = 8.9 ESKD =18 Non-ESKD = 8.4	APACHE II APACHE III SAPS II SOFA	Hospital mortality	ICU and hospital length of stay, discriminatory and calibration performance
Zhang et al. (2022)	China	Retrospective	KTx recipients	428	KTx n = 428	59	55 (12)	NA	NA	NA	SOFA	90-day mortality	ICU length of stay, discriminatory performance of scoring system
Freitas et al. (2018)	Brazil	Retrospective	KTx recipients	413	KTx n = 413	63	51 (14)	Sept 2013 – June 2014	12.8	17.9	APACHE II SAPS III SOFA	Hospital mortality	ICU and hospital length of stay, ICU mortality, sepsis incidence, discriminatory and calibration performance of scoring systems
Goswami et al. (2018)	India	Prospective	CKD and ESKD	100	ESKD n = 94 CKD (stage-4) n= 6	79	39 (14) ‡	Sept 2011-August 2013	34	39	APACHE II SAPS II SOFA	30-day mortality	ICU Length of stay, ICU mortality, discriminatory performance of scoring systems
Akbas et al. (2015)	Turkey	Retrospective	All requiring CRRT	216	ESKD n= 101 AKI‡ n = 115 (2-5 CKD stages n = 45; NKF n = 70)	51	66 [53-73]	2000 - 2007	58	NA	APACHE II	ICU mortality	ICU length of stay, MV utilisation, APACHE-II scores

Oliveira et al. (2013)	Brazil	Prospective	Solid organ transplant recipients	501	KTx n = 271 Other solid organ transplant = 230	65.5	46 (2)	May 2006-Jan 2007	NA	2.6	APACHE II SAPS III	Hospital mortality	ICU and hospital length of stay, predicted mortality and SMR
Juneja et al. (2010)	India	Prospective	ESKD	73	ESKD n = 73	67	54 (15)	May 2007-July 2008	27	NA	APACHE II SOFA	30-day mortality	ICU mortality, ICU and hospital length of stay, predicted death rate and SMR
Manhes et al. (2005)	France	Prospective	All	1,257	ESKD n= 92 Non-ESKD n = 1,165	64	63 (15)	Jan 1996- Dec 1999	ESKD: 28 Non-ESKD: 22	ESKD = 38 Non-ESKD = 28	SAPS II	Hospital mortality	ICU mortality, ICU length of stay, 6-months mortality post ICU discharge, discriminatory and calibration performance of scoring systems
Dara et al. (2004)	USA	Retrospective	All	32,612	ESKD n = 93 Non-ESKD n = 32,519	58	66 [54-76]	Jan 1999- Nov 2002	ESKD = 9 Non-ESKD = 5.5	ESKD = 16 Non-ESKD = 10	APACHE III SOFA	30-day mortality	ICU and hospital mortality, sepsis incidence, ICU length of stay
Uchino et al. (2003)	Australia	Matched controls	All requiring CRRT	70	ESKD n = 38 Matched AKI, n = 32	60.5	ESKD = 45 (16) AKI = 55.5 (21)	3 months	ESKD = 22 AKI = 38	ESKD = 34 AKI = 38	APACHE II SAPS II	ICU and Hospital mortality	ICU and hospital length of stay, MV duration
Clermont et al. (2002)	USA	Prospective	All	1530	ESKD = 57 AKI = 254 Non-ESKD/No-AKI = 1,219	NA	ESKD = 58 (2) AKI = 59 (1) Non-ESKD/ non-AKI =59 (1)	NA	ESKD = 11 AKI = 23 Non-ESKD/non-AKI = 5	ESKD = 14 AKI = 34 Non-ESKD/non-AKI = 9	APACHE III	ICU and hospital mortality	ICU length of stay, predicted mortality and SMR

Abbreviations: AKI, acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; CKD, non-dialysis chronic kidney disease; CRRT, continuous renal replacement therapy; ESKD, end-stage kidney disease on maintenance dialysis; ICU, intensive care unit; IQR, 25th-75th percentile interquartile range; KTx, kidney transplant recipient; MV, mechanical ventilation; NA, not available; SAPS, Simplified Acute Physiology Score; SD, standard deviation; SMR, standardized mortality ratio; SOFA, Sequential Organ Failure Assessment; USA, United States of America; ‡ Study population may include some patients younger than 18 years;

*Non-ESKD = Individuals with or without CKD but not on maintenance dialysis and not having received a kidney transplant

Table 2. Performance Metrics of Predictive Scoring Systems in Patients with Chronic Kidney Disease and End-Stage Kidney Disease.

Study	Subgroup Sample Size (n)	Scoring System	Mean (SD)/Median (IQR) Scores on ICU admission	Discrimination (AUROC [95% CI])	Calibration	Summary
Rana et al. (2024)	ESKD n= 189	SAPS II	Survivors: 33.1 (11.3) Non-survivors: 69.3 (31.1)	NA	Not reported	SAPS II was included in the multivariate analysis and was not statistically significant.
Shimada et al. (2024)	ESKD n = 6, 631 * Non-ESKD n= 121, 503	APACHE II	Overall = 14.0 (11-19) ESKD: 22.0 (18-26)	Non-ESKD = 0.89 [0.88–0.89] ESKD= 0.81 [0.80–0.83]	Calibration plot showed systematic overprediction in ESKD; acceptable fit in non-ESKD.	APACHE III showed better calibration than APACHE II. SOFA and SAPS II exhibited moderate overestimation of hospital mortality despite a good calibration slope. All four scoring systems discriminate mortality risk less effectively in ESKD patients compared to non-ESKD.
		APACHE III	Overall = 53.0 (40-71) ESKD: 78.0 (67-92)	Non-ESKD= 0.90 [0.89–0.90] ESKD= 0.83 [0.82–0.85]	Slight overprediction in ESKD; good fit in non-ESKD.	
		SAPS II	Overall = 28.0 (20-40) ESKD: 43.0 (36-53)	Non-ESKD= 0.89 [0.89–0.90] ESKD= 0.81 [0.80–0.83]	Overprediction in ESKD; good fit in non-ESKD.	
		SOFA	Overall: 4.0 (2-7) ESKD: 8.0 (6-11)	Non-ESKD= 0.85 [0.84–0.85] ESKD= 0.79 [0.77–0.80]	Calibration plot shows close alignment between predicted and observed mortality in both ESKD and non-ESKD, with slight overprediction in ESKD	
Goswami et al. (2018)	ESKD n = 94 CKD (stage-4) n= 6	APACHE II	28.2 (7.53)	0.96 [95% CI not reported]	NA	APACHE II, SAPS II, and SOFA showed excellent discriminatory power. However, no calibration metrics were reported, limiting further assessment of their predictive accuracy in ESKD patients.
		SAPS II	43.0 (16.40)	0.99 [95% CI not reported]		
		SOFA	10.4 (5.20)	0.95 [95% CI not reported]		
Juneja et al. (2010)	ESKD n = 73	APACHE II	NA	0.87 [0.78-0.95]	SMR = 0.48	APACHE II showed excellent discrimination but overpredicted 30-day mortality with SMR< 1. In contrast, SOFA displayed outstanding discrimination though no calibration assessment was reported for SOFA.
		SOFA	NA	0.92 [0.86-0.98]	NA	

Akbas et al. (2015)	ESKD n= 101 AKI‡ n = 115 (2-5 CKD stages n = 45; NKF n = 70)	APACHE II	ESKD = 27.5 (9) AKI = 28 (8)	ESKD = 0.78 [0.55 - 0.89] AKI = 0.52 [0.39 – 0.66]	NA	APACHE II showed acceptable discrimination in ESKD patients compared to poor discrimination in AKI. Calibration was not assessed, and data were insufficient to infer mortality prediction accuracy.
Manhes et al. (2005)	ESKD n= 92 Non-ESKD n = 1,165	SAPS II	ESKD: 45 (21) Non-ESKD: 44 (25)	ESKD = 0.86 [0.82-0.90] Non-ESKD: NA	ESKD: Good calibration observed (38%) versus predicted mortality (41.6%). SMR = 0.91 Non-ESKD: NA	SAPS II demonstrated excellent discrimination, with calibration indicating no misfit. Mortality in ESKD patients was slightly overestimated, as suggest by SMR < 1
Dara et al. (2004)	ESKD n = 93 Non-ESKD n = 32,519	APACHE III	ESKD = 64.0 (47 - 79) Non-ESKD: NA	ESKD = 0.78 [0.68 – 0.86] Non-ESKD: NA	ESKD SMR = 0.74 Non-ESKD: NA	APACHE III demonstrated acceptable discrimination. SMR< 1 indicated overestimation of mortality in ESKD patients. SOFA showed poor discrimination. Calibration was not reported.
		SOFA	ESKD = 6 (5 - 8)	ESKD = 0.66 [0.55 – 0.76]	NA	
Uchino et al. (2003)	ESKD n = 38 Matched AKI, n = 32	APACHE II	ESKD = 22 (6) Matched AKI = 23 (9)	ESKD = 0.82 [0.65 – 0.92] Matched AKI: NA	SMR (ESKD) = 0.92 Matched AKI: NA	In ESKD patients, both APACHE II and SAPS II showed an acceptable discriminatory power and slight overestimation of mortality SMR < 1.
		SAPS II	ESKD = 45 (13) Matched-AKI = 46 (17)	ESKD = 0.85 [0.68 – 0.95] Matched-AKI: NA	SMR (ESKD) = 0.92 Matched-AKI: NA	
Clermont et al. (2002)	ESKD = 57 AKI = 254 Non-ESKD/No-AKI = 1,219	APACHE III	ESKD = 64 (3) AKI = 64 (2) Non-ESKD/No-AKI = 42 (1)	NA	Calibration plot for ESKD patients displayed systematic overestimation of mortality across score ranges. SMR (ESKD) = 0.52	APACHE III discriminatory power not reported. Calibration plots showed consistent overestimation of mortality in ESKD patients, with SMR < 1 confirming this trend.

Abbreviations: AKI; acute kidney injury; AUROC, area under receiver operating characteristic curve; APACHE, Acute Physiology and Chronic Health Evaluation; CI, confidence interval; CKD, non-dialysis chronic kidney disease; ESKD, end-stage kidney disease on maintenance dialysis; ICU, intensive care unit; IQR, 25th-75th percentile interquartile range; NA, not available; NKF, normal kidney function; SAPS, Simplified Acute Physiology Score; SD, standard deviation; SMR, standardized mortality ratios; SOFA, Sequential Organ Failure Assessment.

‡ This subgroup includes both acute- on-chronic kidney disease (not on dialysis at baseline) and normal kidney function as defined by normal baseline creatinine levels (≥ 90 mL/min/1.73 m^2)[41,59].

*Non-ESKD = Individuals with or without CKD but not on maintenance dialysis and not having received a kidney transplant

Table 3. Performance Metrics of Predictive Scoring Systems in Kidney Transplant Recipients.

Study	Subgroup Sample Size (n)	Scoring System	Median [IQR] Scores on ICU Admission	Discrimination (AUROC [95% CI])	Calibration	Summary
Zhang et al. (2022)	KTx n = 428	SOFA Day 1	NA	0.52 [0.44-0.61]	NA	SOFA discrimination improved from Day 1 to Day 3 but remained overall poor, suggesting that later scores better predict 90-day mortality among ICU KTx patients.
		SOFA Day 2	NA	0.65 [0.56-0.75]		
		SOFA Day 3	NA	0.73 [0.63-0.83]		
Freitas et al. (2018)	KTx n = 413	APACHE II	18 [14-23]	0.69 [0.62–0.76]	Calibration was poor with significant deviation between estimated and observed mortality. SMR= 0.65 [0.36 – 0.99]	Both APACHE II and SAPS III demonstrated poor discrimination and calibration. Calibration analysis displayed misfit and SMRs indicated APACHE II overestimated mortality risk, whereas SAPS III underestimated mortality. SOFA had acceptable discrimination, but calibration was not assessed
		SAPS III	47.5 [37–57]	0.73 [0.67–0.80]	Calibration was poor with significant deviation between estimated and observed mortality. SMR = 1.08 [0.6–1.65]	
		SOFA	5 [3–7]	0.71 [0.65–0.78]	Not reported	
Oliveira et al. (2013)	KTx n = 271	APACHE II	NA	0.550 ‡	SMR = 0.17 [0.08–0.31]	Both SAPS III and APACHE II demonstrated poor discrimination. SMRs suggest that APACHE II overestimated mortality, whereas SAPS III underestimated it. Calibration assessment using SMR indicates that APACHE II overestimated mortality risk, whilst SAPS III underestimated mortality.
		SAPS III	NA	0.46 [0.22-0.69]	SMR = 3.42 [1.37–7.04]	

Abbreviations: AUROC, area under receiver operating characteristic curve; APACHE= Acute Physiology and Chronic Health Evaluation; CI, confidence interval; ICU, intensive care unit; IQR, 25th-75 percentile interquartile range; KTx, kidney transplant recipient; NA, not available; SAPS, Simplified Acute Physiology Score; SMR, standardized mortality ratio; SOFA, Sequential Organ Failure Assessment.

‡ The corresponding 95% CI reported in this paper did not include this point estimate.

SUPPLEMENTAL INFORMATION

Performance of Commonly Used Scoring Systems in Predicting Mortality Among Adult Intensive Care Unit Patients with Pre-Existing Kidney Disease: A Systematic Review and Meta-Analysis

Supplement Legend

Supplementary Table 2. PRISMA 2020 Checklist.

Supplementary Table 2. Deviations from protocol.

Supplementary Table 3. Search Strategies.

Supplementary Table 4. List of Excluded Studies.

Supplementary Table 5. Characteristics of Selected ICU Severity of Illness Scoring Systems and Kidney-Related Parameters.

Supplementary Table 6. Statistical results summary of outcomes and GRADE Assessment.

Supplementary Table 7. JBI critical appraisal results for cohort studies.

Supplementary Table 8. PROBAST Risk of Bias Results.

Supplementary Figure 1. Risk of Bias and applicability assessment of included studies using the PROBAST tool.

Supplementary Table 3. PRISMA 2020 Checklist.

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Line 46 – 72
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Background Line 96 – 117
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Background Line 114 – 117
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Methods, Eligibility Criteria Line 137 – 149
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Methods, Data Sources and Searches Line 128 – 135
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplementary File Table 3
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Methods Study Selection Line 151 – 158
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Methods Data Extraction and Quality Assessment Line 160 – 166
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Methods Data Synthesis and Statistical Analysis Line 177 – 189
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Methods Data Synthesis and Statistical Analysis

Section and Topic	Item #	Checklist item	Location where item is reported
			Line 177 – 189
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Methods Data Extraction and Quality Assessment Line 168 – 175
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Methods Data Synthesis and Statistical Analysis Line 177 – 189
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Methods Data Synthesis and Statistical Analysis Line 177 – 189
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	NA
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Methods Data Extraction and Quality Assessment Line 165
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Methods Data Synthesis and Statistical Analysis Line 191 – 207
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	NA
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Methods Data Extraction and Quality Assessment Line 168 – 175
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Results Literature Search Line 209 – 217

Section and Topic	Item #	Checklist item	Location where item is reported
			Figure 1. PRISMA flow diagram
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Supplementary Table 4. List of excluded studies
Study characteristics	17	Cite each included study and present its characteristics.	Results Study Characteristics, Line 219 – 244 Table 1. Study characteristics (pg. 35 – 36)
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Results, Risk of Bias, Line 357 - 365 Figure 2: AUROC estimates for discriminatory performance in patients with ESKD on maintenance dialysis admitted to the ICU, Supplementary table 8: PROBAST Risk of bias results
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table 2: Performance Metrics of Predictive Scoring Systems in Patients with Chronic Kidney Disease and End-Stage Kidney Disease, Table 3: Performance Metrics of Predictive Scoring Systems in Kidney Transplant Recipients

Section and Topic	Item #	Checklist item	Location where item is reported
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Results, Performance of ICU Scoring Systems in Chronic Kidney Disease and End-Stage Kidney Disease, Performance of ICU Scoring Systems in Kidney Transplant Recipients Line 246 – 316
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Results, Figures 2 & 3 Meta-analysis Line 318 - 355
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Results, Risk of bias Line 357 – 365 Supplementary Figure 1
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion Line 379 – 441
	23b	Discuss any limitations of the evidence included in the review.	Discussion Line 443 – 453
	23c	Discuss any limitations of the review processes used.	NA
	23d	Discuss implications of the results for practice, policy, and future research.	Discussion Line 413 – 441
OTHER INFORMATION			
Registration and	24a	Provide registration information for the review, including register name and registration number, or	Methods,

Section and Topic	Item #	Checklist item	Location where item is reported
protocol		state that the review was not registered.	Protocol, Line 124
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Methods, Protocol, Line 122 - 125
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Supplementary table 2
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Acknowledgements, Funding, Line 508 – 515
Competing interests	26	Declare any competing interests of review authors.	Acknowledgements, Disclosures Line 504 – 506
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Methods, Data Synthesis and Statistical Analysis, Line 205 – 207

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. This work is licensed under CC BY 4.0. To view a copy of this license, visit https://creativecommons.org/licenses/by/4.0/

Supplementary Table 2. Deviations from protocol.

Deviation	Reason
1. Age eligibility, a small number of studies included cohorts with patients <18 years old that could not be separated. These studies were flagged for applicability in **Supplementary Table 5.**	Avoid discarding otherwise important metrics for ICU predictive scoring systems when age-stratified results were not available
2. PROBAST was used alongside JBI for risk of bias	PROBAST provides prediction model-specific risk of bias assessment
3. Meta-analysis was not performed	High heterogeneity and variability
4. Subgroup analyses were not performed	Insufficient number of studies for each subpopulation

Supplementary Table 3. Search Strategies.

Ovid MEDLINE(R) ALL <1946 to October 10, 2024>

#	Search	Results
1	APACHE/ or Organ Dysfunction Scores/ or Simplified Acute Physiology Score/	9119
2	(organ adj2 (dysfunction or failure) adj2 (assessment* or score*)).tw,kf.	7719
3	(sofas or sofa score* or mods or lods).tw,kf.	13884
4	apache*.tw,kf.	11749
5	(Simplified Acute Physiology Score* or saps).tw,kf.	5089
6	(Mortality adj (scale* or score* or predict* or probab* or analysis)).tw,kf.	7915
7	Mortality Probability Model*.tw,kf.	139
8	"Acute Physiology And Chronic Health Evaluation".tw,kf.	6589
9	or/1-8	43118
10	Intensive Care Units/	75049
11	(intensive care or icu).tw,kf.	247225
12	critical* ill*.tw,kf.	75214
13	critical care/	62777
14	critical care.tw,kf.	47977
15	or/10-14	338244
16	9 and 15	19423
17	Mortality/	50396
18	(mortality or short term outcome* or long term outcome* or patient outcome* or predicted outcome*).tw,kf. or death*.ti.	1354113
19	17 or 18	1365788
20	16 and 19	13521
21	exp Cohort Studies/	2659722
22	(cohort* or retrospective* or prospective*).ti.	459786
23	(cohort* or retrospective* or prospective*).ab. /freq=2	694154
24	((cohort* or retrospective* or prospective*) adj3 (trial* or stud*)).tw,kf.	1270661
25	validation study/	112767
26	validat*.tw,kf.	846948
27	or/21-26	3947550
28	20 and 27	10248
29	(exp child/ or exp infant/) not exp adult/	1974124
30	((child* or infant* or pediatric or paediatric) not adult*).ti.	1285555
31	exp animals/ not humans/	5266257
32	(animal* or rat or rats or mouse or mice or pig or pigs or rabbit*).ti.	1845069
33	28 not (or/29-32)	9642

Scopus < Inception to 2024 October 10>

(((TITLE-ABS ("intensive care") OR TITLE-ABS (icu) OR TITLE-ABS ("critical* ill*") OR TITLE-ABS ("critical care")) AND ((TITLE-ABS (mortality W/1 TITLE-ABS (scale* OR score* OR predict* OR probab* OR analysis))) OR (TITLE-ABS ("Acute Physiology And Chronic Health Evaluation") OR TITLE-ABS ("mortality probability model*") OR TITLE-ABS ("Simplified Acute Physiology Score*") OR TITLE-ABS (saps) OR TITLE-ABS (sofas) OR TITLE-ABS ("sofa score") OR TITLE-ABS (mods) OR TITLE-ABS (lods) OR TITLE-ABS ("organ dysfunction score*") OR TITLE-ABS ("organ dysfunction assessment*") OR TITLE-ABS ("organ failure score*") OR TITLE-ABS ("organ failure assessment*") OR TITLE-ABS (apache)))) AND NOT (((TITLE (child* OR infant* OR pediatric OR paediatric) AND NOT TITLE (adult*)) OR ((animal* OR rat OR rats OR mouse OR mice OR pig OR pigs OR rabbit*) .ti.)))) AND (TITLE-ABS (prospective*) OR TITLE-ABS (retropective*) OR TITLE-ABS (prospective*) OR TITLE-ABS (cohort*) OR TITLE-ABS (validat*))

Embase Classic+Embase <1947 to 2024 October 10>

1	apache/ or simplified acute physiology score/	31094
2	organ dysfunction score/	1525
3	(organ adj2 (dysfunction or failure) adj2 (assessment* or score*)).tw.	10446
4	exp sequential organ failure assessment score/	19503
5	(sofas or sofa score* or mods or lods).tw.	21374
6	apache.tw.	22986
7	(Simplified Acute Physiology Score* or saps).tw.	8834
8	(Mortality adj (scale* or score* or predict* or probab* or analysis)).tw.	11968
9	Mortality Probability Model*.tw.	201
10	"Acute Physiology And Chronic Health Evaluation".tw.	8003
11	or/1-10	78349
12	intensive care unit/ or medical intensive care unit/ or neurological intensive care unit/ or surgical intensive care unit/	266761
13	(intensive care or icu).tw.	396061
14	critical* ill*.tw.	111039
15	intensive care/	156945
16	critical care.tw.	67149
17	or/12-16	608547
18	11 and 17	42838
19	*mortality/	127767
20	(mortality or short term outcome* or long term outcome* or patient outcome* or predicted outcome*).tw. or death*.ti.	2002433
21	19 or 20	2016076
22	18 and 21	28732
23	exp child/ not exp adult/	2653419
24	((child* or infant* or pediatric or paediatric) not adult*).ti.	1676056
25	(exp animal/ or nonhuman/ or animal experiment/) not exp human/	8343294
26	(animal* or rat or rats or mouse or mice or pig or pigs or rabbit*).ti.	2302423
27	or/23-26	11613905
28	22 not 27	27317
29	conference abstract.pt.	5253454
30	28 not 29	16630
31	*cohort analysis/	49850
32	*prospective study/	45082
33	*retrospective study/	40986
34	validation study/	115246
35	validat*.tw.	1193279
36	(cohort* or retrospective* or prospective*).ti. or (cohort* or retrospective* or prospective*).ab. /freq=2	1650886
37	((cohort* or retrospective* or prospective*) adj3 (trial* or stud*)).tw.	1926511
38	31 or 32 or 33 or 34 or 35 or 36 or 37	3626218
39	30 and 38	9547

Supplementary Table 4. List of Excluded Studies.

Title	Author & Year	Reason for Exclusion
Comparison of Four Severity Assessment Scoring Systems in Critically Ill Patients for Predicting Patient Outcomes: A Prospective Observational Study From a Single Tertiary Center in Central India.	Mishra 2024	Wrong patient population;
APRICOT-Mamba: Acuity Prediction in Intensive Care Unit (ICU): Development and Validation of a Stability, Transitions, and Life-Sustaining Therapies Prediction Model.	Contreras 2024	Wrong outcomes;
The six scoring systems' prognostic value in predicting 24-hour mortality in septic patients.	Djikic 2024	Wrong patient population;
A novel prognostic model to predict mortality in patients with acute-on-chronic liver failure in intensive care unit.	Lin 2024	Wrong patient population;
Prognostic evaluation of quick sequential organ failure assessment score in ICU patients with sepsis across different income settings.	Li 2024	Wrong patient population;
Evaluating Prognostic Bias of Critical Illness Severity Scores Based on Age, Sex, and Primary Language in the United States: A Retrospective Multicenter Study.	Liu 2024	Wrong outcomes;
Modified Cardiovascular Sequential Organ Failure Assessment Score in Sepsis: External Validation in Intensive Care Unit Patients.	Ko 2023	Wrong patient population;
Validated Prognostic Scores to Predict Outcomes in ECLS-Bridged Patients to Lung Transplantation.	Faccioli 2023	Wrong patient population;
Evaluation of medication regimen complexity as a predictor for mortality.	Sikora 2023	Wrong intervention;
External validation of the ISARIC 4C Mortality Score to predict in-hospital mortality among patients with COVID-19 in a Canadian intensive care unit: a single-centre historical cohort study.	Vallipuram 2023	Wrong patient population;
Development and validation of a prediction model for in-hospital death in patients with heart failure and atrial fibrillation.	Yan 2023	Wrong patient population;
Prospective Evaluation of a Dynamic Acuity Score for Regularly Assessing a Critically Ill Patient's Risk of Mortality.	Kramer 2023	Wrong patient population;
Validation of the CLIF-C OF Score and CLIF-C ACLF Score to Predict Transplant-Free Survival in Patients with Liver Cirrhosis and Concomitant Need for Intensive Care Unit Treatment.	Nagel 2023	Wrong patient population;
Association of clinical prediction scores with hospital mortality in an adult medical and surgical intensive care unit in Kenya.	Brotherton 2023	Wrong patient population;
APACHE scoring as an indicator of mortality rate in ICU patients: a cohort study.	Mumtaz 2023	Wrong patient population;
A Comparison of ICU Mortality Scoring Systems Applied to COVID-19.	Monk 2023	Wrong patient population;
Risk factors for hospital mortality in intensive care unit survivors: a retrospective cohort study.	ESilva 2023	Wrong patient population;
Validation of the Acute Physiology and Chronic Health Evaluation (APACHE) II Score in COVID-19 Patients Admitted to the Intensive Care Unit in Times of Resource Scarcity.	Fernandes 2023	Wrong patient population;
Comparison of APACHE II and APACHE IV score as predictors of mortality in patients with septic shock in intensive care unit: A prospective observational study.	Bloria 2023	Wrong patient population;
Prognostic Performance of Sequential Organ Failure Assessment, Acute Physiology and Chronic Health Evaluation III, and Simplified Acute Physiology Score II Scores in Patients with Suspected Infection According to Intensive Care Unit Type.	Hwang 2023	Wrong patient population;
Validity of the total SOFA score in patients >= 80 years old acutely admitted to intensive care units: a post-hoc analysis of the VIP2 prospective, international cohort study.	Polok 2023	Wrong outcomes;
Investigating the Utility of the SOFA Score and Creating a Modified SOFA Score for Predicting Mortality in the Intensive Care Units in a Tertiary Hospital in Jordan.	Abu-Humaidan 2023	Wrong patient population;
Assessment of severity scoring systems for predicting mortality in critically ill patients receiving continuous renal replacement therapy.	Park 2023	Wrong patient population;

Automated APACHE II and SOFA score calculation using real-world electronic medical record data in a single center.	Mutchmore 2023	Wrong outcomes;
Modified National Early Warning Score (MNEWS) in predicting the mortality of intensive care unit patients.	Wang 2023	Wrong patient population;
A first-level customization study of SAPS II with Norwegian Intensive Care and Pandemic Registry (NIPaR) data.	Bruserud 2023	Wrong patient population;
External Validation of Mortality Prediction Models for Critical Illness Reveals Preserved Discrimination but Poor Calibration.	Cox 2023	Wrong patient population;
Variation of the SOFA score and mortality in patients with severe burns: A cohort study.	Calles 2023	Wrong patient population;
Comparison of Mortality Prediction Scores in Intermediate-Care Patients with Liver Cirrhosis at a German University Transplant Centre: A Prospective Study.	Jahn 2023	Wrong patient population;
Predictive value of the APACHE II score in cardiogenic shock patients treated with a percutaneous left ventricular assist device.	Mierke 2022	Wrong patient population;
Epidemiology and risk prediction of patients with severe burns admitted to a burn intensive care unit in a burn center in beijing: A 5-year retrospective study.	Wang 2022	Wrong patient population;
Comparison of mNUTRIC-S2 and mNUTRIC scores to assess nutritional risk and predict intensive care unit mortality.	Kim 2022	Wrong intervention;
Prediction of Inhospital Mortality in Critically Ill Patients With Sepsis: Confirmation of the Added Value of 24-Hour Lactate to Acute Physiology and Chronic Health Evaluation IV.	Baysan 2022	Wrong patient population;
Development and Internal Validation of a New Prognostic Model Powered to Predict 28-Day All-Cause Mortality in ICU COVID-19 Patients-The COVID-SOFA Score.	Moisa 2022	Wrong patient population;
Transplantation for EASL-CLIF and APASL acute-on-chronic liver failure (ACLF) patients: The TEA cohort to evaluate long-term post-Transplant outcomes.	Xia 2022	Wrong patient population;
Geriatric Nutritional Risk Index is Associated with Hospital Death in Elderly Patients with Multiple Organ Dysfunction Syndrome: A Retrospective Study Based on the MIMIC-III Database.	Mao 2022	Wrong patient population;
Comparison of Sequential Organ Failure Assessment Score and Sequential Organ Failure Assessment Score with pH in Outcome Prediction among ICU Patients: A Prospective Observational Study.	Agarwal 2022	Wrong outcomes;
Predictive Value of Sequential Organ Failure Assessment, Quick Sequential Organ Failure Assessment, Acute Physiology and Chronic Health Evaluation II, and New Early Warning Signs Scores Estimate Mortality of COVID-19 Patients Requiring Intensive Care Unit	Asmarawati 2022	Wrong patient population;
Data for validation and adjustment of APACHE II score in cardiogenic shock patients treated with a percutaneous left ventricular assist device.	Mierke 2022	Wrong patient population;
Modified Nutrition Risk in Critically Ill Score, A Prognostic Marker of Morbidity and Mortality in Mechanically Ventilated Patients: A Prospective Observational Study.	Dsouza 2022	Wrong intervention;
Cohort study of the APACHE II score and mortality for different types of intensive care unit patients.	Sungono 2022	Wrong patient population;
[Predictive value of sequential organ failure assessment on 28-day mortality in patients with post-cardiac arrest syndrome].	Lin 2022	Wrong patient population;
An improved prognostic model for predicting the mortality of critically ill patients: a retrospective cohort study.	Zhang 2022	Wrong patient population;
Accuracy of conventional disease severity scores in predicting COVID-19 ICU mortality: retrospective single-center study in Turkey.	Yildrim 2022	Wrong patient population;
Comparison of risk scoring systems for critical care patients with upper gastrointestinal bleeding: predicting mortality and length of stay.	Lincoln 2022	Wrong patient population;
Comparative Analysis of Composite Mortality Prediction Scores in Intensive Care Burn Patients.	Obed 2022	Wrong patient population;
Sequential organ failure assessment score as a predictor of the outcomes of patients hospitalized for classical or exertional heatstroke.	Yokoyama 2022	Wrong patient population;
Evaluation of mortality prediction using SOFA and APACHE IV tools in trauma and non-trauma patients admitted to the ICU.	KaramiNiaz 2022	Wrong patient population;

Relationships between RDW, NLR, CAR, and APACHE II scores in the context of predicting the prognosis and mortality in ICU patients.	Deniz 2022	Wrong patient population;
Predict models for prolonged ICU stay using APACHE II, APACHE III and SAPS II scores: A Japanese multicenter retrospective cohort study.	Takekawa 2022	Wrong outcomes;
Mortality prediction models for severe burn patients: Which one is the best?	Yazici 2022	Wrong patient population;
Internal Validation of the Predictive Performance of Models Based on Three ED and ICU Scoring Systems to Predict Inhospital Mortality for Intensive Care Patients Referred from the Emergency Department.	Rahmatinejad 2022	Wrong patient population;
Comparative Study of Sofa, Apache Ii, Saps Ii, as a Predictor of Mortality in Patients of Sepsis Admitted in Medical ICU.	Morkar 2022	Wrong patient population;
Association between the Predicted Value of APACHE IV Scores and Intensive Care Unit Mortality: A Secondary Analysis Based on EICU Dataset.	Xu 2022	Wrong patient population;
Sequential organ failure assessment score improves survival prediction for left ventricular assist device recipients in intensive care.	Chatterjee 2022	Only abstract ;
Association of Sequential Organ Failure Assessment (SOFA) components with mortality.	Polkki 2022	Wrong patient population;
Preintubation Sequential Organ Failure Assessment Score for Predicting COVID-19 Mortality: External Validation Using Electronic Health Record From 86 U.S. Healthcare Systems to Appraise Current Ventilator Triage Algorithms.	Keller 2022	Wrong patient population;
Predictive value of serial evaluation of the Sequential Organ Failure Assessment (SOFA) score for intensive care unit mortality in critically ill patients with COVID-19: a retrospective cohort study.	Gruyters 2022	Wrong patient population;
Superiority of Simplified Acute Physiologic Score II Compared with Acute Physiologic and Chronic Health Evaluation II and Sequential Organ Failure Assessment Scores for Predicting 48-Hour Mortality in Patients Receiving Continuous Kidney Replacement Thera	Jung 2022	Only abstract ;
Which scoring system is effective in predicting mortality in patients with Crimean Congo hemorrhagic fever? A validation study.	Bakir 2022	Wrong patient population;
Mortality prediction in intensive care units including premorbid functional status improved performance and internal validity.	Moser 2022	Wrong patient population;
SAPS III is superior to SOFA for predicting 28-day mortality in sepsis patients based on Sepsis 3.0 criteria.	Zhu 2022	Wrong patient population;
Multicenter International Cohort Validation of a Modified Sequential Organ Failure Assessment Score Using the Richmond Agitation-sedation Scale.	Rakhit 2022	Wrong patient population;
Retrospective Evaluation Of The Accuracy Of Five Different Severity Scores To Predict The Mortality In Burns Patients.	deCarvalho 2021	Wrong patient population;
Sequential organ failure assessment score is superior to other prognostic indices in acute pancreatitis.	Teng 2021	Wrong patient population;
Performance in mortality prediction of SAPS 3 And MPM-III scores among adult patients admitted to the ICU of a private tertiary referral hospital in Tanzania: a retrospective cohort study.	Kassam 2021	Wrong patient population;
ISARIC-4C Mortality Score overestimates risk of death due to COVID-19 in Australian ICU patients: a validation cohort study.	Durie 2021	Wrong patient population;
Validation of the Acute Physiology and Chronic Health Evaluation (APACHE) II and IV Score in COVID-19 Patients.	Vandenbrande 2021	Wrong patient population;
Utility of Acute Physiology and Chronic Health Evaluation (APACHE II) in Predicting Mortality in Patients with Pyogenic Liver Abscess: A Retrospective Study.	Lee 2021	Wrong patient population;
Development and validation of a nomogram to predict the mortality risk in elderly patients with ARF.	Xu 2021	Wrong intervention;
Characteristics and outcomes of patients admitted to adult intensive care units in Hong Kong: a population retrospective cohort study from 2008 to 2018.	Ling 2021	Wrong patient population;
Comparison of four prognostic scales for predicting mortality in patients with severe maternal morbidity.	JonguitudLopez 2021	Wrong patient population;
SAPS 3 in the modified NUTrition RIsk in the Critically ill score has comparable predictive accuracy to APACHE II as a severity marker.	Pasinato 2021	Wrong outcomes;

Comparison of mortality risk evaluation tools efficacy in critically ill COVID-19 patients.	Vicka 2021	Wrong patient population;
Comparison of General and Liver-Specific Prognostic Scores in Their Ability to Predict Mortality in Cirrhotic Patients Admitted to the Intensive Care Unit.	CostaESilva 2021	Wrong patient population;
Predictive capacity of prognostic scores for kidney injury, dialysis, and death in intensive care units.	Vasconcelos 2021	Wrong patient population;
Comparison of prognosis predictive value of 4 disease severity scoring systems in patients with acute respiratory failure in intensive care unit: A STROBE report.	Huang 2021	Wrong patient population;
Dynamic SOFA score assessments to predict outcomes after acute admission of octogenarians to the intensive care unit.	Loyrion 2021	Wrong patient population;
Intensive Care Unit Scoring Systems.	Pellathy 2021	Wrong patient population;
Performance of intensive care unit severity scoring systems across different ethnicities in the USA: a retrospective observational study.	Sarkar 2021	Wrong patient population;
Pilot analysis of the usefulness of mortality risk score systems at resuscitated patients.	Kiss 2021	Wrong patient population;
Evaluation and Validation of Four Scoring Systems: the APACHE IV, SAPS III, MPM0 II, and ICMM in Critically Ill Cancer Patients.	Siddiqui 2020	Wrong patient population;
Comparing Eight Prognostic Scores in Predicting Mortality of Patients with Acute-On-Chronic Liver Failure Who Were Admitted to an ICU: A Single-Center Experience.	Chen 2020	Wrong patient population;
External validation of a prognostic model for intensive care unit mortality: a retrospective study using the Ontario Critical Care Information System.	Priestap 2020	Wrong patient population;
Predicting hospital mortality for intensive care unit patients: Time-series analysis.	Awad 2020	Wrong patient population;
Validation of APACHE II, APACHE III and SAPS II scores in in-hospital and one year mortality prediction in a mixed intensive care unit in Poland: a cohort study.	Czajka 2020	Wrong patient population;
The applicability of commonly used predictive scoring systems in Indigenous Australians with sepsis: An observational study.	Hanson 2020	Wrong patient population;
Investigating SOFA, delta-SOFA and MPM-III for mortality prediction among critically ill patients at a private tertiary hospital ICU in Kenya: A retrospective cohort study.	Lukoko 2020	Wrong patient population;
Mortality Prediction Using SOFA Score in Critically Ill Surgical and Non-Surgical Patients: Which Parameter Is the Most Valuable?.	Fuchs 2020	Wrong patient population;
Derivation and validation of a new nutritional index for predicting 90 days mortality after ICU admission in a Korean population.	Son 2020	Wrong intervention;
The SAPS 3 score as a predictor of hospital mortality in a South African tertiary intensive care unit: A prospective cohort study.	vanderMerwe 2020	Wrong patient population;
Admission diagnosis and mortality risk prediction in a contemporary cardiac intensive care unit population.	Jentzer 2020	Wrong patient population;
Performance of three prognostic models in critically ill patients with cancer: a prospective study.	Martos-Benitez 2020	Wrong patient population;
Mortality prediction by SOFA score in ICU-patients after cardiac surgery; comparison with traditional prognostic-models.	Schoe 2020	Wrong patient population;
Comparison of a modified Sequential Organ Failure Assessment Score using RASS and FOUR.	Telles 2020	Wrong patient population;
Comparing the performance of SOFA, TPA combined with SOFA and APACHE-II for predicting ICU mortality in critically ill surgical patients: A secondary analysis.	Zhang 2020	Wrong patient population;
A new simplified and accurate sa-SOFA score.	Vacheron 2020	Wrong patient population;
The prognostic accuracy evaluation of SAPS 3, SOFA and APACHE II scores for mortality prediction in the surgical ICU: an external validation study and decision-making analysis.	Falcao 2019	Wrong patient population;

ACUTE PHYSIOLOGY AND CHRONIC HEALTH EVALUATION (APACHE) II SCORE - THE CLINICAL PREDICTOR IN NEUROSURGICAL INTENSIVE CARE UNIT.	Akavipat 2019	Wrong patient population;
External validation of the Simplified Mortality Score for the Intensive Care Unit (SMS-ICU).	Granholm 2019	Wrong patient population;
The use of APACHE II, SOFA, SAPS 3, C-reactive protein/albumin ratio, and lactate to predict mortality of surgical critically ill patients: A retrospective cohort study.	Basile-Filho 2019	Wrong patient population;
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Evaluation of APACHE II system among intensive care patients at a teaching hospital.	Chiavone 2003	Wrong patient population;
Validation of the multiple organ dysfunction (MOD) score in critically ill medical and surgical patients.	Buckley 2003	Wrong patient population;
Simplified Acute Physiology Score III: a project for a new multidimensional tool for evaluating intensive care unit performance.	Vazquez 2003	Wrong study design;
[Intensive care medicine in the Netherlands, 1997-2001. I. Patient population and treatment outcome].	deJonge 2003	Only abstract ;
Intensive care unit support and Acute Physiology and Chronic Health Evaluation III performance in hematopoietic stem cell transplant recipients.	Afessa 2003	Wrong patient population;
Predictive accuracy of severity scoring system: a prospective cohort study using APACHE III in a Korean intensive care unit.	Ihnsook 2003	Wrong study design;
Evaluation of the P-POSSUM mortality prediction algorithm in Australian surgical intensive care unit patients.	Organ 2002	Only abstract ;
The Multiple Organ Dysfunction Score (MODS) versus the Sequential Organ Failure Assessment (SOFA) score in outcome prediction.	PeresBota 2002	Wrong patient population;
Can we predict prognosis using mortality probability model IIo?.	Arabi 2002	Wrong patient population;

Calibration and discrimination by daily Logistic Organ Dysfunction scoring comparatively with daily Sequential Organ Failure Assessment scoring for predicting hospital mortality in critically ill patients.	Timsit 2002	Wrong study design;
Rating the quality of intensive care units: is it a function of the intensive care unit scoring system?.	Glance 2002	Wrong study design;
Integration of APACHE II and III scoring systems in extremely high risk patients with acute renal failure treated by dialysis.	Chen 2002	Wrong patient population;
Comparison of multiple organ dysfunction scores in the prediction of hospital mortality in the critically ill.	Pettila 2002	Wrong patient population;
External validation of a modified model of Acute Physiology and Chronic Health Evaluation (APACHE) II for orthotopic liver transplant patients.	Arabi 2002	Wrong patient population;
["Simplified Acute Physiology Score" (SAPS II) ina the assessment of severity of illness in surgical intensive care patients].	Agha 2002	Only abstract ;
Prospective independent validation of APACHE III models in an Australian tertiary adult intensive care unit.	Cook 2002	Wrong patient population;
Automatic calculation of a modified APACHE II score using a patient data management system (PDMS).	Junger 2002	Wrong outcomes;
Customized prediction models based on APACHE II and SAPS II scores in patients with prolonged length of stay in the ICU.	Suistomaa 2002	Wrong patient population;
[Severity assessment by APACHE III system in Spain].	VazquezMata 2001	Wrong patient population;
Serial evaluation of the SOFA score to predict outcome in critically ill patients.	Ferreira 2001	Wrong patient population;
Predicting mortality in patients suffering from prolonged critical illness: an assessment of four severity-of-illness measures.	Carson 2001	Wrong patient population;
Evaluation of the logistic organ dysfunction system for the assessment of organ dysfunction and mortality in critically ill patients.	Metnitz 2001	Wrong patient population;
Accuracy of a composite score using daily SAPS II and LOD scores for predicting hospital mortality in ICU patients hospitalized for more than 72 h.	Timsit 2001	Wrong study design;
Short-term prognosis in critically ill patients with cirrhosis assessed by prognostic scoring systems.	Wehler 2001	Wrong patient population;
Outcomes and APACHE II predictions for critically ill patients with acute renal failure requiring dialysis.	Chen 2001	Wrong patient population;
Performance of the score systems Acute Physiology and Chronic Health Evaluation II and III at an interdisciplinary intensive care unit, after customization.	Markgraf 2001	Wrong patient population;
Risk stratification in emergency surgical patients: is the APACHE II score a reliable marker of physiological impairment?.	Koperna 2001	Wrong patient population;
Validation of severity scoring systems SAPS II and APACHE II in a single-center population.	Capuzzo 2000	Wrong patient population;
Ratios of observed to expected mortality are affected by differences in case mix and quality of care.	Metnitz 2000	Wrong patient population;
Performance of APACHE III models in an Australian ICU.	Cook 2000	Wrong patient population;
Effect of mortality rate on the performance of the Acute Physiology and Chronic Health Evaluation II: a simulation study.	Glance 2000	Wrong patient population;
Evaluation of the SOFA score: a single-center experience of a medical intensive care unit in 303 consecutive patients with predominantly cardiovascular disorders. Sequential Organ Failure Assessment.	Janssens 2000	Wrong patient population;
[Application of the Simplified Acute Physiology Score II (SAPS II) in a medical intensive care unit].	Ghuysen 2000	Only abstract ;
Assessment of the performance of five intensive care scoring models within a large Scottish database.	Livingston 2000	Wrong patient population;
Predicting patient outcome from acute renal failure comparing three general severity of illness scoring systems.	Fiaccadori 2000	Wrong setting;

An analysis of excess mortality not predicted to occur by APACHE III in an Australian level III intensive care unit.	Buist 2000	Wrong patient population;
Comparison of Acute Physiology and Chronic Health Evaluation II (APACHE II) and Simplified Acute Physiology Score II (SAPS II) scoring systems in a single Greek intensive care unit.	Katsaragakis 2000	Wrong patient population;
Upper gastrointestinal bleeding in patients with hepatic cirrhosis: clinical course and mortality prediction.	Afessa 2000	Wrong patient population;
Comparison of acute physiology and chronic health evaluations II and III and simplified acute physiology score II: a prospective cohort study evaluating these methods to predict outcome in a German interdisciplinary intensive care unit.	Markgraf 2000	Only abstract ;
Use of the logistic organ dysfunction system to study mortality in an Indian intensive care unit.	Sampath 1999	Wrong study design;
Severity and prognosis in intensive care: prospective application of the APACHE II index.	Costa 1999	Wrong patient population;
Development of a new prognostic system and validation of APACHE II for surgical ICU mortality: a multicenter study in Taiwan.	Kuo 1999	Wrong patient population;
Application of mortality prediction systems to individual intensive care units.	Patel 1999	Wrong patient population;
Evaluation of an interdisciplinary data set for national intensive care unit assessment.	Metnitz 1999	Wrong patient population;
Comparison of outcome from intensive care admission after adjustment for case mix by the APACHE III prognostic system.	Pappachan 1999	Wrong study design;
[Prediction of mortality and quality of life in polytraumatized patients: APACHE II versus APACHE III].	CanovasMartinez 1998	Wrong patient population;
[Value of the Hannover Intensive Score (HIS) in internal medicine intensive care].	vonBierbrauer 1998	Wrong patient population;
[Mathematical model for the predictive value of a test in critically ill patients studies according to APACHE II score and pathology at admission].	Donati 1998	Wrong study design;
Predicting outcome in the intensive care unit using scoring systems: is new better? A comparison of SAPS and SAPS II in a cohort of 1,393 patients. GiViTi Investigators (Gruppo Italiano per la Valutazione degli interventi in Terapia Intensiva). Simplified	Bertolini 1998	Wrong patient population;
Evaluation of acute physiology and chronic health evaluation III predictions of hospital mortality in an independent database.	Zimmerman 1998	Wrong patient population;
Predictive value of severity scoring systems: comparison of four models in Tunisian adult intensive care units.	Nouira 1998	Only abstract ;
[Validation of the acute physiology and chronic health evaluation (APACHE) III scoring system and comparison with APACHE II in German intensive care units].	vonBierbrauer 1998	Wrong patient population;
Evaluation of the uniformity of fit of general outcome prediction models.	Moreno 1998	Wrong patient population;
Evaluation of two outcome prediction models on an independent database.	Moreno 1998	Wrong patient population;
[Risk stratification and prognosis in critical surgical patients using the Acute Physiology, Age and Chronic Health III System (APACHE III)].	Carneiro 1997	Wrong patient population;
[Intensity of treatment and severity of illness in the intensive care unit (ICU)].	Capuzzo 1997	Wrong patient population;
Predictors of mortality in a medical intensive care unit.	Eapen 1997	Wrong patient population;
APACHE II in a postoperative intensive care unit in Thailand.	Lertakyamanee 1997	Only abstract ;
Outcome prediction in intensive care: results of a prospective, multicentre, Portuguese study.	Moreno 1997	Wrong patient population;
Predicting mortality in intensive care patients with acute renal failure treated with dialysis.	Douma 1997	Wrong patient population;

Prediction of outcome from intensive care: a prospective cohort study comparing Acute Physiology and Chronic Health Evaluation II and III prognostic systems in a United Kingdom intensive care unit.	Beck 1997	Wrong patient population;
Patient outcome and intensive care resource allocation using APACHE II.	Lim 1996	Only abstract ;
The performance of SAPS II in a cohort of patients admitted to 99 Italian ICUs: results from GiViTI. Gruppo Italiano per la Valutazione degli interventi in Terapia Intensiva.	Apolone 1996	Wrong patient population;
A comparison of the Acute Physiology and Chronic Health Evaluation (APACHE) II score and the Trauma-Injury Severity Score (TRISS) for outcome assessment in intensive care unit trauma patients.	Wong 1996	Wrong patient population;
Application of the APACHE III prognostic system in Brazilian intensive care units: a prospective multicenter study.	Bastos 1996	Wrong patient population;
Mortality predicted by APACHE II. The effect of changes in physiological values and post-ICU hospital mortality.	Goldhill 1996	Wrong outcomes;
The Logistic Organ Dysfunction system. A new way to assess organ dysfunction in the intensive care unit. ICU Scoring Group.	LeGall 1996	Wrong patient population;
Prediction of survival of critically ill patients by admission comorbidity.	Poses 1996	Wrong intervention;
Factors affecting the performance of the models in the Mortality Probability Model II system and strategies of customization: a simulation study.	Zhu 1996	Wrong patient population;
[Severity scores underestimate the seriousness of acute renal failure after emergency surgery].	Frikha 1995	Wrong patient population;
The severity of disease measurements among Thai medical intensive care unit patients.	Kiatboonsri 1995	Only abstract ;
Comparison of APACHE II and III scoring systems for mortality prediction in critical surgical illness.	Barie 1995	Wrong patient population;
[Evaluation of the prognosis of critically ill surgical patients by APACHE II score system].	Wu 1995	Wrong patient population;
The use of APACHE III to evaluate ICU length of stay, resource use, and mortality after coronary artery by-pass surgery.	Becker 1995	Wrong patient population;
[Comparison of APACHE-II AND APACHE-III for classification of disease severity of intensive care patients].	Bein 1995	Only abstract ;
[Assessment of intensive therapy: 4-year experience using the Apache II severity score].	Feri 1995	Wrong patient population;
APACHE II scoring for predicting outcome in cerebral malaria.	Wilairatana 1995	Wrong patient population;
A comparison of severity of illness scoring systems for intensive care unit patients: results of a multicenter, multinational study. The European/North American Severity Study Group.	Castella 1995	Wrong patient population;
Evaluation of predictive ability of APACHE II system and hospital outcome in Canadian intensive care unit patients.	Wong 1995	Wrong patient population;
The predictive value of four scoring systems in liver transplant recipients.	Bein 1995	Wrong patient population;
Use of daily Acute Physiology and Chronic Health Evaluation (APACHE) II scores to predict individual patient survival rate.	Rogers 1994	Only abstract ;
Intensive Care Society's Acute Physiology and Chronic Health Evaluation (APACHE II) study in Britain and Ireland: a prospective, multicenter, cohort study comparing two methods for predicting outcome for adult intensive care patients.	Rowan 1994	Wrong patient population;
Daily prognostic estimates for critically ill adults in intensive care units: results from a prospective, multicenter, inception cohort analysis.	Wagner 1994	Wrong patient population;
Mortality probability models for patients in the intensive care unit for 48 or 72 hours: a prospective, multicenter study.	Lemeshow 1994	Wrong study design;
A prospective comparison of two multiple organ dysfunction/failure scoring systems for prediction of mortality in critical surgical illness.	Barie 1994	Wrong patient population;
Verification of the Acute Physiology and Chronic Health Evaluation scoring system in a Hong Kong intensive care unit.	Oh 1993	Only abstract ;

Validation of APACHE II score in a surgical intensive care unit.	Chen 1993	Wrong patient population;
Acute physiology and chronic health evaluation (APACHE II) scoring in the Medical Intensive Care Unit, National University Hospital, Singapore.	Lee 1993	Wrong patient population;
A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study.	LeGall 1993	Wrong patient population;
Intensive Care Society's APACHE II study in Britain and Ireland--II: Outcome comparisons of intensive care units after adjustment for case mix by the American APACHE II method.	Rowan 1993	Wrong patient population;
Intensive Care Society's APACHE II study in Britain and Ireland--I: Variations in case mix of adult admissions to general intensive care units and impact on outcome.	Rowan 1993	Wrong patient population;
[Mortality in an intensive care unit: predictive value of APACHE II severity score versus maximum APACHE].	Dougnac 1993	Wrong patient population;
Mortality Probability Models (MPM II) based on an international cohort of intensive care unit patients.	Lemeshow 1993	Wrong patient population;
Evaluation of the consistency of Acute Physiology and Chronic Health Evaluation (APACHE II) scoring in a surgical intensive care unit.	Berger 1992	Only abstract ;
Mortality prediction models in intensive care: acute physiology and chronic health evaluation II and mortality prediction model compared.	Castella 1991	Wrong patient population;
Acute Physiology and Chronic Health Evaluation (APACHE II) score and outcome in the surgical intensive care unit: an analysis of multiple intervention and outcome variables in 1,238 patients.	Rutledge 1991	Wrong patient population;
Critical Care Scoring System--new concept based on hemodynamic data.	Yeung 1990	Only abstract ;
Outcome prediction models on admission in a medical intensive care unit: do they predict individual outcome?.	Schafer 1990	Wrong patient population;
A critical study of the APACHE II scoring system using earlier data collection.	Waters 1990	Wrong patient population;
Systems for scoring severity of illness in intensive care.	Turner 1989	Wrong patient population;
Prediction of outcome from critical illness. A comparison of clinical judgment with a prediction rule.	Brannen 1989	Wrong outcomes;
[Prognostic accuracy and efficacy of treatment at intensive care units evaluated by the APACHE II system].	MilaniJunior 1989	Only abstract ;
[Severity evaluation system: APACHE II, SAPS. National experience in a unit of medical intensive therapy].	Dougnac 1989	Wrong patient population;
Failure of APACHE II alone as a predictor of mortality in patients receiving total parenteral nutrition.	Hopefl 1989	Wrong patient population;
Audit of intensive care: a 30 month experience using the Apache II severity of disease classification system.	Jacobs 1988	Wrong patient population;
Comparison of clinical assessment with APACHE II for predicting mortality risk in patients admitted to a medical intensive care unit.	Kruse 1988	Wrong patient population;
Predicting deaths among intensive care unit patients.	Chang 1988	Wrong patient population;
Validation of the mortality prediction model for ICU patients.	Teres 1987	Wrong patient population;
APACHE-acute physiology and chronic health evaluation: a physiologically based classification system.	Knaus 1981	Wrong outcomes;
Predictive Ability of Scoring Systems for Mortality in Older Adults in Intensive Care Unit of a University Hospital: A Single-Center Retrospective Cohort Study	Azakli 2024	Wrong patient population;
Retrospective Evaluation of the Accuracy of Five Different Severity Scores To Predict the Mortality in Burn Patients	DeCarvalho 2024	Wrong patient population;
The APACHE-II score and the effect of discharge practices on readmission and mortality in intensive care patients	Doganci 2024	Wrong patient population;
Clinical characteristics and mortality prediction of patients admitted to the Hong Kong East Cluster intensive care units in the COVID-19 fifth wave	Man 2024	Wrong patient population;

A tertiary care center-based study of a novel 'ICU Mortality and Prolonged Stay Risk Scoring System'	Widyastuti 2024	Wrong patient population;
External validation of SAPS II score reported to the Norwegian Intensive Care and Pandemic Registry (NIPaR)	Buanes 2023	Wrong patient population;
PROGNOSTIC VALUE OF APACHE II SCORE, SOFA SCORE AND BIOMARKERS IN PATIENTS OF SEPSIS AND SEPTIC SHOCK - A COMPARATIVE STUDY	Rani 2023	Wrong patient population;
Comparison of the Poisoning Severity Score, Sequential Organ Failure Assessment Score, and Acute Physiology and Chronic Health Evaluation II Score with Lactate to assess the outcome in Acute Organophosphorus Poisoning	KrishnaMoorthy 2023	Wrong patient population;
Validation of Sepsis-3 using survival analysis and clinical evaluation of quick SOFA, SIRS, and burn-specific SIRS for sepsis in burn patients with suspected infection	Yoon 2023	Wrong patient population;
Evaluating Prognostic Bias of Critical Illness Severity Scores Based on Age, Gender, and Primary Language in the USA: A Retrospective Multicenter Study	Liu 2022	Wrong outcomes;
Updating mortality risk estimation in intensive care units from high-dimensional electronic health records with incomplete data	Bouvarel 2022	Wrong patient population;
UTILITY OF APACHEII, SAPS II, AND SOFA SCORES AS INDICATORS OF SEVERITY OF SEPSIS AND PREDICTORS OF MORTALITY IN A TERTIARY CARE HOSPITAL	Mittal 2022	Wrong patient population;
Predictive Value of Sequential Organ Failure Assessment (SOFA), Quick Sequential Organ Failure Assessment (qSOFA), Acute Physiology and Chronic Health Evaluation (APACHE II), and New Early Warning Signs (NEWS-2) Scores Estimate Mortality of COVID-19 Patie	Asmarawati 2022	Wrong patient population;
SOFAMONIA: Comparison of the original SOFA score with the proposed new score including serum ammonia	Zanuto 2021	Wrong outcomes;
Categorical Apache IV prediction of ICU and 90 day mortality	Bergmans 2021	Wrong patient population;
Comparison of Sensitivity, Specificity and Accuracy of APACHE II, SAPS II and SOFA Scoring Systems as Predictors of Mortality in ICU Patients	Furqan 2021	Wrong patient population;
NUTRIC-S proposal: Using SAPS 3 for mortality prediction in nutritional risk ICU patients	Toledo 2020	Wrong patient population;
Erratum: The use of APACHE II, SOFA, SAPS 3, C-reactive protein/albumin ratio, and lactate to predict mortality of surgical critically ill patients: A retrospective cohort study: Erratum (Medicine (2019) 98 26 (e16204))	Anonymous 2019	Wrong patient population;
Comparison of APACHE II and SAPS II scoring systems in prediction of critically ill patient's outcome	Aminiahidashti 2019	Wrong patient population;
Combined anatomic and physiologic scoring systems for predicting in-hospital mortality in ICU patients with severe trauma: A multicenter observational cohort study	Ma 2019	Wrong patient population;
Performance of the Acute Physiology and Chronic Health Evaluation II (APACHE II) in the prediction of hospital mortality in a mixed ICU in Singapore	Lew 2019	Wrong study design;
Application of APACHE-II and SOFA score as a predictive outcome in Ramathibodi surgical intensive care unit	Pornwaragron 2019	Wrong outcomes;
Comparison of mortality estimation by using the disease severity standardized scoring systems of APACHE II GSC and APACHE II 4 score	Sejahrood 2018	Wrong patient population;
Accuracy and performance assessment of apache iv and saps 3 in geriatric patients admitted to the intensive care unit	KorkmazToker 2018	Wrong patient population;
Clinical effectiveness of modified sequential organ failure assessment scoring system for predicting ICU indexing scores	Babamohamadi 2016	Wrong patient population;
Single-centre validation of the EASL-CLIF Consortium definition of acute-on-chronic liver failure and CLIF-SOFA for prediction of mortality in cirrhosis	Silva 2015	Wrong patient population;
Evaluation of probability of survival using APACHE II and TRISS method in orthopaedic polytrauma patients in a tertiary care centre	Agarwal 2015	Wrong patient population;
Sequential Organ Failure Assessment (SOFA) score as a predictor of outcome in patients admitted in a medical ICU	Faraz 2015	Wrong study design;
Validation of SAPS-3 and APACHE-III in Mediterranean area	Rivera-Lopez 2014	Wrong patient population;

Prognostic usefulness of sabadell score in critically ill patients hospitalized at internal medicine service	Nunez-Armendariz 2014	Wrong patient population;
Comparing acute physiology and chronic health evaluation (APACHE) IV and simplified acute physiology (SAPA) III scoring methods in predicting mortality rate in patients admitted to intensive care unit	Yaghoubi 2014	Wrong patient population;
Evaluation of patient mortality in intensive care units using the APACHE IIscoring system	Soleimani 2014	Wrong patient population;
Why the surgical patients are so critical in their intensive care unit arrival?	Basile-Filho 2013	Wrong patient population;
Clinical accuracy of RIFLE and acute kidney injury network (AKIN) criteria for predicting hospital mortality in critically Ill patients with multi-organ dysfunction syndrome	Ratanarat 2013	Wrong intervention;
Verification of validity of mpm ii for neurological patients in intensive care units	Kim 2011	Wrong patient population;
Validation of six mortality prediction systems for ICU surgical populations	Timmers 2011	Only abstract ;
The effectiveness of scoring systems and various biochemical parameters in predicting survival in a respiratory intensive care unit	Yildiz 2010	Wrong patient population;
Profile and severity of the patients of intensive care units: Prospective application of the APACHE II index	deFreitas 2010	Wrong patient population;
Comparison of Apache II, SOFA, and modified SOFA scores in predicting mortality of surgical patients in intensive care unit at Dr. Hasan Sadikin General Hospital	Halim 2009	Wrong patient population;
The predictive capability of APACHE II score in determining mortality among critically ill surgical population	Hashem 2008	Wrong study design;
Combining Sequential Organ Failure Assessment (SOFA) score with Acute Physiology and Chronic Health Evaluation (APACHE) II score to predict hospital mortality of critically ill patients	Ho 2007	Wrong patient population;
Validating the use of the APACHE II score in a tertiary South African ICU	vanderMerwe 2005	Wrong patient population;
Modified organ system failure score for critically III patients with acute renal failure requiring dialysis	Chen 2003	Wrong patient population;
Can we measure ICU performance with the SAPS II?	Aegerter 2003	No English version available;
Customised prediction models based on APACHE II and SAPS II scores in patients with prolonged length of stay in the ICU	Suistomaa 2002	Wrong patient population;
APACHE III scoring system in critically III patients with acute renal failure requiring dialysis	Chen 2002	Wrong patient population;
Use of the simplified acute physiology score II (SAPS II) in a medical intensive care unit	Ghuysen 2000	Wrong patient population;
Validation of Mortality Probability Models II (MPM II) at admission (MPM II-0), at 24 hours (MPM 11-24), and at 48 hours (MPM II-48) compared with the hospital mortality predictions from APACHE II and SAPS II measured in the first and second days of ICU s	SerranoHernandez 2000	Wrong patient population;
The use of maximum SOFA score to quantify organ dysfunction/failure in intensive care. Results of a prospective, multicentre study	Moreno 1999	Wrong patient population;
Hannover Intensive Score (HIS) in medical care medicine	VonBierbrauer 1998	Only abstract ;
Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: Results of a multicenter, prospective study	Vincent 1998	Wrong patient population;
Scoring systems. Validation of APACHE III and comparison to APACHE II in a German intensive care unit	VonBierbrauer 1998	Wrong patient population;
Severity scores underestimate the seriousness of acute renal failure following emergency surgery	Frikha 1995	Wrong patient population;
Comparison of two severity-of-disease classification systems (APACHE II and APACHE III) in critically ill patients	Bein 1995	Wrong patient population;
A comparison of severity of illness scoring systems for intensive care unit patients: Results of a multicenter, multinational study	Castella 1995	Only abstract ;

Scope and limitations of score systems in intensive-care medicine	Bein 1993	Wrong outcomes;
A simplified severity index for intensive care patients. Results of a prospective study in 280 cases	Bedock 1985	Only abstract ;
Adverse Sequential Organ Failure Assessment Score as a Predictor of Mortality in Patients Requiring Critical Care in Pakistan	Janjua 2024	Wrong patient population;
The Sequential Organ Failure Assessment (SOFA) Score: has the time come for an update?	Moreno 2023	Wrong outcomes;
Construction and evaluation of a risk prediction model for pulmonary infection-associated acute kidney injury in intensive care units	Cao 2023	Wrong outcomes;
Comparison of 6 Mortality Risk Scores for Prediction of 1-Year Mortality Risk in Older Adults with Multimorbidity	Schneider 2022	Wrong patient population;
Serial Evaluation of Sequential Organ Failure Assessment Score in Predicting 1-Year Mortality in Critically Ill Patients	Ralib 2022	Wrong patient population;
An easy-to-use nomogram for predicting in-hospital mortality risk in COVID-19: a retrospective cohort study in a university hospital	Acar 2021	Wrong patient population;
Regional performance variation in external validation of four prediction models for severity of COVID-19 at hospital admission: An observational multi-centre cohort study	Wickstr√∏m 2021	Wrong patient population;
Validation of prognostic scores in extracorporeal life support: A multi-centric retrospective study	Fisser 2021	Wrong patient population;
Are prognostic tools losing accuracy? Development and performance of a novel age-calibrated severity scoring system for critically ill patients	Menezes 2020	Wrong study design;
Validation of END-of-life ScorING-system to identify the dying patient: A prospective analysis	Villa 2020	Wrong intervention;
The SOFA score - Development, utility and challenges of accurate assessment in clinical trials	Lambden 2019	Wrong outcomes;
Mortality of patients with acute kidney injury requiring renal replacement therapy	Czempik 2018	Wrong patient population;
Predicting mortality and hospitalization of older adults by the multimorbidity frailty index	Wen 2017	Wrong intervention;
Using patient admission characteristics alone to predict mortality of critically ill patients: A comparison of 3 prognostic scores	Ho 2016	Wrong patient population;
Evaluation of Acute Physiology and Chronic Health Evaluation II and sequential organ failure assessment scoring systems for prognostication of outcomes among Intensive Care Unit,Ä≤s patients	Hosseini 2016	Wrong patient population;
Scoring systems in assessing survival of critically ill ICU patients	Sekulic 2015	Wrong patient population;
External validation of the intensive care national audit & research centre (ICNARC) risk prediction model in critical care units in Scotland	Harrison 2014	Wrong patient population;
Development and validation of the critical care outcome prediction equation, version 4	Duke 2013	Wrong patient population;
The use of infection probability score and sequential organ failure assessment scoring systems in predicting mechanical ventilation requirement and duration	Honarmand 2009	Wrong outcomes;
Severity of illness and outcome in ICU patients in the Netherlands: Results from the NICE registry 2006-2007	deLange 2009	Wrong patient population;
SAPS 3 admission score: An external validation in a general intensive care population	Ledoux 2008	Wrong patient population;
Predicting death and readmission after intensive care discharge	Campbell 2008	Wrong setting;
Apache II and Apache III prognostic markers. Experience in three Mexican intensive care units	Olivares-Dur√°n 2005	Only abstract ;
A comparison of admission and worst 24-hour Acute Physiology and Chronic Health Evaluation II scores in predicting hospital mortality: A retrospective cohort study	Ho 2005	Wrong study design;

Reliability and accuracy of Sequential Organ Failure Assessment (SOFA) scoring	Arts 2005	Wrong outcomes;
Multiple organ system failure in critically ill cirrhotic patients: A comparison of two multiple organ dysfunction/failure scoring systems	Tsai 2004	Wrong patient population;
Organ system failure scoring system can predict hospital mortality in critically III cirrhotic patients	Tsai 2003	Wrong patient population;
Role of serum creatinine and prognostic scoring systems in assessing hospital mortality in critically ill cirrhotic patients with upper gastrointestinal bleeding	Chen 2003	Wrong patient population;
The SOFA score to evaluate organ failure and prognosis in the intensive care unit patients	Kim 2004	Wrong patient population;
Validation of organ failure scoring systems in objective illness characterization	Siemiatkowski 2002	Wrong outcomes;
Assessment of performance of four mortality prediction systems in a Saudi Arabian intensive care unit	Arabi 2002	Wrong patient population;
Use of the Simplified Acute Physiology Score (SAPS II) for assessment of disease severity in surgical intensive care patients	Agha 2002	Wrong outcomes;
Unidad de terapia intensiva en pos de mejorar calidad de vida y no de prolongar agon√≠a	Gambino 2000	Wrong patient population;
Customization of SAPS II for the assessment of severity in Italian ICU patients. ARCHIDIA. Archivio Diagnostico.	Sicignano 2000	Only abstract ;
Comparison of different scoring systems (APACHE III, SAPSII, MPM II0-72): Value of daily measurement in 303 consecutive patients	Janssens 1999	Wrong patient population;
Intensive care improves patient survival	Sprung 1999	Wrong patient population;
Statistical modeling of prognostic indices	Livianu 1999	Wrong study design;
Comparison of SAPS II, MPM II24 and SAPS in intensive care	Cominotti 1999	Wrong patient population;
How changes in SOFA score can predict out-come	Ferreira 1999	Wrong outcomes;
Predictive value of severity scoring systems: comparison of four models in three mexican intensive care units included in the multicenter database of intensive care	Ceron 1999	Wrong study design;
Prognostic scoring for critically ill hospitalized patients.	Ahluwalia 1999	Wrong patient population;
Comparison of APACHE II and day 1 multiple organ dysfunction score in critically ill medical patients	Matchett 1999	Wrong patient population;
Comparison of 3 severity of illness scoring ststems for imtemsivk cari unit (icu) patients	Livxanu 1998	Only abstract ;
Comparison of severity systems (APACHE II, SAPS II, and MPM II) in ICU patients	Lin 1998	Wrong patient population;
An IC;D-9 based illness severity score (ICISS) out performs apache II in predicting survival, hospital charges and length of stay in surgical intensive care unit patients	Huynh 1998	Wrong patient population;
Prognostic value of first-day and seventh-day score of APACHE III scoring system in critically ill medical patients	Yang 1998	Wrong patient population;
The correlation of organ failure indices with in-hospital mortality	Afessa 1998	Wrong study design;
Predicting Outcome in the Intensive Care Unit Using Scoring Systems: Is New Better? A Comparison of SAPS and SAPS II in a Cohort of 1,393 Patients	Bertolini 1998	Wrong patient population;
Predictive value of a combined physiologic-therapeutic scoring system (MARIS) and comparison to only physiologically (APACHE II) or the therapeutically (TISS) based systems in medical intensive care medicine	VonBierbrauer 1997	Wrong patient population;
Evaluation of different score systems for the prognosis of morbidity and mortality on an anaesthesiological ICU	Schulze 1996	Wrong patient population;
The Influence of length of stay in the ICU on power of discrimination of a multipurpose severity score (SAPS)	Sicignano 1996	Wrong outcomes;

Evaluation of severity scoring systems in ICUs-translation, conversion and definition ambiguities as a source of inter-observer variability in Apache II, SAPS and OSF	F√©ry-Lemonnier 1995	Wrong patient population;
Predicting outcome in ICU patients	Suter 1994	Wrong patient population;
Use of APACHE II classification to evaluate outcome and response to therapy in acute renal failure patients in a surgical intensive care unit	vanBommel 1995	Wrong patient population;
Prospective comparison of clinical judgment and apache ii score in predicting the outcome in critically 111 surgical patients	Meyer 1992	Wrong patient population;
The APACHE III prognostic system: Risk prediction of hospital mortality for critically III hospitalized adults	Knaus 1991	Wrong patient population;
Determinants of immediate survival among chronic respiratory insufficiency patients admitted to an intensive care unit for acute respiratory failure; A prospective multicenter study	Portier 1992	Wrong patient population;
A comparison of APACHE II and a clinical sickness score: A study of 97 consecutive admissions to a District General Hospital Intensive Care Unit	SINCLAIR 1991	Wrong patient population;
Use of the APACHE II scoring method for registering patients receiving intensive care at a central hospital	Hartmann-Andersen 1989	Wrong outcomes;
A comparison of methods to predict mortality of intensive care unit patients	Lemeshow 1987	Wrong patient population;
APACHE II: A severity of disease classification system	Knaus 1985	Wrong patient population;
One year's experience with the APACHE II severity of disease classification system in a general intensive care unit	JACOBS 1987	Wrong patient population;

Supplementary Table 5. Characteristics of Selected ICU Severity of Illness Scoring Systems and Kidney-Related Parameters.

Scoring Systems	Year Published	Kidney aspects	Time of score calculation	Variables
APACHE II	1985	Creatinine, Chronic dialysis	Worst value from preceding 24 hours since ICU admission	Age Clinical variables: Non-operative or emergency post-op Elective post-op Cirrhosis with portal hypertension, encephalopathy, or hepatic failure NYHA Class IV angina Chronic hypoxia, or chronic restrictive/obstructive lung disease, or respiratory dependency Increased CO_2 or Polycythemia Chronic dialysis Immunocompromised (e.g., immune-suppression, chemotherapy, radiation) Temperature Mean arterial pressure Heart Rate Respiratory rate Oxygenation Arterial pH Serum sodium, potassium, Creatinine Hematocrit White blood cells Glascow Coma Scale
APACHE III	1991	Creatinine, BUN, urine output	First 24 hours post ICU admission	Age Comorbid factors: AIDS Hepatic failure Lymphoma Metastatic solid tumour Leukemia/multiple myeloma Immunosuppression Cirrhosis ICU admission diagnosis

				Medical Elective surgical Emergency surgical Most abnormal value within initial 24 hours is used to calculate score: Heat rate Mean Arterial Pressure Temperature Respiratory rate $PaO_2/P(A\text{-}a)O_2$ Hematocrit White blood cells Sodium, potassium, creatinine, BUN, albumin, bilirubin Urine output Glucose Arterial pH Glasgow Coma Scale
SAPS II	1994	serum urea or BUN, urine output	First 24 hours post ICU admission	Age Type of admission Scheduled surgical Unscheduled surgical Medical Comorbidities: AIDS Hematologic malignancy Metastatic cancer Heart rate Systolic blood pressure Temperature PaO_2/FiO_2 (if ventilated) Urine output Serum urea or BUN, potassium, sodium, bicarbonate, bilirubin White blood cells Glasgow Coma Scale
SAPS III	2005	Creatinine	Within 1 hour of ICU admission	Age Length of stay before ICU admission (days) Intrahospital location before ICU admission:

	Emergency room
	Other ICU
	Ward
	Use of major therapeutic options before ICU admission:
	Vasoactive drugs
	Other/none
	Planned/unplanned ICU admission
	Surgical status at ICU admission
	Scheduled surgery
	No surgery
	Unplanned surgery
	Comorbid factors:
	Cancer therapy
	NYHA class IV heart failure
	Hematological cancer
	Cirrhosis
	AIDS
	Metastatic cancer
	Reason for ICU admission:
	Cardiovascular
	Neurological
	Renal
	Respiratory
	Hepatic
	Haematological
	Metabolic
	Digestive
	Severe trauma
	Other
	Oxygenation (PaO_2 , FiO_2)
	Temperature
	Heart rate
	Systolic blood pressure
	Creatinine
	Total bilirubin
	Arterial pH

				Leukocytes, platelets Glascow Coma Scale
SOFA	1996	creatinine or urine output	Every 24 hours post ICU admission	Respiratory: PaO_2/FiO_2 Respiratory support Coagulation: Platelets Liver: Bilirubin Cardiovascular: Mean arterial pressure Vasopressors required (dopamine, dobutamine, norepinephrine/epinephrine) Central Nervous System: Glascow Coma Scale Renal: Creatinine or Urine output

Abbreviations: AIDS = acquired immunodeficiency syndrome, APACHE = Acute Physiology and Chronic Health Evaluation, BUN = Blood Urea Nitrogen, CO_2 = Carbon dioxide, FiO_2 = Fraction of inspired oxygen, ICU = Intensive Care Unit, NYHA = New York Heart Association, $P(A\text{-}a)O_2$ = Alveolar-arterial oxygen gradient, PaO_2 = Partial pressure of oxygen in arterial blood, pH = hydrogen ion concentration, SAPS = Simplified Acute Physiology Score, SOFA = Sequential Organ Failure Assessment

Supplementary Table 6. Statistical results summary of outcomes and GRADE Assessment.

Outcomes	Number of studies	Overall Risk of Bias	Quality of Evidence (GRADE)
Discriminatory Accuracy for ESKD Patients			
APACHE II	4	High	**Low**
APACHE III	2	High	**Low**
SAPS II	3	High	**Low**
SOFA	3	High	**Very low**
Discriminatory Accuracy for Kidney Transplant Patients			
SAPS III	2	High	**Very low**
SOFA	2	High	**Very low**

Abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; GRADE = Grading of Recommendations Assessment, Development and Evaluation; SAPS = Simplified Acute Physiology Score, SOFA = Sequential Organ Failure Assessment

GRADE Judging the certainty of discrimination performance estimates of prognostic models

High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Supplementary Table 7. JBI critical appraisal results for cohort studies.

Study (year)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Total* (%)
Rana et al. (2024)	N/A	N/A	0.5	1	1	1	0.5	0.5	0.5	N/A	0	5/8 (62.5 %)
Shimada et al. (2024)	1	1	1	0.5	0.5	1	1	1	1	N/A	1	9/10 (90.0 %)
Zhang et al. (2022)	N/A	N/A	1	1	1	1	1	1	0.5	0	1	7.5/9 (83.3 %)
Freitas et al. (2018)	N/A	1	1	1	1	1	1	0.5	0.5	0	1	8/10 (80.0 %)
Goswami et al. (2018)	N/A	N/A	0	0.5	0.5	1	1	1	0.5	N/A	1	5.5/8 (68.7. %)
Akbas et al. (2015)	0.5	1	0.5	0.5	0.5	1	1	1	1	N/A	1	8/10 (80.0 %)
Oliveira et al. (2013)	0.5	1	1	0.5	0.5	1	1	1	1	N/A	1	8.5/10 (85.0 %)
Juneja et al. (2010)	N/A	N/A	1	0.5	0	1	1	1	1	N/A	0.5	6/8 (75.0 %)
Manhes et al. (2005)	N/A	N/A	0.5	1	1	1	1	1	0.5	0	1	7/9 (77.8 %)
Dara et al. (2004)	N/A	N/A	0.5	0.5	0	1	1	1	1	N/A	0.5	5.5/8 (68.8 %)
Uchino et al. (2003)	1	1	1	0.5	0.5	1	1	1	0	0	1	8/10 (80.0 %)
Clermont et al. (2002)	1	1	1	0.5	0	1	1	1	1	N/A	0.5	8/10 (80.0 %)

1 = Yes, 0= No, 0.5 = Unclear, N/A = not applicable
* Tota score is calculated after removing any inapplicable items

JBI critical appraisal checklist for cohort studies

Q1 Were the groups similar and recruited from the same population?
Q2 Were the exposures measured similarly to assign people to both exposed and unexposed groups?
Q3 Was the exposed measured in a valid and reliable way?
Q4 Were confounding factors identified?
Q5 Were strategies to deal with confounding factors stated?
Q6 Were the groups/participants free of the outcomes at the start of the study (or at the moment of exposure)?
Q7 Were the outcomes measured in a valid and reliable way?
Q8 Was the follow-up time reported and sufficient to be long enough for outcomes to occur?
Q9 Was follow-up complete, and if not, were the reasons to loss to follow-up described and explored?
Q10 Were strategies to address incomplete follow-up utilized?
Q11 Was appropriate statistical analysis used?

Supplementary Table 8. PROBAST Risk of Bias Results*

Study (year)	Participants	Predictors	Outcome	Analysis	Overall ROB	Applicability concerns
Rana et al. (2024)	+	+	?	_	_	_**
Shimada et al. (2024)	+	+	+	+	+	+
Zhang et al. (2022)	+	_	+	_	_	+
Freitas et al. (2018)	+	+	+	_	_	_**
Goswami et al. (2018)	+	+	+	_	_	_**
Akbas et al. (2015)	+	+	+	_	_	_**
Oliveira et al. (2013)	+	+	+	_	_	+
Juneja et al. (2010)	+	+	+	_	_	+
Manhes et al. (2005)	+	+	+	_	_	+
Dara et al. (2004)	+	+	+	_	_	+
Uchino et al. (2003)	+	+	+	_	_	+
Clermont et al. (2002)	+	+	+	_	_	+

Abbreviations: PROBAST = Prediction model Risk Of Bias Assessment Tool; ROB = risk of bias.

* + indicates low ROB/low concern regarding applicability.
− indicates high ROB/high concern regarding applicability.
? indicates unclear ROB/unclear concern regarding applicability.

** Unclear or inappropriate age specification (i.e., inclusion of patients <18 years old or lack of reporting of age criteria)

Supplementary Figure 1. Risk of Bias and applicability assessment of included studies using the PROBAST tool.

The top panel provides a summary of each domain. The bottom bar plot displays the overall assessment of studies rated as low, unclear, or high risk of bias or applicability concerns.

Abbreviations: PROBAST, Prediction model Risk Of Bias ASsessment Tool; ROB, risk of bias.

Chapter 3. Severity of Chronic Kidney Disease and Clinical Outcomes Following Admission to the Intensive Care Unit

PREFACE

Hajar El wadia is the primary author of this manuscript, in collaboration with Drs Hundemer, Clark, and Wald. Hajar was responsible for writing the data creation plan, conducting the analyses using SAS software, interpreting the results, and writing this manuscript with feedback from her supervisor, Dr. Hundemer, and ICES analyst Nickolas Beauregard.

This project was reviewed and submitted to the primary office at ICES uOttawa (TRIM 0901 428 000). ICES is a designated health-data custodian under Ontario's privacy legislation, authorized under PHIPA to use health-related data for analysis, evaluation, and planning. Secure access to these data is governed by policies and procedures that are approved by the Information and Privacy Commissioner of Ontario.

Data were obtained from de-identified and linked health administrative databases housed at ICES. Datasets were linked using unique encoded identifiers and analyzed at ICES. All analyses were conducted within the secure ICES environment. The datasets from this study are held securely in coded form at ICES. Although legal data sharing agreements between ICES and data providers prohibit ICES from making datasets publicly available, confidential access may be granted to researchers who meet prespecified criteria (see ices.on.ca/use-ices-data/ for more information).

The full dataset creation plan and underlying analytic code are available from the authors on request, with the understanding that some programs rely on coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification outside the ICES environment. The analyses, conclusions, opinions and statements expressed herein are solely those of the authors and do not reflect those of the funding or data sources.

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KEY POINTS

Question: How is chronic kidney disease (CKD) severity associated with mortality, kidney replacement therapy (KRT), and length of stay following intensive care unit (ICU) admission?

Findings: In this population-based cohort of 531,090 Canadians admitted to ICU, CKD was present in 25%. Increasing CKD severity was associated with progressively higher mortality, greater risk of 90-day KRT dependence, and longer ICU and hospital stays. Mortality risk peaked in non-dialysis-dependent stage 5 CKD and was lower among patients receiving maintenance dialysis.

Meaning: CKD severity is a strong predictor of adverse outcomes following ICU admission and should inform risk stratification, prognostication, and goals-of-care discussions.

ABSTRACT

Importance: Individuals with chronic kidney disease (CKD) are admitted to the intensive care unit (ICU) at disproportionately high rates relative to their prevalence in the general population. However, the relationship between pre-existing CKD severity and outcomes following ICU admission remains uncertain.

Objective: To evaluate the association between CKD severity and health outcomes following ICU admission.

Design: Population-based cohort study from November 1, 2008 to February 28,2021.

Setting: All ICUs across Ontario, Canada.

Participants: Consecutive adult (≥18 years) residents of Ontario admitted to an ICU during the study period who had a baseline outpatient serum creatinine measurement within 7-365 days prior to admission.

Exposure: CKD severity classified according to baseline outpatient estimated glomerular filtration rate (eGFR) Kidney Disease Improving Global Outcomes (KDIGO) criteria.

Main Outcomes and Measures: Mortality (ICU, hospital, and 90-day), kidney replacement therapy (KRT; ICU and 90-day dependence), and length of stay.

Results: The study included 531,090 adults admitted to ICU. The mean (SD) age was 67 (15) years, and 43% were female. One in four individuals had pre-existing CKD including 12% with stage 3a CKD (eGFR 45–59 mL/min/1.73 m^2), 7% with stage 3b CKD (eGFR 30–44 mL/min/1.73 m^2), 3% with stage 4 CKD (eGFR 15–29 mL/min/1.73

m^2), 1% with non-dialysis-dependent stage 5 CKD (eGFR <15 mL/min/1.73 m^2), and 2% on maintenance dialysis. Compared to individuals without CKD, CKD severity was progressively associated with increased mortality risk up to non-dialysis-dependent stage 5 CKD. However, mortality risk was lower for individuals on maintenance dialysis compared to those with non-dialysis-dependent stage 5 CKD. KRT dependence at 90 days also increased in parallel with CKD severity. Stages 3a, 3b, 4, and 5 (previously non-dialysis-dependent) CKD were associated with approximately 4-fold, 9-fold, 50-fold, and 400-fold higher odds for KRT dependence at 90 days, respectively. The presence and severity of pre-existing CKD was also associated with prolonged length of stay.

Conclusions and Relevance: The presence and severity of CKD is strongly linked to adverse health outcomes following ICU admission. These findings will inform risk prognostication, goals-of-care discussions, resource allocation, and health policy initiatives for this large proportion of the ICU population.

INTRODUCTION

Chronic kidney disease (CKD) is associated with substantial morbidity and mortality worldwide.[1-4] Its global burden has increased alongside diabetes, hypertension, and cardiovascular disease, and CKD now affects approximately 10-15% of adults.[5] These shared comorbidities combined with metabolic derangements, heightened inflammation, and impaired drug clearance predispose individuals with CKD to critical illness.[6-8] Consequently, individuals with CKD, particularly those with end-stage kidney disease (ESKD), are admitted to intensive care units (ICU) at rates disproportionate to their prevalence in the general population.[9-11]

The relationship between CKD and outcomes following ICU admission remains incompletely characterized. Prior studies have largely focused on acute kidney injury (AKI), particularly AKI requiring kidney replacement therapy (KRT), or on individuals with ESKD receiving maintenance dialysis.[12-18] The impact of CKD severity by stage on both short-term and long-term outcomes following ICU admission remains uncertain. Furthermore, most studies have been limited to selected populations, single centers, or small sample sizes, limiting generalizability. A clearer understanding of how CKD severity influences clinical trajectories following critical illness may inform risk stratification, prognostication, and resource allocation.

Herein, we conducted a population-based cohort study of adults admitted to ICUs across Ontario, Canada, to examine the association between pre-existing CKD severity and outcomes following ICU admission. Universal health coverage in Ontario enables

comprehensive capture of laboratory data and outcomes via provincial health care administrative databases across a large, unselected population.

METHODS

Study Design and Setting

We conducted a population-based retrospective cohort study in Ontario, Canada, using linked healthcare databases held at ICES (formerly, Institute for Clinical Evaluative Sciences). Ontario is Canada's most populous province, with over 16 million residents.[19] ICES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement. The use of data in this project is authorized under section 45 of Ontario's Personal Health Information Protection Act (PHIPA) and does not require review by a Research Ethics Board. Reporting follows guidelines for observational studies (**eTable 1**).[20,21]

Data Sources

Baseline characteristics and outcomes were ascertained from de-identified, linked administrative databases housed at ICES. Demographic and vital status information was obtained from the Ontario Registered Persons Database (RPDB). Diagnostic and procedural information from all hospitalizations was collected using the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD). Diagnostic information from emergency room visits was determined using the National Ambulatory Care Reporting System (NACRS). Dialysis information was obtained from the Ontario

Health Insurance Plan (OHIP) database, which contains all health claims for inpatient and outpatient physician services. Kidney transplant information was obtained from the Canadian Organ Replacement Registry (CORR) and OHIP. Baseline serum creatinine was obtained from the Ontario Laboratories Information System (OLIS), which captures laboratory tests for all individuals in Ontario, and CORR. ICU-specific information was collected using the Critical Care Information System (CCIS). These datasets were linked using unique encoded identifiers and analysed at ICES. The databases were complete for all variables used except for rural residence and neighborhood income quintile, which were missing in <0.5% of individuals. Definitions for study variables are provided in **eTable 2**. Loss to follow-up occurred only through emigration (<0.5% annually).[22]

Cohort Definition

All Ontario, Canada residents aged ≥18 years admitted to an ICU between November 1, 2008 and February 28, 2021 were included. The ICU admission date served as the index date. For individuals with multiple ICU admissions, only the first was included. Exclusions included prior kidney transplant, absence of baseline estimated glomerular filtrate rate (eGFR), or ineligibility for OHIP coverage.

Exposure

CKD stage was defined using baseline eGFR derived from a single outpatient serum creatinine value obtained 7 to 365 days prior to admission, using the measurement closest to admission when multiple were available.[23] eGFR was calculated using the 2021 CKD Epidemiology Collaboration (CKD-EPI) formula.[24] CKD severity was

classified according to Kidney Disease Improving Global Outcomes (KDIGO) eGFR stages: no CKD (eGFR ≥60 mL/min/1.73 m^2), stage 3a (eGFR 45-59 mL/min/1.73 m^2), stage 3b (eGFR 30-44 mL/min/1.73 m^2), stage 4 (eGFR 15-29 mL/min/1.73 m^2), non-dialysis-dependent stage 5 (eGFR <15 mL/min/1.73 m^2), and maintenance dialysis.[25] Albuminuria criteria were not included due to limited availability.

Outcomes

The primary outcome was all-cause mortality, captured at three times: (1) during ICU stay, (2) during hospital stay, and (3) within 90 days following ICU admission. Secondary outcomes included KRT requirement during ICU stay, KRT dependence at 90 days among survivors, and ICU and hospital length of stay among survivors.

Statistical Analysis

Baseline characteristics were summarized by CKD stage. Continuous variables were presented as means (standard deviation [SD]) or medians (interquartile range [IQR]), as appropriate. Categorical variables were presented as numbers (%). Logistic regression was used to estimate crude and adjusted associations between CKD stage and mortality or KRT outcomes. Individuals receiving maintenance dialysis were excluded from KRT analyses. Covariates were selected *a priori* based upon clinical knowledge, prior literature, and availability within ICES: age, sex, rural residence, neighbourhood income quintile, comorbidities (coronary artery disease, myocardial infarction, diabetes mellitus, hypertension, congestive heart failure, arrhythmia, stroke, chronic liver disease, chronic obstructive pulmonary disease, HIV infection, cancer, and

alcoholism),[26] healthcare utilization (emergency room visits, hospitalizations, and nephrology consults) within one year prior to index, use of vasopressors on ICU admission, use of mechanical ventilation on ICU admission, severity of illness according to the Multiple Organ Dysfunction Score (MODS) on ICU admission but subtracting the contribution of the MODS renal component (determined according to serum creatinine), sepsis, and severe sepsis (including septic shock).[27] MODS is an ICU severity of illness score which evaluates six organ systems (respiratory, renal, hepatic, cardiovascular, hematologic, and neurologic) on a 0 (normal) to 4 (severe dysfunction) scale which is uniformly captured for all ICU admissions in Ontario at the time of ICU admission. Sepsis and severe sepsis (including septic shock) were determined using a validated definition for identification within administrative data.[28,29] Length of stay was compared using Kruskal-Wallis testing. A sensitivity analysis was conducted where individuals without baseline serum creatinine values were included and assigned an imputed eGFR of 75 mL/min/1.73 m^2, an accepted approach for estimating missing baseline kidney function.[30] Statistical significance was defined as 95% confidence intervals (CI) that did not overlap with 1.0 and two-sided p-values <0.05. Analyses were conducted using SAS version 8.3 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Baseline Characteristics

Among 848,202 Ontario residents admitted to ICU within the accrual period, 531,090 met eligibility criteria (**Figure 1**). The cohort consisted of 398,296 (75%) individuals without CKD, 63,825 (12%) with stage 3a CKD, 38,744 (7%) with stage 3b CKD, 17,207 (3%) with stage 4 CKD, 3,626 (1%) with non-dialysis-dependent stage 5 CKD, and 9,392 (2%) on maintenance dialysis. Baseline characteristics are displayed in **Table 1**. The mean (SD) age was 67 (15) years, and 43% were female.

Mortality

Across all time frames, individuals without CKD had the lowest mortality percentage. The absolute mortality percentage increased progressively by CKD stage up stage 4, followed by lower mortality among individuals with non-dialysis-dependent stage 5 CKD and those receiving maintenance dialysis (**Figures 2A-C**).

Figure 2D displays the crude and adjusted odds ratios (OR) for the associations between CKD stage and mortality. For all mortality time frames in multivariable adjusted models and relative to individuals without CKD, individuals with CKD experienced a higher mortality risk. The mortality risk increased progressively up to non-dialysis-dependent stage 5 CKD. However, mortality risk was lower for individuals on maintenance dialysis compared to those with non-dialysis-dependent stage 5 CKD. For example, relative to individuals without CKD, stages 3a, 3b, 4, and 5 (non-dialysis-dependent) CKD were associated with 17%, 45%, 2-fold, and 2.4-fold higher odds for

90-day mortality, respectively. However, individuals on maintenance dialysis experienced lower odds for 90-day mortality (OR 2.12 [95% CI 2.00-2.24]) relative to those with non-dialysis-dependent stage 5 CKD (OR 2.41 [95% CI 2.22-2.61]) and comparable to those with stage 4 CKD (OR 2.06 [95% CI 1.98-2.14]).

Kidney Replacement Therapy

The proportion of individuals requiring KRT during ICU stay and remaining KRT dependent at 90 days increased markedly with CKD severity (**Figures 3A-B**). For instance, KRT dependence at 90 days among survivors progressively increased by CKD stage as follows: no baseline CKD 0.2%, stage 3a 0.5%, stage 3b 1.3%, stage 4 8.2%, and non-dialysis-dependent stage 5 45.3%.

Figure 3C displays the crude and adjusted ORs for the association between CKD stage and KRT outcomes. For both time frames in multivariable adjusted models and relative to individuals without CKD, need for KRT increased progressively by CKD severity. For example, risk for KRT dependence at 90 days among survivors increased based on CKD severity as follows: stage 3a (OR 3.58 [95% CI 3.05-4.21]), stage 3b (OR 8.60 [95% CI 7.41-9.98]), stage 4 (OR 47.7 [95% CI 41.7-54.6]), and previously non-dialysis-dependent stage 5 (OR 414.4 [95% CI 359.3-477.9]).

Figure 4 displays the proportion of individuals who initiated KRT in ICU, survived to 90 days post-ICU admission, and remained KRT dependent at 90 days by CKD stage. This

proportion increased progressively as follows: no CKD 7.2%, stage 3a 14.2%, stage 3b 22.5%, stage 4 50.3%, and previously non-dialysis-dependent stage 5 83.8%.

Length of Stay

eTable 3 displays the median lengths of stay among survivors according to CKD stages. Length of stay increased progressively by CKD stage, except among individuals on maintenance dialysis. For instance, the median (IQR) hospital length of stay increased as follows: no baseline CKD 6 (4-12) days, stage 3a 8 (4-16) days, stage 3b 9 (5-18) days, stage 4 11 (6-21) days, and non-dialysis-dependent stage 5 12 (6-24) days. However, individuals on maintenance dialysis had shorter median hospital length of stay (9 [5-19] days) than individuals with stage 4 or non-dialysis-dependent stage 5 CKD.

Sensitivity Analysis

A sensitivity analysis including individuals with no available outpatient baseline serum creatinine measurements (assigned an imputed baseline eGFR of 75 mL/min/1.73 m^2) yielded comparable results to the primary analysis (**eTables 4–5** and **eFigures 1–2**).

DISCUSSION

In this large, population-based study of 531,090 Canadian adults admitted to the ICU, one in four individuals had pre-existing CKD. This included 12% with stage 3a, 7% with stage 3b, 3% with stage 4, 1% with non-dialysis-dependent stage 5, and 2% on maintenance dialysis. Compared with individuals without CKD, CKD severity was progressively associated with increased mortality risk up to non-dialysis-dependent stage 5 CKD. However, mortality risk was lower for individuals on maintenance dialysis relative to those with non-dialysis-dependent stage 5 CKD and comparable to those with stage 4 CKD. Risk for KRT in ICU and KRT dependence at 90 days also increased in parallel with CKD severity. Specifically, stages 3a, 3b, 4, and 5 (previously non-dialysis-dependent) CKD experienced approximately 4-fold, 9-fold, 50-fold, and 400-fold higher odds for KRT dependence at 90 days, respectively. The presence and severity of CKD was also associated with a greater length of ICU and hospital stay.

An enhanced understanding of the links between CKD severity and ICU-related outcomes is important due to the disproportionate representation of individuals with CKD in the ICU setting. The prevalence of CKD among Canadian adults is 12.5%.[31] Yet in this diverse, unselected, and population-wide cohort, we found that the prevalence of CKD among the ICU population (25%) was double that observed in the general population. This enrichment of CKD among ICU populations is consistent with prior work.[32] This over-representation relative to the general population is magnified further when considering individuals on maintenance dialysis, who have been shown to have an estimated 25- to 30-fold higher rate of ICU admission.[33] Given the over-

representation in the ICU and inherent susceptibility to complications (e.g., fluid overload, electrolyte derangements, increased cardiovascular/infection risks), understanding how CKD severity influences ICU outcomes is important for risk prognostication, goals-of-care discussions, resource allocation, and health policy initiatives.

Despite this, the relationship between CKD and ICU outcomes has not previously been well established. Most prior studies linking kidney dysfunction to ICU outcomes have focused on AKI, with a smaller number focused on outcomes for individuals on maintenance dialysis.[12-18] Yet the much broader non-dialysis-CKD population has not been well studied in this regard. One of the largest studies on this topic involved a Swedish ICU registry of approximately 100,000 individuals who were classified into five groups (ESKD, CKD, AKI, AKI on CKD, or normal kidney function) to compare mortality and KRT dependence.[14] The study found that pre-existing CKD significantly increased risk of both death and KRT dependence. However, a major limitation of this study is that CKD was identified using International Classification of Diseases (ICD) codes which have poor sensitivity in capturing the presence and severity of CKD thus leading to high rates of misclassification.[34-36] Accordingly, the Swedish study reported a much lower prevalence of CKD in the ICU population (4%) than has been reported in this and other studies (≥20%).[14] Furthermore, this approach also does not allow for stratification of individuals by CKD stage, which is well-established as an important risk factor for CKD progression and cardiovascular events.[25]

The present study now extends the evidence base on the relationship between CKD and ICU outcomes. By using a large population-based cohort of individuals with outpatient baseline serum creatinine values and comprehensive outcome capture, we were able to accurately and reliably characterize CKD staging and its association with clinical outcomes following ICU admission. We found that mortality risk increased progressively up to non-dialysis-dependent stage 5 CKD; however, mortality risk for individuals on maintenance dialysis was lower than for those with non-dialysis-dependent stage 5 CKD and comparable to those with stage 4 CKD. This phenomenon of individuals on maintenance dialysis having an equal or lower mortality risk following critical illness than those with advanced non-dialysis-dependent CKD has been suggested in prior studies.[14,37,38] The reasons behind this remain unclear, but could relate to better control of volume and metabolic derangements with dialysis, a lower threshold for transferring individuals on maintenance dialysis to the ICU, and that individuals receiving maintenance dialysis who are admitted to the ICU represent a healthier subset of the overall dialysis population, with ICU transfer perhaps not within the goals of care for sicker individuals on dialysis. Lastly, patients with advanced CKD can potentially develop indications for ICU admission with relatively little to no acute inter-current illness. For patients with ESKD on maintenance dialysis, missed dialysis treatments or non-adherence to dietary restrictions can result in life-threatening fluid overload or hyperkalemia. These life-threatening complications may warrant ICU admission but typically resolve quickly with dialysis treatment. Severity of illness scoring at time of admission, which we adjusted for in this study, may not necessarily capture these nuances.

Our findings also highlight that the risk of KRT in the ICU and KRT dependence at 90 days increases exponentially by baseline CKD stage. KRT dependence at 90 days is an important time point as this represents a well-accepted definition for ESKD.[39-41] Notably, among individuals who survived to day 90, 45.3% with previously non-dialysis-dependent stage 5 CKD and 8.2% with stage 4 CKD became dialysis dependent following ICU admission. More specifically, among individuals who survived to day 90 and required KRT initiation during their ICU stay, 83.8% with previously non-dialysis-dependent stage 5 CKD and 50.3% with stage 4 CKD remained dialysis dependent following ICU admission. This information will serve to inform prognostic discussions with patients and families surrounding expected kidney outcomes following critical illness for individuals with pre-existing advanced CKD. This study also provides the strongest evidence to date on the link between CKD and hospital length of stay following ICU admission. CKD severity paralleled length of stay with the notable exception of individuals on maintenance dialysis who experience shorter stays than those with non-dialysis-dependent stages 4 and 5 CKD.

Strengths and Limitations

The strengths and novelty of this study include a large unselected population-based cohort, comprehensive assessment of outpatient baseline serum creatinine values to accurately classify CKD severity, and complete capture of outcome events using provincial data registries. However, we acknowledge several limitations. First, the study is observational which allowed for determination of association but not causation. Notably, we accounted for numerous potential confounders including demographics,

comorbidities, and severity of illness (e.g., MODS score, mechanical ventilation, vasopressor use, sepsis, and septic shock). However, unobserved confounding may still have occurred. Second, CKD in this study was defined exclusively by eGFR and not albuminuria. This related to the vast majority of individuals not having a measure of albuminuria within one year prior to index and those that did appeared to be non-random (e.g., more commonly measured in individuals with diabetes). Therefore, these results should be interpreted in the context of CKD defined by eGFR only rather than albuminuria. Third, while the use of provincial health data registries provided a large population-based cohort of individuals with a wide spectrum of CKD severity admitted to the ICU which was necessary to answer the research question, this also limited the granularity of certain variables. For instance, the health administrative databases used did not define the exact reason for ICU admission on a case-by-case basis. However, we did account for disease-related factors such as comorbidities, severity of illness measures, and presence of sepsis/septic shock to help account for this. Finally, we investigated KRT dependence at 90 days as a study outcome as it is a previously established definition for ESKD.[39-41] Given that this is a binary outcome at a pre-specified time point, it does not allow for a competing risk analysis. Therefore, we limited this analysis to individuals who survived to day 90 (whom we feel this outcome is primarily meaningful to) such that there was no competing risk of death.

CONCLUSIONS

In summary, this population-based cohort study represents the largest study to date comprehensively detailing the association between pre-existing CKD severity and clinical trajectories following ICU admission. CKD is exceedingly common among the ICU population being present in 25% of individuals admitted to the ICU. The presence and severity of CKD is strongly linked to adverse health outcomes following ICU admission including death, ESKD, and prolonged length of stay. These findings will inform risk prognostication, goals-of-care discussions, resource allocation, and health policy initiatives for this large portion of the ICU population.

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CONFLICT OF INTEREST DISCLOSURES

SAS has received speaking fees and an unrestricted educational grant from Vantive.

RW has received speaker and consulting fees from Vantive.

DATA SHARING STATEMENT

The dataset from this study is held securely in coded form at ICES. While legal data sharing agreements between ICES and data providers (e.g., healthcare organizations and government) prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS (email: das@ices.on.ca). The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

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TABLES

Table 1. Baseline Characteristics of the Study Cohort.

Characteristic	Total	Baseline eGFR Categories, mL/min/1.73 m^2					
		≥60	**45-59**	**30-44**	**15-29**	**<15 (Non-Dialysis)**	**Dialysis Dependent**
N (%)	531,090	398,296 (75)	63,825 (12)	38,744 (7)	17,207 (3)	3,626 (1)	9,392 (2)
Age, Years, Mean (SD)	67 (15)	64 (15)	77 (10)	78 (10)	77 (11)	72 (13)	66 (14)
Sex, N (%)							
Female	228,290 (43)	163,736 (41)	30,651 (48)	19,870 (51)	8,629 (50)	1,740 (48)	3,664 (39)
Male	302,800 (57)	234,560 (59)	33,174 (52)	18,874 (49)	8,578 (50)	1,886 (52)	5,728 (61)

Baseline Kidney Characteristics							
Creatinine, μmol/L, Median (IQR)	82 (68-102)	75 (64-86)	110 (96-122)	141 (123-158)	210 (180-245)	405 (346-495)	621 (444-815)
eGFR, mL/min/1.73 m^2, Median (IQR)[a]	81 (60-96)	89 (76-100)	53 (49-57)	39 (35-42)	24 (20-27)	12 (9-13)	7 (5-11)
Neighborhood Income Quintile, N (%)[b]							
Quintile 1 (Lowest)	118,556 (22)	86,747 (22)	14,618 (23)	9,296 (24)	4,307 (25)	925 (26)	2,663 (28)
Quintile 2	111,416 (21)	82,634 (21)	13,595 (21)	8,529 (22)	3,814 (22)	791 (22)	2,053 (22)
Quintile 3	105,222 (20)	79,088 (20)	12,628 (20)	7,636 (20)	3,375 (20)	744 (21)	1,751 (19)

Quintile 4	99,082 (19)	75,502 (19)	11,631 (18)	6,777 (17)	2,976 (17)	615 (17)	1,581 (17)
Quintile 5 (Highest)	94,884 (18)	72,878 (18)	11,137 (17)	6,381 (16)	2,668 (16)	538 (15)	1,282 (14)
Rural Residence, N (%)[c]	75,857 (14)	57,797 (15)	9,036 (14)	5,286 (14)	2,174 (13)	457 (13)	1,107 (12)
Comorbidities, N (%)							
Coronary Artery Disease	115,772 (22)	81,925 (21)	16,443 (26)	9,823 (25)	4,299 (25)	744 (21)	2,538 (27)
Myocardial Infarction	51,036 (10)	32,224 (8)	7,995 (13)	5,853 (15)	2,962 (17)	512 (14)	1,490 (16)
Congestive Heart Failure	82,501 (16)	41,496 (10)	15,753 (25)	13,348 (34)	7,668 (45)	1,399 (39)	2,837 (30)

Arrhythmia	53,631 (10)	33,375 (8)	9,718 (15)	6,539 (17)	2,839 (16)	318 (9)	842 (9)
Stroke	18,773 (4)	12,823 (3)	2,926 (5)	1,785 (5)	730 (4)	133 (4)	376 (4)
Hypertension	250,430 (47)	169,540 (43)	37,304 (58)	23,928 (62)	11,011 (64)	2,432 (67)	6,215 (66)
Diabetes Mellitus	178,642 (34)	116,460 (29)	25,592 (40)	18,818 (49)	9,856 (57)	2,235 (62)	5,681 (60)
COPD	55,782 (11)	38,009 (10)	8,292 (13)	5,604 (14)	2,586 (15)	376 (10)	915 (10)
Chronic Liver Disease	7,156 (1)	5,138 (1)	808 (1)	673 (2)	320 (2)	45 (1)	172 (2)
Alcoholism	12,104 (2)	10,916 (3)	624 (1)	366 (1)	122 (1)	18 (0)	58 (1)
Cancer	162,075 (31)	122,431 (31)	20,130 (32)	11,742 (30)	4,806 (28)	884 (24)	2,082 (22)
HIV Infection	1,504 (0)	1,249 (0)	107 (0)	63 (0)	25 (0)	12 (0)	48 (1)
Charlson Comorbidity Index							

Category, N (%)							
≤2	326,273 (61)	271,734 (68)	33,828 (53)	14,678 (38)	3,935 (23)	723 (20)	1,375 (15)
3-4	123,782 (23)	79,445 (20)	18,896 (30)	14,086 (36)	7,066 (41)	1,410 (39)	2,879 (31)
≥5	81,035 (15)	47,117 (12)	11,101 (17)	9,980 (26)	6,206 (36)	1,493 (41)	5,138 (55)
ICU Admission Characteristics							
Vasopressor Use, N (%)	137,544 (26)	101,179 (25)	17,707 (28)	10,529 (27)	4,568 (27)	898 (25)	2,663 (28)
Mechanical Ventilation, N (%)	363,532 (68)	270,221 (68)	44,519 (70)	27,496 (71)	12,309 (72)	2,570 (71)	6,417 (68)
Sepsis, N (%)	40,176 (8)	26,475 (7)	5,746 (9)	4,094 (11)	2,050 (12)	394 (11)	1,417 (15)
Severe Sepsis (Including Septic	31,259 (6)	19,877 (5)	4,696 (7)	3,473 (9)	1,824 (11)	353 (10)	1,036 (11)

Shock), N (%)							
Multiple Organ Dysfunction Score (MODS) Category, N (%)							
0	157,371 (30)	141,419 (36)	11,562 (18)	3,119 (8)	744 (4)	128 (4)	399 (4)
1-4	249,100 (47)	172,210 (43)	36,010 (56)	24,479 (63)	10,373 (60)	1,737 (48)	4,291 (46)
5-8	103,442 (19)	71,513 (18)	13,363 (21)	8,975 (23)	4,832 (28)	1,351 (37)	3,408 (36)
9-12	19,356 (4)	11,990 (3)	2,682 (4)	2,018 (5)	1,159 (7)	363 (10)	1,144 (12)
≥13	1,821 (0)	1,164 (0)	208 (0)	153 (0)	99 (1)	47 (1)	150 (2)
Healthcare Utilization Within 1 Year Prior to Index							

Hospitalization, N (%)							
Emergency Room Visit	323,890 (61)	233,478 (59)	40,786 (64)	26,696 (69)	12,774 (74)	2,689 (74)	7,467 (80)
Prior Hospitalization	155,472 (29)	104,584 (26)	20,901 (33)	15,047 (39)	7,997 (46)	1,693 (47)	5,250 (56)

[a] Calculated using the 2021 creatinine-based CKD-EPI equation.[24]

[b] Neighborhood income quintile missing in 1,930 individuals (0.4% of cohort).

[c] Rural defined as residing in a location with population <10,000 persons, missing in 993 individuals (0.2% of cohort).

Abbreviations: COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus; ICU, intensive care unit; SD, standard deviation.

FIGURES

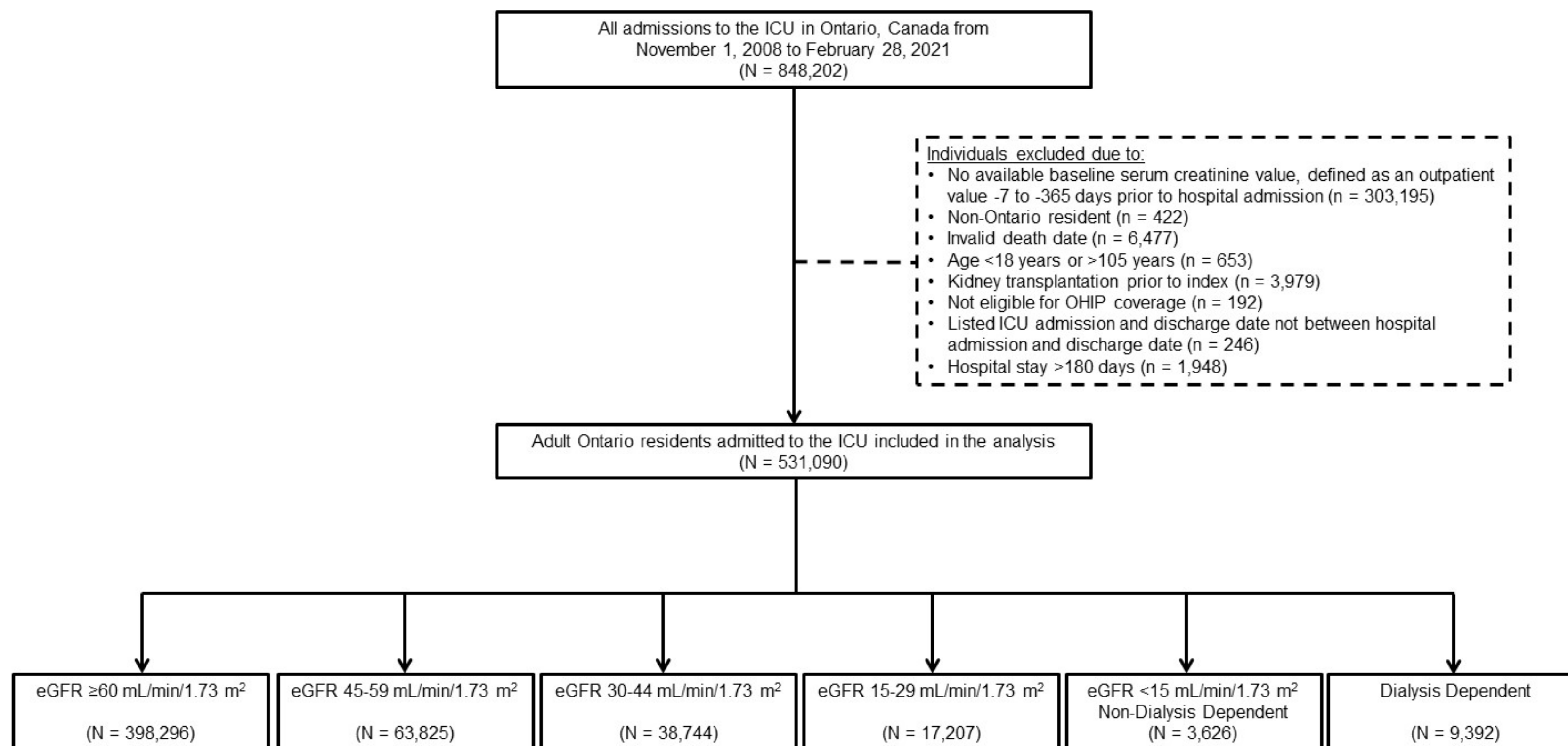
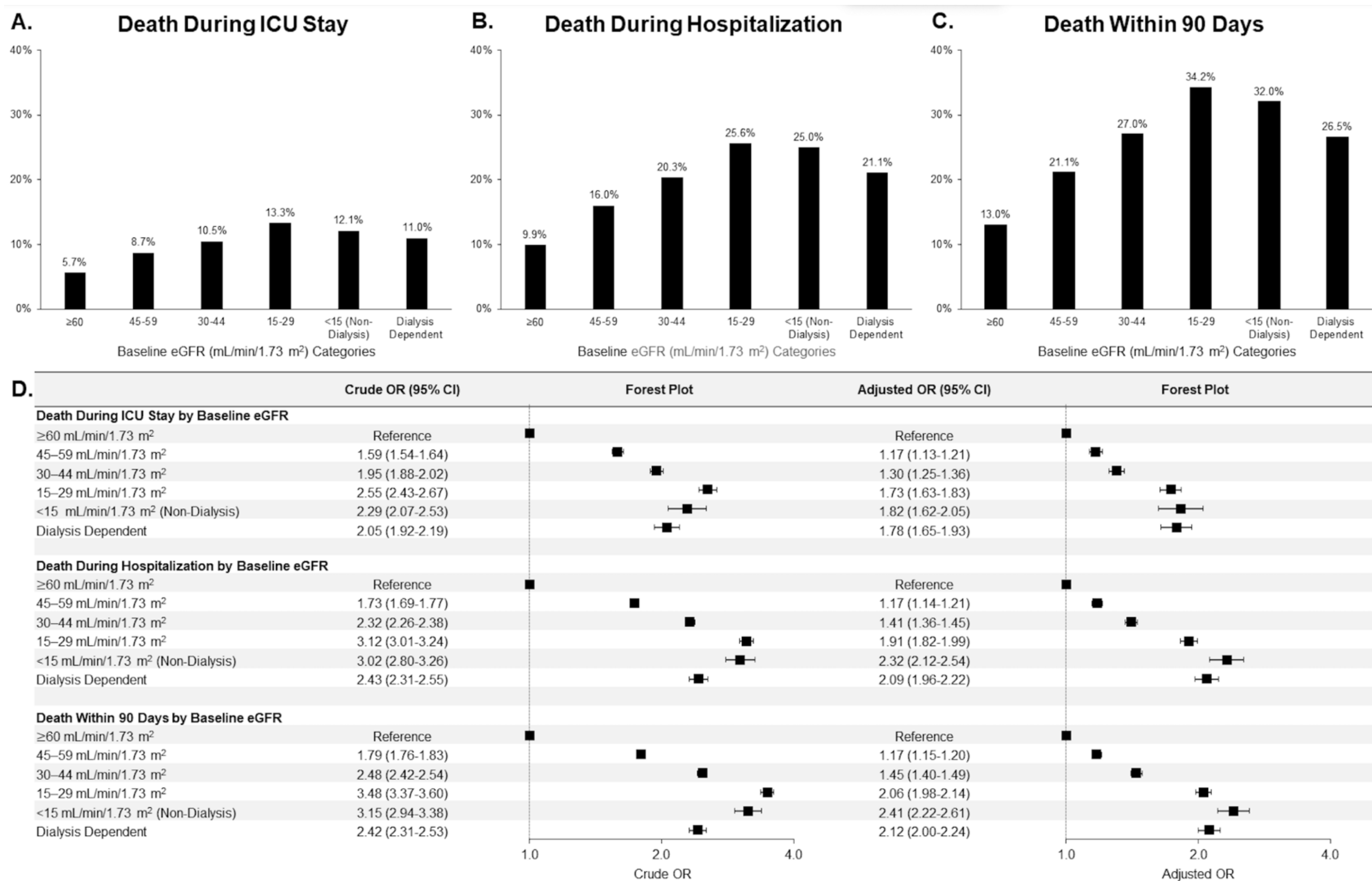


Figure 1. Study Flowchart.

Abbreviations: eGFR, estimated glomerular filtration rate; ICU, intensive care unit; OHIP, Ontario Health Insurance Plan.



	Crude OR (95% CI)	Adjusted OR (95% CI)
Death During ICU Stay by Baseline eGFR		
≥60 mL/min/1.73 m²	Reference	Reference
45–59 mL/min/1.73 m²	1.59 (1.54-1.64)	1.17 (1.13-1.21)
30–44 mL/min/1.73 m²	1.95 (1.88-2.02)	1.30 (1.25-1.36)
15–29 mL/min/1.73 m²	2.55 (2.43-2.67)	1.73 (1.63-1.83)
<15 mL/min/1.73 m² (Non-Dialysis)	2.29 (2.07-2.53)	1.82 (1.62-2.05)
Dialysis Dependent	2.05 (1.92-2.19)	1.78 (1.65-1.93)
Death During Hospitalization by Baseline eGFR		
≥60 mL/min/1.73 m²	Reference	Reference
45–59 mL/min/1.73 m²	1.73 (1.69-1.77)	1.17 (1.14-1.21)
30–44 mL/min/1.73 m²	2.32 (2.26-2.38)	1.41 (1.36-1.45)
15–29 mL/min/1.73 m²	3.12 (3.01-3.24)	1.91 (1.82-1.99)
<15 mL/min/1.73 m² (Non-Dialysis)	3.02 (2.80-3.26)	2.32 (2.12-2.54)
Dialysis Dependent	2.43 (2.31-2.55)	2.09 (1.96-2.22)
Death Within 90 Days by Baseline eGFR		
≥60 mL/min/1.73 m²	Reference	Reference
45–59 mL/min/1.73 m²	1.79 (1.76-1.83)	1.17 (1.15-1.20)
30–44 mL/min/1.73 m²	2.48 (2.42-2.54)	1.45 (1.40-1.49)
15–29 mL/min/1.73 m²	3.48 (3.37-3.60)	2.06 (1.98-2.14)
<15 mL/min/1.73 m² (Non-Dialysis)	3.15 (2.94-3.38)	2.41 (2.22-2.61)
Dialysis Dependent	2.42 (2.31-2.53)	2.12 (2.00-2.24)

Figure 2. Mortality During ICU Stay, During Hospitalization, and Within 90 Days Following ICU Admission According to Pre-Existing CKD Severity.

A) Absolute percentage of death during ICU stay. B) Absolute percentage of death during hospitalization. C) Absolute percentage of death within 90 days. D) Crude and adjusted ORs (95% CIs) for the association between CKD severity and death. Adjusted models adjusted for the following additional variables: age, sex, rural residence, neighbourhood income quintile, comorbidities (coronary artery disease, myocardial infarction, diabetes mellitus, hypertension, congestive heart failure, arrhythmia, stroke, chronic liver disease, chronic obstructive pulmonary disease, HIV infection, cancer, and alcoholism), healthcare utilization (emergency room visits, hospitalizations, and nephrology consults) within one year prior to index, use of vasopressors on ICU admission, use of mechanical ventilation on ICU admission, severity of illness according to MODS (but subtracting the MODS renal component), sepsis, and severe sepsis (including septic shock).

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus; ICU, intensive care unit; MODS, Multiple Organ Dysfunction Score; OR, odds ratio.

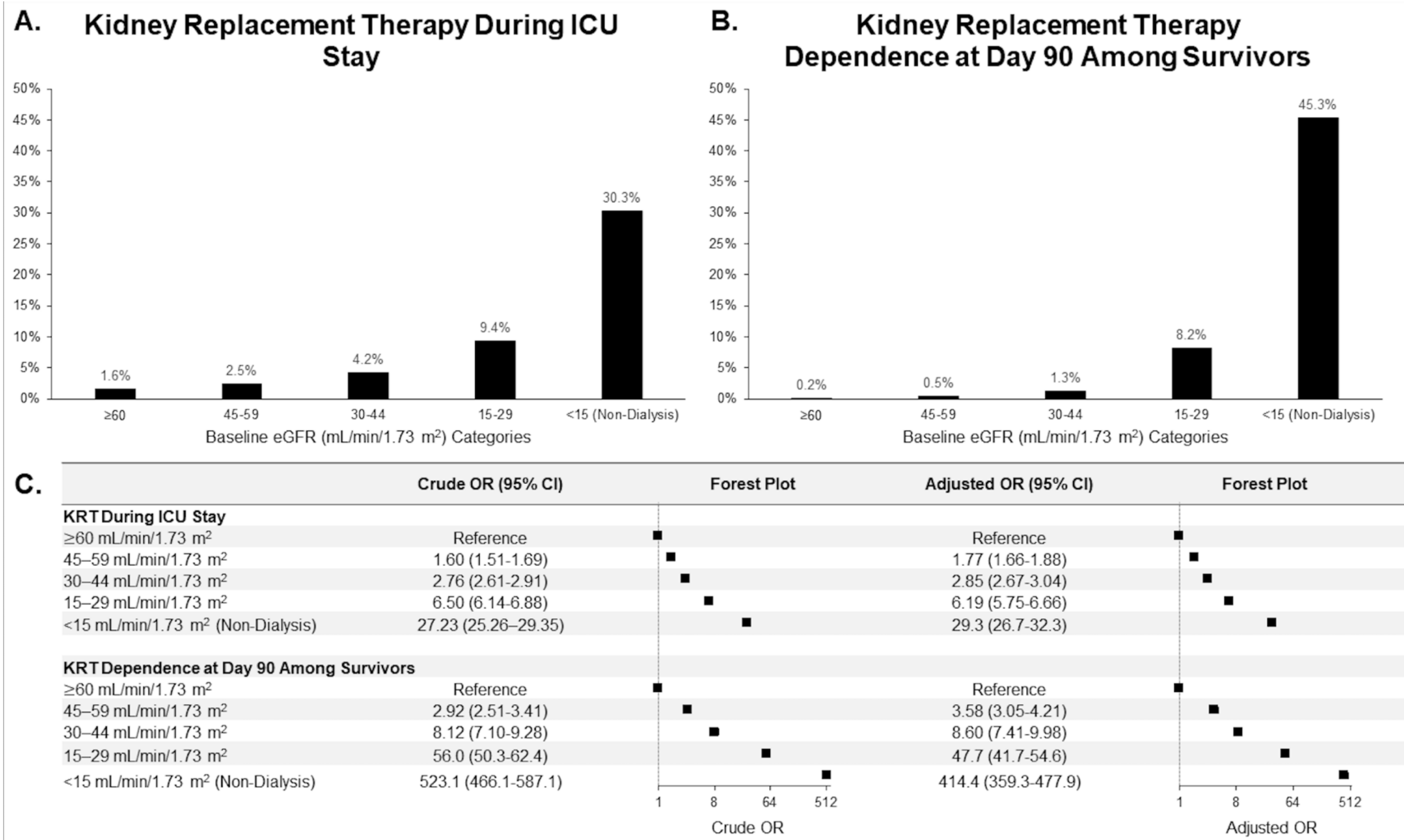


Figure 3. Kidney Replacement Therapy Initiation During ICU Stay and Dependence at 90 Days Following ICU Admission According to Pre-Existing CKD Severity.

A) Absolute percentage of kidney replacement therapy initiation during ICU stay. B) Absolute percentage of kidney replacement therapy dependence at day 90 among survivors. C) Crude and adjusted ORs (95% CIs) for the association

between CKD severity and kidney replacement therapy outcomes. Adjusted models adjusted for the following additional variables: age, sex, rural residence, neighbourhood income quintile, comorbidities (coronary artery disease, myocardial infarction, diabetes mellitus, hypertension, congestive heart failure, arrhythmia, stroke, chronic liver disease, chronic obstructive pulmonary disease, HIV infection, cancer, and alcoholism), healthcare utilization (emergency room visits, hospitalizations, and nephrology consults) within one year prior to index, use of vasopressors on ICU admission, use of mechanical ventilation on ICU admission, severity of illness according to MODS (but subtracting the MODS renal component), sepsis, and severe sepsis (including septic shock).

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus; ICU, intensive care unit; MODS, Multiple Organ Dysfunction Score; OR, odds ratio.

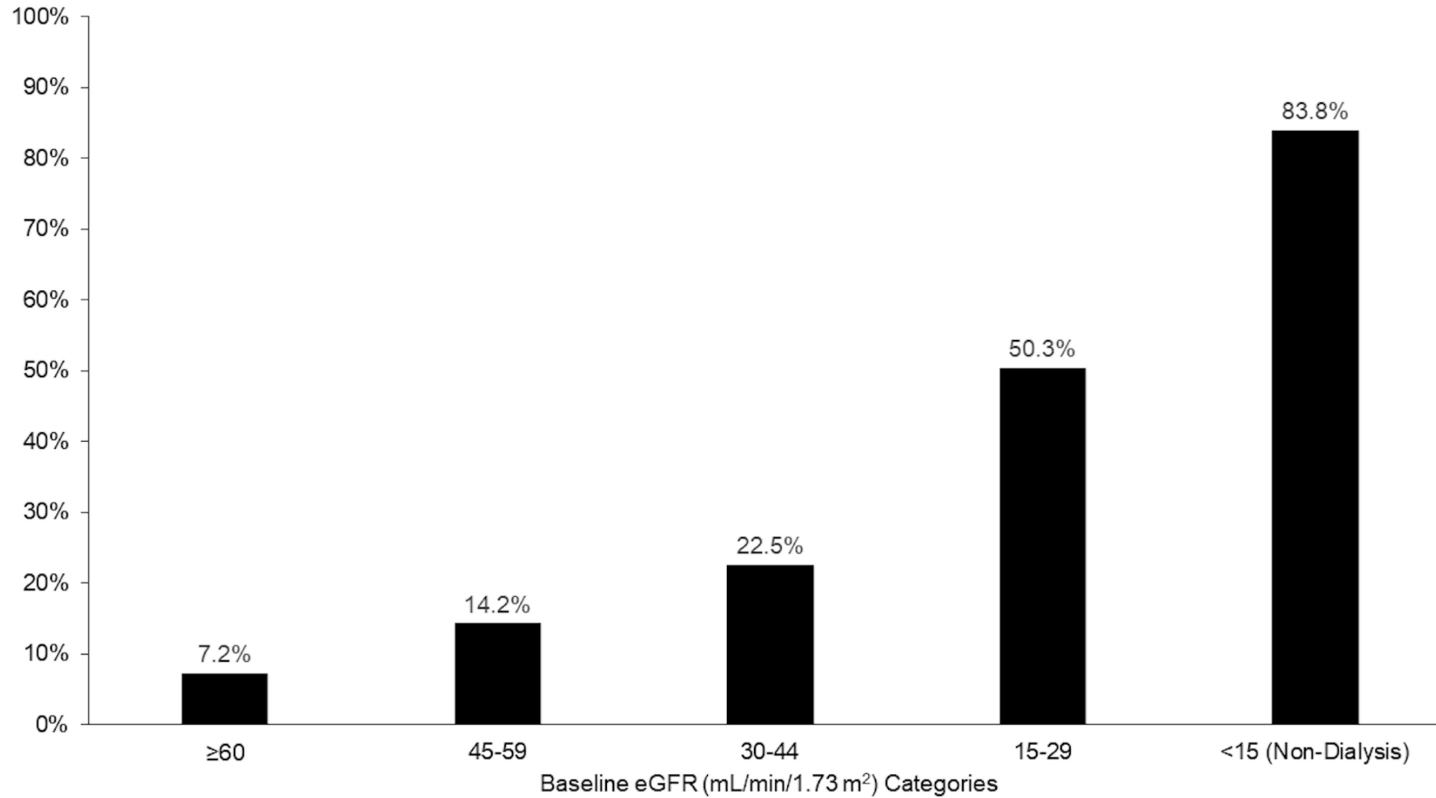


Figure 4. Kidney Replacement Therapy Dependence at 90 Days Among Survivors Who Initiated Kidney Replacement Therapy in the ICU.

Abbreviations: eGFR, estimated glomerular filtration rate; ICU, intensive care unit.

SUPPLEMENTAL INFORMATION

Severity of Chronic Kidney Disease and Outcomes Following Admission to the Intensive Care Unit

ITEM	PAGE
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eFigure 2. Kidney Replacement Therapy Initiation During ICU Stay and Dependence at 90 Days Following ICU Admission According to Pre-Existing CKD Severity for Sensitivity Analysis Including Individuals Missing Baseline Outpatient Serum Creatinine Values (Assigned Baseline eGFR of 75 mL/min/1.73 m^2).	22

eTable 1. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) REporting of Studies Conducted Using Observational Routinely-Collected Health Data (RECORD) Statement Checklists.

		STROBE items	RECORD items	Location in manuscript where items are reported
Title and Abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Title page, Abstract
Background rationale	2	Explain the scientific background and rationale for the investigation being reported		Introduction
Objectives	3	State specific objectives, including any prespecified hypotheses		Introduction
Study Design	4	Present key elements of study design early in the paper		Methods
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection		Methods
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be	Methods, Figure 1

			referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Table 1, Supplemental Table S2
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group		Methods, eTable 2
Bias	9	Describe any efforts to address potential sources of bias		Methods
Study size	10	Explain how the study size was arrived at		Methods, Figure 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why		Methods, Table 1
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed		Methods

		(e) Describe any sensitivity analyses		
Data access and cleaning methods			RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	Methods
Linkage			RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	Methods
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Results, Figure 1
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)		Results, Table 1
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure		Results

		Cross-sectional study - Report numbers of outcome events or summary measures		
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		Results, Figures 2-4, eTable 3
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses		Results, eFigures 1-2, eTables 4-5
Key results	18	Summarise key results with reference to study objectives		Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Discussion
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence		Discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results		Discussion
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original		Acknowledgements, Funding/Support

	study on which the present article is based		
Accessibility of protocol, raw data, and programming code		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Data Sharing Statement

eTable2. Definitions for Patient Characteristics and Clinical Variables.

Variables	Description	Data Source	Code(s)
Baseline serum creatinine	most recent measurement -7 to -365 days prior to ICU admission date	OLIS CORR	OLIS: LOINC code 14682-9 CORR: creatinine results and date of creatinine test
Multiple Organ Dysfunction Score (MODS)	Objective scale to measure the severity of the multiple organ dysfunction syndrome using platelet count, serum bilirubin, serum creatinine, pressure adjusted heart rate, Glascow Coma Scale, blood gases (PO2/FiO2)	CCIS	MODSCENTRALVENOUSPRESSURE, MODSFIO2, MODSGLASGOWCOMASCORE MODSHAEMATOLOGIC MODSHEARTRATE MODSHEPATIC MODSMEANARTERIALPRESSURE MODSPO2 MODSRENAL MODSRESPIRATORYRATIO MODSCORE MODSSUBMISSIONDATETIME
Mechanical ventilation	Mechanical: Invasive ventilation (Yes/No)	CCIS	NA
Vasopressors	Intravenous Inotropic /Vasoactive Medication, Multiple IV Vasoactive/ Inotropic Medication, single IV Vasoactive/ Inotropic Medication	CCIS	NA
Sepsis	A hospitalization with explicit diagnosis of sepsis, with or without organ dysfunction	CIHI	A03.9, A02.1, A20.7, A21.7, A22.7, A23.9, A24.1, A26.7, A28.0, A28.2, A32.7, A39.2, A39.3, A39.4, A40, A40.0, A40.1, A40.2, A40.3, A40.8, A40.9, A41, A41.0, A41.1, A41.2, A41.3, A41.4, A41.5, A41.50, A41.51, A41.52, A41.58, A41.8, A41.80, A41.88, A41.9, A42.7, B00.7, B37.7, P36.0, P36.1, P36.2, P36.3, P36.4, P36.5, P36.8, P36.9, P35.2, P37.2 and P37.5
Severe Sepsis (including Septic Shock)	Sepsis in addition to one or more acute organ dysfunction	CIHI CCIS	Sepsis code + organ dysfunction code in any of the six systems, including: *Respiratory*: J96.0, J96.9, J80, R09.2 *Cardiovascular*: R57.0, R57.1, R57.2, R57.8, R57.9, I95.1, I95.8, I95.9 *Renal*: N17.0, N17.1, N17.2, N17.8, N17.9 *Hepatic*: K72.0, K72.9, K76.3 *Neurologic*: F05.0, F05.9, G93.1, G93.4, G93.80 *Hematologic*: D69.5, D69.6, D65 *CCI Codes:* 1.GZ.31.CA-ND, 1.GZ.31.CR-ND, 1.GZ.31.GP-ND with extent attribute = ”EX”
Outcomes			
90-day mortality	index date + 90 days or date of death in RPDB	RPDB	NA

Hospital mortality	hospital discharge date or date of death RPDB	RPDB	NA
ICU mortality	Date of death in RPDB <= ICU discharge date	RPDB	NA
KRT initiation in ICU	OHIP fee codes for dialysis between index date and ICU discharge date	OHIP	OHIP fee codes for dialysis: G323, G330, G331, G860, G861, G862, G863, G864, G865, G866, R849, R850, G325, G326, G333, G083, G091, G085, G295, G082, G090, G092, G093, G094, G294, G095, G096, R850, H540, H740
90-day KRT dependency	OHIP fee codes for dialysis 90 days after index date +/- 7 days	OHIP	OHIP fee codes for dialysis: G323, G330, G331, G860, G861, G862, G863, G864, G865, G866, R849, R850, G325, G326, G333, G083, G091, G085, G295, G082, G090, G092, G093, G094, G294, G095, G096, R850, H540, H740
Hospital length of stay	Hospital discharge date – hospital admission date	DAD	NA
ICU length of stay	ICU discharge date – ICU admission date If hospital discharge date in DAD is less than ICU discharge date in CCIS, replace ICU discharge date with hospital discharge date.	CCIS DAD	NA
Demographics			
Index date	ICU admission date	CCIS	NA
Age		RPDB	NA
Sex		RPDB	NA
Rural status	defined as residing in a location with population <10,000 persons	RPDB	NA
Neighbourhood Income Quintile	Proxy for Socioeconomic Status (SES)	RPDB	NA
Comorbidities, 2 years prior to index date			
Myocardial Infarction	Myocardial Infarction including STEMI and NSTEMI	OHIP DAD SDS NACRS	OHIP diagnosis code(s): 410 ICD-10 code(s): I21
Diabetes Mellitus	From autoimmune to lifestyle related diabetes mellitus, other defined causes, and unspecified diabetes	OHIP DAD SDS NACRS	OHIP diagnosis code(s): 250 ICD-10 code(s): E10, E11, E13, E14
Coronary Artery Disease	Full spectrum of ischemic heart disease	OHIP DAD SDS NACRS	OHIP diagnosis code(s): 411-414 ICD-10 code(s): I20, I22 - I25

Congestive Heart Failure	Heart failure (congestive or left ventricular) and unspecified heart failure	OHIP DAD SDS NACRS	OHIP diagnosis code(s): 428; ICD-10 code(s): I500, I501, I509
Arrhythmia	Supraventricular or ventricular arrhythmias, atrial fibrillation, and atrial flutter	OHIP DAD SDS NACRS	OHIP diagnosis code(s): 427; ICD-10 code(s): I480, I481
Hypertension	Ranging from uncomplicated high blood pressure to hypertension with serious organ damage	OHIP DAD SDS NACRS	ICD-10 code(s): I10-I15
Stroke	Excluding TIA	OHIP DAD SDS NACRS	OHIP diagnosis code(s): 430, 431, 432, 434, 436; ICD-10 code(s): I60-I64
Chronic Liver Disease	Chronic hepatic failure, chronic hepatitis, fibrosis and cirrhosis of liver	OHIP DAD SDS NACRS	OHIP diagnosis code(s): 571, 573 ICD-10 code(s): K721, K73, K74
Chronic Obstructive Pulmonary Disease	Chronic bronchitis, emphysema, long-term disease diseases of the lower airways related to smoking or long-term exposure to lung irritants	OHIP DAD SDS NACRS	OHIP diagnosis code(s): 491, 492, 496, ICD-10 code(s): J41-J44
HIV Infection	HIV confirmed infection, but no specific HIV-related condition or complications are documented	OHIP DAD SDS NACRS	OHIP diagnosis code(s): 042, 043, 044 ICD-10 code(s): B24
Cancer	Malignant neoplasms of the digestive system, respiratory organs and skin, other sites and tissues	OHIP DAD SDS NACRS	OHIP diagnosis code(s): 140-239, ICD-10 code(s): C00-C26, C30-C44, C45-C97
Alcohol misuse	Alcohol dependence or chronic alcohol abuse	OHIP	OHIP diagnosis code(s): 303
Charlson Comorbidity Index Score	Score derived from inpatient records in the 5 years prior to index date, including records from the index hospitalization	DAD	%charlson ICES macro
Health care services use within 1 year of index hospitalization			
Pre-admission Dialysis	OHIP fee codes for dialysis in the 14 days prior to hospital admission date	OHIP	OHIP fee codes for dialysis: G323, G330, G331, G860, G861, G862, G863, G864, G865, G866, R849, R850, G325, G326, G333, G083, G091, G085, G295, G082, G090, G092, G093, G094, G294, G095, G096, R850, H540, H740
ER visits	excluding planned visits, over the past 1 year	NACRS	NA
Prior hospitalizations	Number of hospitalisations prior to index date, over the past 1 year	DAD	NA
Nephrologist consults	OHIP fee code(s) in the previous year billed by a physician with specialty code ‘16’ (Nephrology)	OHIP	SPEC 16

Critical care/emergency medicine consults	OHIP fee code(s) in the previous year billed by a physician with specialty code ‘11’ (Critical Care Medicine) or ‘12’ (Emergency Medicine)	OHIP	SPEC 11, SPEC 12

Abbreviations:

CCIS: Critical Care Information System, **CIHI**: Canadian Institute of Health Information, **DAD**: Discharge Abstract Database, **ER**: Emergency Room, **HIV**: Human Immunodeficiency Virus, **ICU**: Intensive Care Unit, **ICES**: Institute for Clinical Evaluative Sciences, **IPDB**: ICES Physician Database, **KRT**: Kidney Replacement Therapy, **LSI**: Life Support Information, **NA:** Not available, **NACRS**: National Ambulatory Care Reporting System, **NOS:** not otherwise specified, **NSTEMI**: non-ST elevation myocardial infarction, **OHIP**: Ontario Health Insurance Plan, **OLIS**: Ontario Laboratories Information System, **RPDB**: Registered Persons Database, **STEMI**: ST elevation myocardial infarction, **TIA**: Transient Ischemic Attack

eTable 3. Length of ICU and Hospital Stay Among Survivors by CKD Stage.

Outcome	**Baseline eGFR Categories, mL/min/1.73 m^2**						**P-Value**
	≥60	**45-59**	**30-44**	**15-29**	**<15 (Non-Dialysis)**	**Dialysis Dependent**	
ICU Length of Stay, Days							
Median (IQR)	2 (1-4)	2 (1-4)	3 (1-5)	3 (1-5)	3 (2-5)	3 (1-5)	<0.001
Hospital Length of Stay, Days							
Median (IQR)	6 (4-12)	8 (4-16)	9 (5-18)	11 (6-21)	12 (6-24)	9 (5-19)	<0.001

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; IQR, 25th-75th percentile interquartile range; SD, standard deviation.

eTable 4. Baseline Characteristics of Individuals with Missing Baseline Outpatient Serum Creatinine Values.

Characteristics	
N	293,861
Age, Years, Mean (SD)	59 (18)
Sex, N (%)	
Female	115,408 (39)
Male	178,453 (61)
Neighborhood Income Quintile, N (%)[a]	
Quintile 1 (Lowest)	71,775 (25)
Quintile 2	62,022 (21)
Quintile 3	56,758 (19)
Quintile 4	52,755 (18)
Quintile 5 (Highest)	48,898 (17)
Rural Residence, N (%)[b]	50,872 (17)
Comorbidities, N (%)	
Coronary Artery Disease	37,245 (13)
Myocardial Infarction	23,885 (8)
Congestive Heart Failure	24,475 (8)
Arrhythmia	16,225 (6)
Stroke	8,679 (3)
Hypertension	89,238 (30)

Diabetes Mellitus	47,281 (16)
COPD	24,831 (9)
Chronic Liver Disease	1,279 (0)
Alcoholism	8,530 (3)
Cancer	48,262 (16)
HIV Infection	691 (0)
Charlson Comorbidity Index Category, N (%)	
≤2	224,918 (77)
3-4	45,532 (15)
≥5	23,411 (8)
ICU Admission Characteristics	
Vasopressor Use, N (%)	61,240 (21)
Mechanical Ventilation, N (%)	177,459 (60)
Sepsis, N (%)	19,384 (7)
Severe Sepsis (including Septic Shock), N (%)	14,340 (5)
Multiple Organ Dysfunction Score (MODS) Category, N (%)	
0	111,535 (38)
1-4	126,400 (43)
5-8	45,953 (16)
9-12	8,925 (3)
≥13	1,048 (0)

Healthcare Utilization Within 1 Year Prior to Index Hospitalization, N (%)	
Emergency Room Visit	158,515 (54)
Prior Hospitalization	53,785 (18)

[a] Neighborhood income quintile missing in 1,653 individuals (0.4% of cohort).

[b] Rural defined as residing in a location with population <10,000 persons, missing in 603 individuals (0.2% of cohort).

Abbreviations: COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus; ICU, intensive care unit; SD, standard deviation.

eTable 5. Baseline Characteristics of the Study Cohort Including Individuals Missing Baseline Outpatient Serum Creatinine Values (Assigned Baseline eGFR of 75 mL/min/1.73 m^2).

Characteristic	Total	Baseline eGFR Categories, mL/min/1.73 m^2					
		≥60	45-59	30-44	15-29	<15 (Non-Dialysis)	Dialysis Dependent
N (%)	824,951	691,068 (84)	63,825 (8)	38,744 (5)	17,207 (2)	3,626 (0)	9,392 (1)
Age, Years, Mean (SD)	67 (15)	64 (15)	77 (10)	78 (10)	77 (11)	72 (13)	66 (14)
Sex, N (%)							
Female	343,698 (42)	278,705 (40)	30,651 (48)	19,870 (51)	8,629 (50)	1,740 (48)	4,103 (39)
Male	481,253 (58)	412,363 (60)	33,174 (52)	18,874 (49)	8,578 (50)	1,886 (52)	6,378 (61)
Baseline Kidney Characteristics							
Creatinine, µmol/L, Median (IQR)	82 (68-102)	75 (64-86)	110 (96-122)	141 (123-158)	210 (180-245)	405 (346-495)	621 (444-815)

eGFR, mL/min/1.73 m^2, Median (IQR)[a]	81 (60-96)	89 (76-100)	53 (49-57)	39 (35-42)	24 (20-27)	12 (9-13)	7 (5-11)
Neighborhood Income Quintile, N (%)[b]							
Quintile 1 (Lowest)	190,331 (22)	158,200 (23)	14,618 (23)	9,296 (24)	4,307 (25)	925 (26)	2,985 (29)
Quintile 2	173,438 (21)	144,393 (21)	13,595 (21)	8,529 (22)	3,814 (22)	791 (22)	2,316 (22)
Quintile 3	161,980 (20)	135,670 (20)	12,628 (20)	7,636 (20)	3,375 (20)	744 (21)	1,927 (19)
Quintile 4	151,837 (18)	128,072 (19)	11,631 (18)	6,777 (18)	2,976 (17)	615 (17)	1,766 (17)
Quintile 5 (Highest)	143,782 (18)	121,638 (18)	11,137 (18)	6,381 (17)	2,668 (16)	538 (15)	1,420 (14)
Rural Residence, N (%)[c]	126,729 (15)	108,537 (16)	9,036 (14)	5,286 (14)	2,174 (13)	457 (13)	1,239 (12)
Comorbidities, N (%)							
Coronary Artery	153,017 (19)	118,896 (17)	16,443 (26)	9,823 (25)	4,299 (25)	744 (21)	2,812 (27)

Disease							
Myocardial Infarction	74,921 (9)	55,909 (8)	7,995 (13)	5,853 (15)	2,962 (17)	512 (14)	1,690 (16)
Congestive Heart Failure	106,976 (13)	65,624 (10)	15,753 (25)	13,348 (34)	7,668 (45)	1,399 (39)	3,184 (30)
Arrhythmia	69,856 (8)	49,494 (7)	9,718 (15)	6,539 (17)	2,839 (17)	318 (9)	948 (9)
Stroke	27,452 (3)	21,468 (3)	2,926 (5)	1,785 (5)	730 (4)	133 (4)	410 (4)
Hypertension	339,668 (41)	258,074 (37)	37,304 (58)	23,928 (62)	11,011 (64)	2,432 (67)	6,919 (66)
Diabetes Mellitus	225,923 (27)	163,139 (24)	25,592 (40)	18,818 (49)	9,856 (57)	2,235 (62)	6,283 (60)
COPD	80,613 (10)	62,733 (9)	8,292 (13)	5,604 (15)	2,586 (15)	376 (10)	1,022 (10)
Chronic Liver Disease	8,435 (1)	6,406 (1)	808 (1)	673 (2)	320 (2)	45 (1)	183 (2)
Alcoholism	20,634 (3)	19,430 (3)	624 (1)	366 (1)	122 (1)	18 (1)	74 (1)
Cancer	210,337 (26)	170,482 (25)	20,130 (32)	11,742 (30)	4,806 (28)	884 (24)	2,293 (22)
HIV Infection	2,195 (0)	1,934 (0)	107 (0)	63 (0)	25 (0)	12 (0)	54 (1)

Charlson Comorbidity Index Category, N (%)							
≤2	551,191 (67)	496,488 (72)	33,828 (53)	14,678 (38)	3,935 (23)	723 (20)	1,539 (15)
3 - 4	169,314 (21)	124,652 (18)	18,896 (30)	14,086 (36)	7,066 (41)	1,410 (39)	3,204 (31)
≥5	104,446 (13)	69,928 (10)	11,101 (17)	9,980 (26)	6,206 (36)	1,493 (41)	5,738 (55)
ICU Admission Characteristics							
Vasopressor Use, N (%)	198,784 (24)	162,133 (23)	17,707 (28)	10,529 (27)	4,568 (27)	898 (25)	2,949 (28)
Mechanical Ventilation, N (%)	540,991 (66)	447,007 (65)	44,519 (70)	27,496 (71)	12,309 (72)	2,570 (71)	7,090 (68)
Sepsis, N (%)	59,560 (7)	45,704 (7)	5,746 (9)	4,094 (11)	2,050 (12)	394 (11)	1,572 (15)
Severe Sepsis (including Septic Shock), N (%)	45,599 (6)	34,112 (5)	4,696 (7)	3,473 (9)	1,824 (11)	353 (10)	1,141 (11)

Multiple Organ Dysfunction Score (MODS) Category, N (%)							
0	268,906 (33)	252,900 (37)	11,562 (18)	3,119 (8)	744 (4)	128 (4)	453 (4)
1-4	375,500 (46)	298,072 (43)	36,010 (56)	24,479 (63)	10,373 (60)	1,737 (48)	4,829 (46)
5-8	149,395 (18)	117,098 (17)	13,363 (21)	8,975 (23)	4,832 (28)	1,351 (37)	3,776 (36)
9-12	28,281 (3)	20,801 (3)	2,682 (4)	2,018 (5)	1,159 (7)	363 (10)	1,258 (12)
≥13	2,869 (0)	2,197 (0)	208 (0)	153 (0)	99 (1)	47 (1)	165 (2)
Healthcare Utilization Within 1 Year Prior to Index Hospitalization, N (%)							
Emergency Room	342,554 (42)	299,956 (43)	40,786 (64)	26,696 (69)	12,774 (74)	2,689 (74)	8,340 (80)

Visit							
Prior Hospitalization	209,257 (25)	157,722 (23)	20,901 (33)	15,047 (39)	7,997 (46)	1,693 (47)	5,897 (56)

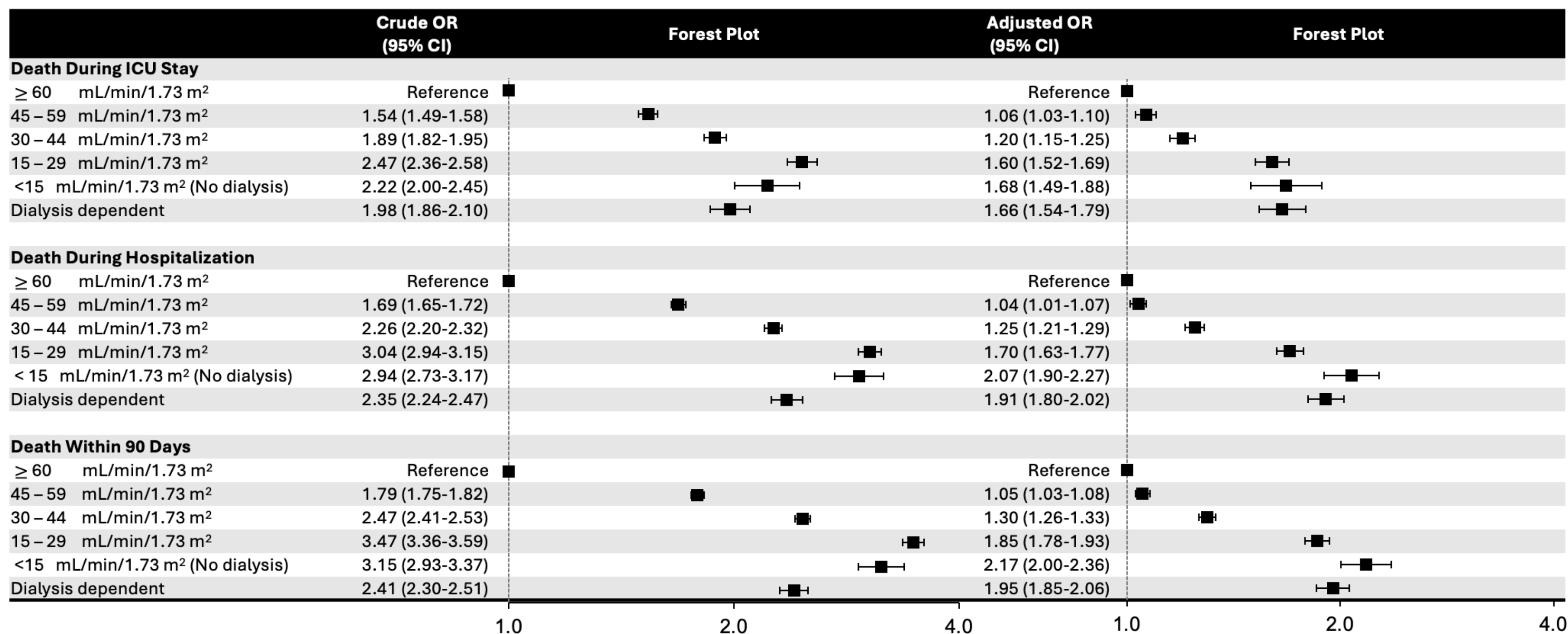
[a] Calculated using the 2021 creatinine-based CKD-EPI equation.[24]

[b] Neighborhood income quintile missing in 3,583 individuals (0.4% of cohort).

[c] Rural defined as residing in a location with population <10,000 persons, missing in 1,596 individuals (0.2% of cohort).

Abbreviations: COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus; ICU, intensive care unit; SD, standard deviation.

eFigure 1. Mortality Risk During ICU Stay, During Hospitalization, and Within 90 Days Following ICU Admission According to Pre-Existing CKD Severity for Sensitivity Analysis Including Individuals Missing Baseline Outpatient Serum Creatinine Values (Assigned Baseline eGFR of 75 mL/min/1.73 m^2).



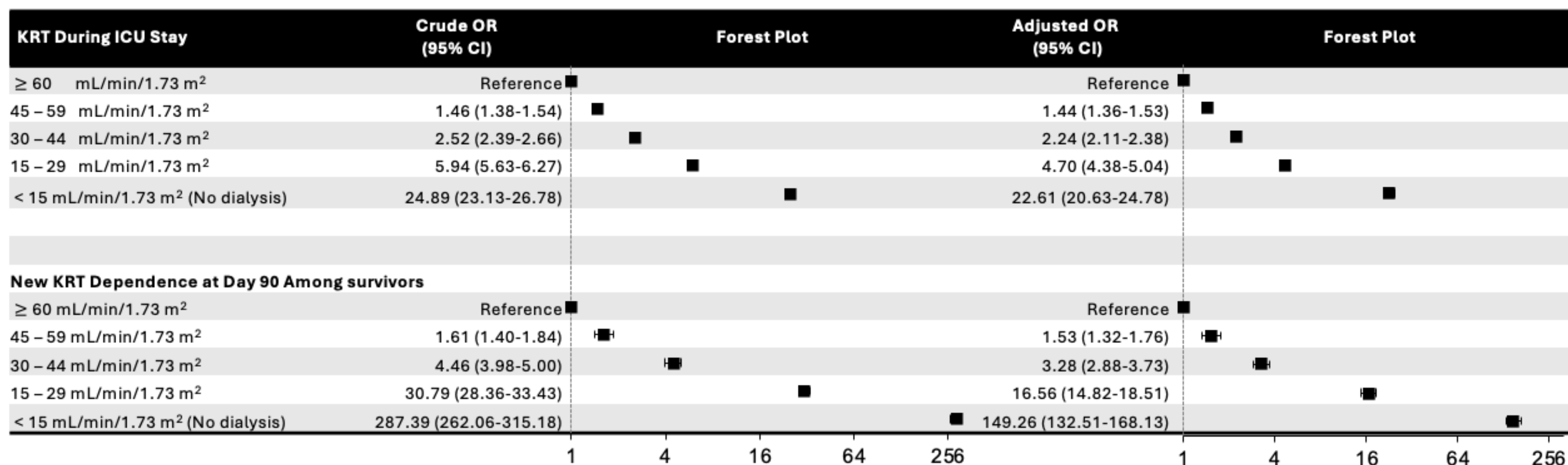
	Crude OR (95% CI)	Forest Plot	Adjusted OR (95% CI)	Forest Plot
Death During ICU Stay				
≥ 60 mL/min/1.73 m²	Reference		Reference	
45 – 59 mL/min/1.73 m²	1.54 (1.49-1.58)		1.06 (1.03-1.10)	
30 – 44 mL/min/1.73 m²	1.89 (1.82-1.95)		1.20 (1.15-1.25)	
15 – 29 mL/min/1.73 m²	2.47 (2.36-2.58)		1.60 (1.52-1.69)	
<15 mL/min/1.73 m² (No dialysis)	2.22 (2.00-2.45)		1.68 (1.49-1.88)	
Dialysis dependent	1.98 (1.86-2.10)		1.66 (1.54-1.79)	
Death During Hospitalization				
≥ 60 mL/min/1.73 m²	Reference		Reference	
45 – 59 mL/min/1.73 m²	1.69 (1.65-1.72)		1.04 (1.01-1.07)	
30 – 44 mL/min/1.73 m²	2.26 (2.20-2.32)		1.25 (1.21-1.29)	
15 – 29 mL/min/1.73 m²	3.04 (2.94-3.15)		1.70 (1.63-1.77)	
< 15 mL/min/1.73 m² (No dialysis)	2.94 (2.73-3.17)		2.07 (1.90-2.27)	
Dialysis dependent	2.35 (2.24-2.47)		1.91 (1.80-2.02)	
Death Within 90 Days				
≥ 60 mL/min/1.73 m²	Reference		Reference	
45 – 59 mL/min/1.73 m²	1.79 (1.75-1.82)		1.05 (1.03-1.08)	
30 – 44 mL/min/1.73 m²	2.47 (2.41-2.53)		1.30 (1.26-1.33)	
15 – 29 mL/min/1.73 m²	3.47 (3.36-3.59)		1.85 (1.78-1.93)	
<15 mL/min/1.73 m² (No dialysis)	3.15 (2.93-3.37)		2.17 (2.00-2.36)	
Dialysis dependent	2.41 (2.30-2.51)		1.95 (1.85-2.06)	

In this sensitivity analysis, ICU patients with missing baseline serum creatinine were assumed to have preserved kidney function, set to 75 mL/min/1.73 m^2, and included in the full cohort (N=824,951).

Crude and adjusted ORs (95% CIs) for the association between CKD severity and death are shown above. Adjusted models adjusted for the following additional variables: age, sex, rural residence, neighbourhood income quintile, comorbidities (coronary artery disease, myocardial infarction, diabetes mellitus, hypertension, congestive heart failure, arrhythmia, stroke, chronic liver disease, chronic obstructive pulmonary disease, HIV infection, cancer, and alcoholism), healthcare utilization (nephrology consults, emergency room visits, and hospitalizations) within one year prior to index, use of vasopressors on ICU admission, use of mechanical ventilation on ICU admission, severity of illness according to MODS (but subtracting the MODS renal component), sepsis, and severe sepsis (including septic shock).

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus; ICU, intensive care unit; MODS, Multiple Organ Dysfunction Score; OR, odds ratio

eFigure 2. Kidney Replacement Therapy Initiation During ICU Stay and Dependence at 90 Days Following ICU Admission According to Pre-Existing CKD Severity for Sensitivity Analysis Including Individuals Missing Baseline Outpatient Serum Creatinine Values (Assigned Baseline eGFR of 75 mL/min/1.73 m^2).



KRT During ICU Stay	Crude OR (95% CI)	Adjusted OR (95% CI)
≥ 60 mL/min/1.73 m²	Reference	Reference
45 – 59 mL/min/1.73 m²	1.46 (1.38-1.54)	1.44 (1.36-1.53)
30 – 44 mL/min/1.73 m²	2.52 (2.39-2.66)	2.24 (2.11-2.38)
15 – 29 mL/min/1.73 m²	5.94 (5.63-6.27)	4.70 (4.38-5.04)
< 15 mL/min/1.73 m² (No dialysis)	24.89 (23.13-26.78)	22.61 (20.63-24.78)
New KRT Dependence at Day 90 Among survivors		
≥ 60 mL/min/1.73 m²	Reference	Reference
45 – 59 mL/min/1.73 m²	1.61 (1.40-1.84)	1.53 (1.32-1.76)
30 – 44 mL/min/1.73 m²	4.46 (3.98-5.00)	3.28 (2.88-3.73)
15 – 29 mL/min/1.73 m²	30.79 (28.36-33.43)	16.56 (14.82-18.51)
< 15 mL/min/1.73 m² (No dialysis)	287.39 (262.06-315.18)	149.26 (132.51-168.13)

In this sensitivity analysis, ICU patients with missing baseline serum creatinine were assumed to have preserved kidney function, set to 75 mL/min/1.73 m^2, and included in the full cohort (N = 814,470).

Crude and adjusted ORs (95% CIs) for the association between CKD severity and kidney replacement therapy outcomes for ICU patients with no history of dialysis prior to ICU admission. Adjusted models adjusted for the following additional variables: age, sex, rural residence, neighbourhood income quintile, comorbidities (coronary artery disease, myocardial infarction, diabetes mellitus, hypertension, congestive heart failure, arrhythmia, stroke, chronic liver disease, chronic obstructive pulmonary disease, HIV infection, cancer, and alcoholism), healthcare utilization (nephrology consults, emergency room visits, and hospitalizations) within one year prior to index, use of vasopressors on ICU admission, use of mechanical ventilation on ICU admission, severity of illness according to MODS (but subtracting the MODS renal component), sepsis, and severe sepsis (including septic shock).

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus; ICU, intensive care unit; MODS, Multiple Organ Dysfunction Score; OR, odds ratio.

CHAPTER 4: INTEGRATED DISCUSSION

4.1 Summary of Findings

This thesis project aimed to evaluate the performance of commonly used ICU predictive scoring systems and assess the association between CKD and clinical outcomes after ICU admission through two studies: a systematic review of published studies evaluating the prognostic performance of ICU scoring systems for mortality prediction among individuals with pre-existing kidney disease; and a large population-based cohort study assessing ICU outcomes across the spectrum of CKD severity using real-world data from ICES in Ontario, Canada.

Systematic Review

Only 12 studies were identified that evaluated the prognostic performance of APACHE II, APACHE III, SAPS II, SAPS III, and SOFA scores among patients with CKD, ESKD on dialysis, or kidney transplant recipients. A striking finding was the disproportionate emphasis on ESKD populations and the scarce availability of data for non-dialysis dependent CKD individuals, which constitutes the largest kidney disease subgroup in both the general and ICU populations (**Chapter 2**). Only 51 patients with CKD were identified across all included studies out of a total of 578,027 patients admitted to ICU, highlighting a major evidence gap.

Overall, the discrimination metrics were acceptable for most scoring systems in the ESKD population (**Chapter 2**). However, APACHE II, APACHE III, SAPS II, and SOFA overestimated mortality risk in ESKD patients as reflected by the low calibration slopes and standardized mortality ratios.

In contrast, the predictive performance of the same scoring systems in kidney transplant recipients exhibited both poor discrimination and inconsistent calibration, with both over- and underestimation of mortality risk reported depending on the model and cohort. The included studies demonstrated substantial methodological heterogeneity and limitations, including small sample sizes, incomplete or inconsistent calibration reporting, and moderate to high risk of bias. These limitations further suggest a restricted clinical utility of the commonly used ICU scoring systems in ESKD and transplant recipient subgroups, highlighting the need for further kidney specific validation studies on prognostic and predictive tools in the ICU.

Population-Based Cohort Study

The population-based ICES cohort study complements the systematic review by providing real-world estimates of ICU outcomes across CKD stages. Among the 531,090 adults admitted to ICU across Ontario, one in four had baseline CKD (**Chapter 3**). This highlights the vulnerability of individuals with pre-existing kidney disease to acute illness, hemodynamic instability, cardiovascular events, and infections. Mortality increased with worsening CKD up to non-dialysis dependent stage 5 CKD, defined by an eGFR of less than 15 mL/min/1.73 m^2, at which point individuals experienced more than twofold higher odds of mortality compared to those without CKD (**Chapter 3**). Notably, individuals on maintenance dialysis had lower mortality risk compared to non-dialysis-dependent stage 5 CKD and stage 4 CKD. This phenomenon may be attributable to dialysis-dependent ICU patients representing a distinct clinical subset. The underlying explanations are not yet fully understood but may include more

effective management of fluid status and metabolic disturbances through dialysis, a greater propensity to admit patients receiving maintenance dialysis to the ICU, and the possibility that those on chronic dialysis who are ultimately transferred to the ICU constitute a relatively healthier subgroup at baseline within the broader dialysis population, as ICU-level care may not align with the goals of care for the more severely ill dialysis patients.

In contrast, KRT outcomes illustrated a more significant association by CKD stages. The increased odd ratios for KRT relative to no CKD reinforces the narrow physiologic reserve of individuals with advanced CKD, for whom acute illness stressors can rapidly precipitate sustained kidney failure. Similarly, length of stay increased with CKD severity, suggesting higher complexity of care and maybe slower recovery trajectories. However, individuals on maintenance dialysis had slightly shorter lengths of stay than those with advanced non-dialysis CKD. This pattern likely reflects the same factors contributing to the observed phenomenon of lower mortality in chronic dialysis patients, including selective ICU admission of comparatively healthier dialysis population. Collectively, these findings illustrate a dynamic and severity-dependent relationship between CKD and ICU outcomes. This is not captured by the commonly used scoring systems in the ICU. Hence, CKD adjusted predictive models, or the incorporation of pre-existing kidney disease status, may improve the accuracy of mortality prediction and prognostication for this subgroup when admitted to the ICU.

4.2 Interpretation in the Context of Related Literature

A major theme emerging from our systematic review findings is the persistent difficulty in identifying and accurately classifying CKD across the acute care research field. Much of

the existing ICU literature groups kidney patients into broad categories (e.g., CKD, non-dialysis CKD, ESKD, and AKI) without meaningful clinical stratification by CKD stages. This lack of granularity limits interpretation of outcomes and obscures stage specific mortality risk. These limitations likely reflect challenges in accurately capturing true baseline kidney function and the limited availability of preadmission outpatient laboratory measurements, which can lead to misclassification of CKD.[67]

Our population-based cohort study contributes uniquely by leveraging eGFR based definition of CKD using outpatient creatinine measurements to classify CKD severity prior to ICU admission. In contrast, most existing critical care cohort studies relied on diagnostic codes only to report the CKD prevalence in the ICU. For instance, a study reported CKD prevalence in the ICU around 4%[68], despite evidence that 12% or more of adults in the general population are affected by CKD and have higher risks for ICU admission.[69,70] Our cohort study identified CKD in 25% of ICU admissions, consistent with studies demonstrating that ICD coding lacks sensitivity for CKD identification.[71,72] By incorporating outpatient eGFR laboratory values, our findings reveal a substantially larger and previously underestimated CKD population entering the ICU.

Non-dialysis CKD patients have been shown to experience high rates of critical illness in existing literature, consistent with our findings demonstrating worse outcomes with increasing CKD severity.[73] The risk is strongly driven by comorbid conditions, especially congestive heart failure and cardiovascular disease, which were proven to increase the risk of hospitalization with critical illness along demographic factors in patients with stages 3 and 4 CKD.[73] These observations complement our findings that mortality and dialysis

dependence increase with worsening CKD stages in non-dialysis patients, and highlight the important role of multimorbidity in shaping outcomes for CKD patients.

Similarly, dialysis-dependent ESKD patients represent a high-risk population with heterogeneous outcomes.[74,75] While they are often admitted for sepsis, cardiac events, or cardiac arrest, their mortality risk is often overestimated by clinicians and the predictive scoring systems.[18,76] Several studies have shown that dialysis itself is not an independent predictor of death in the ICU.[18,77] Our findings align with this pattern, showing that CKD stages rather than dialysis status was more strongly associated with mortality and kidney-related outcomes following ICU admission.

Furthermore, evidence suggests that frailty markers, rather than the acute illness severity alone, are the primary determinants of long-term outcomes in dialysis-dependent patients.[74] Even in high-risk settings such as sepsis or viral pneumonia, chronic dialysis patients do not consistently show worse survival rates compared to their counterparts without dialysis dependence.[75,78,79] Together, these findings reinforce that dialysis patients should not be considered a uniformly frail group in critical care setting; rather, they represent a spectrum of risk shaped by comorbidity patterns, functional status, and time since dialysis initiation.

Our systematic review further highlights important gaps in prognostic guidelines for CKD populations admitted to the ICU. Although scoring systems such as APACHE II/III, SAPS II/III, and SOFA remain widely used, their performance metrics are inconsistent in CKD and ESKD populations. Some studies have documented overestimation of mortality in dialysis-

dependent ESKD patients[18,20,77,80,81], while others have reported inconsistent findings.[82,83] Similar limitations have been reported among kidney transplant recipients, where commonly used ICU scoring systems demonstrated poorer performance metrics for mortality prediction.[32,84,85] Together, the existing literature and our findings converge on several critical themes: the importance of accurate CKD staging, integration of outpatient kidney function data, and consideration of disease severity and frailty when interpreting ICU outcomes and applying prognostic tools in critical care.

4.3 Strengths and Limitations

This thesis examined the association between CKD severity and ICU outcomes by synthesizing evidence through a systematic review and contextualizing these findings through a population-based retrospective cohort study specific to Ontario, Canada. The systematic review provides a structured synthesis of the existing validation studies of the ICU predictive scoring systems, while the population-based retrospective cohort study offers contemporary data and real-world estimates of ICU outcomes across CKD stages.

The ICES-based retrospective cohort study is a major strength of this thesis. The large, population-based sample provides excellent statistical power to characterize associations between CKD severity and ICU outcomes. Because outpatient baseline serum creatinine values were available, CKD could be classified by eGFR into clinically meaningful stages rather on relying on diagnostic codes. This allowed a nuanced assessment of risks across the CKD severity spectrum from preserved kidney function to maintenance dialysis. The

use of linked provincial health registries ensured a near complete capture of mortality, KRT use, and length of stay outcomes.

Nevertheless, the nature of the observational study limits causal inference. Although extensive adjustments for measured confounders was performed (**Chapter 1, Figure 1**), residual confounders cannot be excluded. An additional limitation is that CKD was defined exclusively using eGFR. Although we sought to include albuminuria in the definition of baseline CKD, outpatient measurements were unavailable for the majority of patients in the cohort. Furthermore, those with available albuminuria data were not representative of the overall population, precluding its inclusion without introducing selection bias.

The systematic review brings complementary strengths to this thesis. The broad search across multiple databases maximizes the likelihood of capturing relevant studies, and the structured data extraction and interpretation allowed the comparison of performance across variety of commonly used ICU scoring systems. However, many of the included studies were not designed to validate the predictive scoring systems in individuals with pre-existing kidney disease. Moreover, calibration metrics were not always reported, and estimates were heterogeneous, which limited our capacity to perform quantitative pooling and derive a pooled effect. Hence, the systematic review could not provide robust conclusions about how common ICU scoring system perform in the CKD population, which highlights a major unresolved knowledge gap.

Overall, the systematic review shows that predictive scoring tools are inaccurate when used for ESKD and transplant recipients and that the existing evidence for CKD population

is very limited. The ICES cohort study then addresses part of this gap by evaluating the ICU outcomes across the different CKD stages in a large population-based study.

4.4 Implication for Future Research in Critical Care

Applying the *Donabedian SPO* framework (**Chapter 1**) provides a unifying lens through which we interpret the implications of our findings. At the structural level, the commonly used ICU predictive scoring systems are not fully calibrated for non-dialysis CKD, ESKD on dialysis, or kidney transplant populations. These limitations could constrain accurate risk stratification, ICU triage, and clinical decision making. By integrating evidence from our systematic review and population-based cohort study, this thesis demonstrates how limitations in prognostic tools (structure) and related clinical decision making (process) could be associated with significant differences in patient outcomes and predicted mortality risks. Through this framework, we emphasize that improving critical care delivery for CKD populations requires further investigations to address measurement gaps and refine prognostic processes, with particular emphasis on mortality risk estimation rather than reliance on dialysis status alone during ICU admission decisions. Building on this foundation, our findings identify opportunities to improve prognostication for clinicians, support more informed ICU triage and care decisions, and guide critical care system design for patients with CKD, ESKD, and kidney transplant recipients.

First, there is a clear need to validate ICU mortality prediction tools that incorporate baseline kidney function. It has been shown that existing scoring systems tend to overestimate mortality in ESKD and perform poorly or inconsistently in kidney transplant recipients (**Chapter 2**). Previous studies have reported that over- or underestimation of mortality is expected when these scores are applied to specific populations and have

advocated for population-specific models in this regard[43]. However, such approaches remain largely agnostic to baseline CKD and have not been specifically adapted or validated for populations with CKD or ESKD, in whom baseline kidney function measures are inherently constrained.

In contrast, the performance of these scoring systems in non-dialysis CKD populations remains largely unknown, representing a key knowledge gap and an important direction for future work using ICES data. Our findings reinforce this need and suggest that future prognostic tools should incorporate outpatient baseline kidney function and dialysis modality to better reflect underlying kidney disease. An important next step for this project is to evaluate the discrimination and calibration of commonly used ICU scoring systems among patients with pre-existing CKD using population-based data from ICES. To our knowledge, no prior studies have formerly validated these commonly used ICU scoring systems in non-dialysis CKD population. This validation study is essential to ensure equitable application of ICU prognostic tools and appropriate resource allocation for patients with pre-existing CKD within the critical care system. This work would potentially provide an opportunity to assess whether recalibration or CKD specific modification of existing ICU scores improves their prognostic performance in this specific population.

Second, our cohort study revealed that ICU admission represents a pivotal moment in kidney disease trajectory for patients with advanced CKD. Among survivors, dialysis dependence after ICU admission was common (45% in stage 5 CKD and 8.2% in stage 4 CKD) by day 90 following ICU admission. These results echo findings by *Rimes-Stigare et al.*, showing that CKD carries a high-risk of progression to ESKD requiring

dialysis or kidney transplant.[68] Hence, future research should therefore aim to refine post-ICU kidney prognostication, including models that estimate not only survival but also likelihood of kidney recovery, dialysis dependence, and long-term care needs after ICU admission.

Third, improving early detection and staging of CKD remains essential. The limited sensitivity of ICD codes stresses that future research should focus on incorporation of outpatient laboratory data, particularly creatinine and albuminuria measurements, to improve CKD ascertainment in acute care research.[71,72]

Finally, all of the above suggested implications highlight the need for a structured advance care planning and improved prognostic communication in advanced CKD and ESKD patients. Although chronic dialysis patients have been shown to value realistic understanding of their prognosis, many clinicians do not routinely provide prognostic estimates or incorporate them into shared decision-making, despite the high morbidity and mortality in this population.[76,86,87] The heterogeneous outcomes observed among the dialysis population, ranging from survival advantages in septic shock to high readmission rates and comorbidity-related mortality, further reinforces the need for nuanced and individualized conversations with these patients. Embedding prognostication tools and standardized advanced care planning into outpatient CKD and dialysis clinics could enhance alignment of care with patient goals and subsequently improve the quality of care for this population.

4.5 Conclusion

Overall, we examined two dimensions of the intersection between CKD and critical illness as illustrated by our assessment of how well the commonly used ICU predictive scoring systems perform in patients with pre-existing kidney disease, and how ICU outcomes vary across the CKD severity stages in a large population-based cohort. Together, these findings improve our understanding or risk assessment among kidney patients admitted to the intensive care and highlight opportunities to strengthen prognostication, clinical decision-making, and research tools.

The systematic review and meta-analysis demonstrated that commonly used ICU scoring systems have been inconsistently evaluated in kidney disease populations and often exhibiting reduced discrimination power or miscalibration. These limitations suggest that the chronic physiological changes inherent to CKD and ESKD patients may not be fully accounted for in these models, which were originally developed for the general ICU population. Thus, mortality risks may be overestimated in the CKD population. This calls for the need for kidney-specific adaptation of these tools.

In parallel, the ICES cohort study provided new population-level evidence on outcomes following ICU admission across the CKD stages. Increasing CKD severity was associated with progressively higher risk of short-term and long-term mortality, as well as other kidney outcomes among survivors. Yet, patients with stage 5 CKD on dialysis showed lower mortality risk when compared to non-dialysis stage 5 CKD and stage 4 CKD patients. This reinforces emerging evidence that dialysis dependence alone is not an indicator of poor prognosis in the acute setting. These findings are crucial to a

literature that rarely distinguishes ICU outcomes by CKD stages and help clarify prognostic expectations for patients, families, and clinicians.

In summary, this project provides integrated evidence that enhances the understanding of critical illness outcome in CKD patients. It also challenges assumptions embedded in commonly used ICU scoring systems and lays the groundwork for improving prognostication and care planning for a growing and medically complex patient population. Future work informed by these findings has the potential to improve clinical decision-making, guide resource allocation, and ultimately improve the quality of critical care delivered to patients living with kidney disease.

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APPENDIX

Journal Submission Confirmation Emails

Manuscript 1: Performance of ICU Scoring Systems in Patients with Pre-Existing Kidney Disease: A Systematic Review and Meta-Analysis

Submission Confirmation

Thank you for your submission

Submitted to	Kidney International Reports
Manuscript ID	KIR-01-26-0217
Title	Performance of ICU Scoring Systems in Patients with Pre-Existing Kidney Disease: A Systematic Review and Meta-Analysis
Authors	El Wadia, Hajar Karim, Marisha Buh, Amos Kabli, Abdulghani O Biyani, Nandini Shorr, Risa Lee, Inok Fremont, Deena Wald, Ron English, Shane W Silver, Samuel Akbari, Ayub Knoll, Greg Clark, Edward Hundemer, Gregory
Date Submitted	28-Jan-2026

Manuscript 2 : Severity of Chronic Kidney Disease and Outcomes Following Admission to the Intensive Care Unit

26-Jan-2026

Dear Dr. Hundemer:

Your manuscript entitled "Severity of Chronic Kidney Disease and Outcomes Following Admission to the Intensive Care Unit: A Population-Based Cohort Study" has been successfully submitted online and is presently being given full consideration for publication in Kidney International.

Your manuscript ID is KI-01-26-0186.

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