MAJOR ADVERSE EVENTS IN CRITICALLY ILL PATIENTS WITH ACUTE RESPIRATORY DISTRESS SYNDROME

by

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ABSTRACT

Acute kidney injury (AKI) is common among patients with COVID-19 or sepsis. The incidence of AKI may increase when these patients develop acute respiratory distress syndrome (ARDS), which is often associated with poorer patient outcomes and higher mortality rates. Major adverse kidney events (MAKEs) - a composite of the need for renal replacement therapy (RRT), a decline in eGFR of <75% from baseline, or all-cause mortality - are considered a reliable long-term measure of AKI's impact on patient outcomes.

This thesis aimed to evaluate the existing evidence regarding the incidence and risk factors of AKI in COVID-19 patients with ARDS. Additionally, it sought to determine the incidence and clinical risk factors of MAKE-365 in patients with AKI, both with and without COVID-19 ARDS. The thesis also examined the associations between novel kidney biomarkers (including plasma Cystatin C, urinary NGAL, urinary [TIMP-2]*[IGFBP-7], and urinary CCL-14) and MAKE-365 in ICU patients with sepsis and AKI. Lastly, it evaluated the predictive capabilities of these kidney biomarkers in combination with clinical predictive models for MAKE-365.

Firstly, a systematic review and meta-analysis were conducted to examine the incidence and risk factors of AKI in COVID-19 patients with ARDS. This review, which included 31 studies, found a higher incidence of AKI in COVID-19 patients with ARDS compared to those without. The study identified several risk factors associated with worse outcomes, including advanced age, male gender, and pre-existing conditions such as hypertension, diabetes, obesity, and CKD.

Secondly, a retrospective cohort study was carried out on ARDS patients to assess the occurrence of MAKEs up to 365 days post-ICU admission in both non-COVID-19 and COVID-19 cohorts. The incidence of MAKE-365 was more common in the non-COVID-19 cohort. CKD and high bilirubin levels were identified as predictors for MAKE-365 in both cohorts, with additional risk factors such as older age and diabetes in the COVID-19 cohort and lower albumin levels in the non-COVID-19 cohort.

Finally, another retrospective cohort study was conducted to assess MAKE-365 development and evaluate the predictive ability of kidney biomarkers for MAKE-365 in septic patients, regardless of ARDS status. The prevalence of MAKE-365 was higher in septic patients with AKI, irrespective of ARDS status. Among the evaluated biomarkers, urinary [TIMP-2]*[IGFBP-7] showed the most promise for predicting MAKE-365, particularly when combined with the clinical prediction model.

Overall, this thesis underscores the importance of identifying patients at risk of MAKE-365 development in critically ill patients using clinical predictors in conjunction with kidney biomarkers. However, the utility of these biomarker combinations must be confirmed in larger, external prospective cohorts to ensure the findings' generalizability and specificity to the patient population used in this study.

LIST OF PUBLICATIONS

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TABLE OF CONTENTS

1. INTRODUCTION....1
1.1 BACKGROUND....2
1.2 PATHOPHYSIOLOGY of AKI....6
1.3 ARDS AND KIDNEY DYSFUNCTION....10
1.4 COVID-19 AND KIDNEY DYSFUNCTION....14
1.5 DIAGNOSIS of AKI....17
1.6 KIDNEY BIOMARKERS....18
1.6.1 CYSTATIN C....19
1.6.2 NGAL....20
1.6.3 TIMP-2 and IGFBP-7....22
1.6.4 CCL-14:....27
1.7 PREVENTION AND TREATMENT....31
1.8 CONCLUSION....34
1.9 HYPOTHESES....35
1.10 AIMS....35
1.11 OBJECTIVES....36
2 INCIDENCE AND RISK FACTORS OF ACUTE KIDNEY INJURY IN COVID-19 PATIENTS WITH AND WITHOUT ACUTE RESPIRATORY DISTRESS SYNDROME: A SYSTEMATIC REVIEW....37
2.1 INTRODUCTION....37
2.2 ABSTRACT....39
2.3 BACKGROUND....41
2.4 MATERIALS AND METHODS....43
2.4.1 Study Selection....44
2.4.2 Data Extraction and Quality Assessment....44
2.4.3 Data Synthesis and Analysis....45
2.5 RESULTS:....45
2.5.1 Study selection....45
2.5.2 Study characteristics....47
2.5.3 Quality Assessment and Risk of Bias....50
2.5.4 Results of individual studies....51
2.5.5 Synthesis of results....58
2.6 DISCUSSION:....62
2.7 CONCLUSION....66

2.8 SUMMARY OF THE CHAPTER....66
3 INCIDENCE OF MAJOR ADVERSE KIDNEY EVENTS AFTER ICU ADMISSION IN COVID-19 AND NON-COVID-19 ARDS PATIENTS....68
3.1 INTRODUCTION....68
3.2 BACKGROUND....70
3.3 HYPOTHESIS....72
3.4 AIM....72
3.5 METHODS....73
3.5.1 Study Design and Setting:....73
3.5.2 Eligibility criteria:....73
3.5.3 Participants:....74
3.5.4 Study outcomes and definitions:....74
3.5.5 Data collection:....75
3.5.6 Follow-up and study period:....78
3.5.7 Data Management:....78
3.5.8 Statistical analysis:....79
3.6 RESULTS....80
3.6.1 Characteristics of ARDS patients in COVID-19 vs non-COVID-19 groups 81
3.6.2 Characteristics of AKI patients in both groups....85
3.6.3 The incidence of MAKEs:....89
3.6.4 Individual MAKE outcome:....91
3.6.5 Factors Associated with MAKEs:....93
3.6.6 Time-to-Event of individual MAKE outcome:....98
3.6.7 The eGFR and mortality after initiating RRT:....100
3.6.8 Factors Associated with Acute Kidney Injury:....102
3.6.9 Renal recovery:....105
3.7 DISCUSSION....108
3.8 CONCLUSION....118
3.9 SUMMARY OF THE CHAPTER....119
4 KIDNEY BIOMARKERS AND MAJOR ADVERSE KIDNEY EVENTS IN CRITICALLY ILL PATIENTS WITH SEPSIS IN THE PRESENCE OR ABSENCE OF ACUTE RESPIRATORY DISTRESS SYNDROME....120
4.1 INTRODUCTION....120
4.2 BACKGROUND....122
4.3 HYPOTHESIS....125
4.4 AIMS....125

4.5 METHODS 126
4.5.1 Study Design and Setting: 126
4.5.2 Ethical Approvals: 126
4.5.3 Participants: 127
4.5.4 Eligibility criteria: 127
4.5.5 Study Outcomes: 128
4.5.6 Definitions: 128
4.5.7 Data Collection: 129
4.5.8 Follow-up and study period: 131
4.5.9 Data Management: 131
4.5.10 Patient Sample Processing: 132
4.5.11 Biomarker assays: 132
4.5.12 Statistical analysis: 137
4.6 RESULTS 139
4.6.1 Characteristics of sepsis patients with and without ARDS: 140
4.6.2 Incidence of MAKEs in sepsis patients with or without MAKE-365: 143
4.6.3 Characteristics of sepsis patients with or without MAKE-365: 144
4.6.4 Kidney Biomarkers in sepsis patients with or without MAKEs: 146
4.6.5 Biomarker Performance: 149
4.6.6 Optimal cut-off values of Kidney biomarkers: 152
4.6.7 Time-to-event of MAKE outcome: 154
4.7 DISCUSSION 155
4.8 CONCLUSION 165
4.9 SUMMARY OF THE CHAPTER 166
5 GENERAL DISCUSSION 167
5.1 AKI in COVID-19 PATIENTS (with or without ARDS) 169
5.2 MAJOR ADVERSE KIDNEY EVENTS in PATIENTS WITH ARDS 173
5.3 KIDNEY BIOMARKERS FOR PREDICTING MAKE-365 176
5.4 STRENGTHS AND LIMITATION 178
5.4.1 STRENGTHS 178
5.4.2 LIMITATIONS 178
5.5 SUGGESTIONS FOR FUTURE WORK 179
5.6 CONCLUSION 181
6 LIST OF REFERENCES 183
7 LIST OF APPENDICES 226

LIST OF FIGURES

Figure 1.1. AKI conceptual model, adapted from Murray et al. (2008). 3

Figure 1.2. Basic physiologic mechanisms of the kidney and the processes involved in urine formation. Adapted from Karki (2017). 6

Figure 1.3. ARDS and kidney function. Adapted from Husain-Syed et al. (2016).....13

Figure 1.4. Proposed mechanistic involvement of TIMP-2 and IGFBP-7 in AKI development. Adapted from Kashani et al. (2013). 24

Figure 1.5. Proposed mechanism of CCL14. Adapted from Hoste et al. (2020). 29

Figure 2.1. PRISMA flow diagram of included studies. 46

Figure 2.2. Funnel plot for detection of publication bias. 51

Figure 2.3. Forest plot of pooled AKI incidence in overall cohorts. 59

Figure 2.4. Forest plot of the pooled AKI incidence showing the increased rate in ARDS (A) compared to non-ARDS (B) cohorts. 60

Figure 2.5. Forest plot demonstrating the need for RRT in ARDS (A) compared with non-ARDS (B) COVID-19 cohort. 61

Figure 2.6. Forest plot for mortality risk among patients with AKI associated with COVID-19. 61

Figure 3.1. Modified CONSORT Diagram. 80

Figure 3.2. Kaplan-Meier Curves for Time to Event of Individual MAKE Outcome....99

Figure 3.3 Comparison of Median eGFR on Day 1 and Day 365 Following ICU Admission in Patients who Received RRT within 30 days. 102

Figure 4.1. Representative standard curve for human cystatin C ELISA. 133

Figure 4.2. Representative standard curve for human NGAL ELISA. 134

Figure 4.3. Representative standard curve for human CCL-14 ELISA. 136

Figure 4.4. Nephrocheck® Test Preparation Process 137
Figure 4.5. Modified CONSORT Diagram for the study.....139
Figure 4.6. Boxplots of kidney biomarkers in patients with vs without MAKE-365...148
Figure 4.7. The area under the ROC curve results for the different kidney biomarkers alone to predict MAKE-365 in sepsis patients. 150
Figure 4.8 The area under the ROC curve results for the combination of plasma Cystatin C (A), urinary NGAL (B), urinary CCL-14 (C), or urinary [TIMP-2]*[IGFBP-7] (D) with the Clinical model for the prediction of MAKE-365 in sepsis patients. 151
Figure 4.9 The area under the ROC curve for optimal cut-off values of kidney biomarkers to predict MAKE-365 in patients with sepsis.....153
Figure 4.10. Kaplan-Meier curves of the Time to Event of MAKEs at 365 days in sepsis patients with AKI and ARDS or without ARDS. 154

LIST OF TABLES

Table 1.1. ARDS Berlin definition 11

Table 1.2. KDIGO classification system for AKI development. Adapted from Kellum et al. (2012). 17

Table 2.1. Characteristics of the included studies in patients with COVID-19. 48

Table 2.2. Outcomes of the included studies in patients with COVID-19. 52

Table 3.1. Data collected 77

Table 3.2. The demographic and clinical characteristics of COVID-19 vs non-COVID-19 groups 81

Table 3.3. Demographic and clinical characteristics of AKI patients in the COVID-19 vs non-COVID-19 groups. 86

Table 3.4. The incidence of MAKEs outcome and cause of MAKEs in COVID-19 vs non-COVID-19 groups 90

Table 3.5. The incidence of individual MAKE outcome during one-year follow-up in COVID-19 vs non-COVID-19 groups 92

Table 3.6. Binomial logistic regression analysis of factors associated with MAKE-30 in COVID-19 vs non-COVID-19 groups 94

Table 3.7. Binomial logistic regression analysis of factors associated with MAKE-90 in COVID-19 vs non-COVID-19 groups 95

Table 3.8. Binomial logistic regression analysis of factors associated with MAKE-180 in COVID-19 vs non-COVID-19 groups 96

Table 3.9. Binomial logistic regression analysis of factors associated with MAKE-365 in COVID-19 vs non-COVID-19 groups 97

Table 3.10. Comparisons between patients who received RRT and those who did not within 30 days in the COVID-19 group 100
Table 3.11. Comparisons between patients who received RRT and those who did not within 30 days in the non-COVID-19 group 101
Table 3.12. Binomial logistic regression analysis of factors associated with AKI in the COVID-19 vs non-COVID-19 group 104
Table 3.13. Renal recovery of AKI patients at hospital discharge in both group 105
Table 3.14. Incidence of AKI and MAKE-365 across ARDS severity in COVID-19 group 106
Table 3.15. Incidence of AKI and MAKE-365 across ARDS Severity in non-COVID-19 group 107
Table 3.16 Incidence of MAKE among ARDS patients with mainly respiratory infection 107
Table 4.1. Data collected through PICS 130
Table 4.2. The demographic and clinical characteristics of sepsis patients with and without ARDS. 141
Table 4.3. The incidence of MAKEs outcome among the AKI patients in both cohorts. 143
Table 4.4. Characteristics of sepsis patients with and without MAKE-365. 145
Table 4.5. Kidney biomarkers in patients with and without MAKE-30.....147
Table 4.6. Kidney biomarkers in patients with and without MAKE-180.....147
Table 4.7. Kidney biomarkers in patients with and without MAKE-365.....147
Table 4.8. The accuracy of the optimal cut-offs for kidney biomarkers to predict MAKE-365 in critically ill patients.....152

LIST OF ABBREVIATIONS

AKI	Acute kidney injury
ARF	Acute Renal Failure
CKD	Chronic Kidney Disease
ESRD	End-Stage Renal Disease
RRT	Renal Replacement Therapy
ADQI	Acute Dialysis Quality Initiative
RIFLE	Risk, Injury, Failure, Loss of Function and End-stage Renal Disease
AKIN	Acute Kidney Injury Network
KDIGO	Kidney Disease: Improving Global Outcomes
ICU	Intensive Care Unit
MAKE	Major Adverse Kidney Event
eGFR	estimated Glomerular Filtration Rate
SEA	Southeast Asia
SOFA	Sequential Organ Failure Assessment
APACHE II	Acute Physiology and Chronic Health Evaluation II
GFR	Glomerular Filtration Rate
MAP	Mean Arterial Pressure
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
ATP	Adenosine Triphosphate
ARDS	Acute Respiratory Distress Syndrome
FiO_2	Fraction of Inspired Oxygen
PEEP	Positive End-Expiratory Pressure
PaO_2	Partial Pressure of Arterial Oxygen.
IHD	Intermittent Haemodialysis
CRRT	Continuous Renal Replacement Therapy
COVID-19	Coronavirus Disease
IL-6	Interleukin 6
TNFα	Tumour Necrosis Factor-alpha
CRP	C-Reactive Protein
NGAL	Neutrophil Gelatinase-Associated Lipocalin

SIRS	Systemic Inflammatory Response Syndrome
TIMP-2	Tissue Inhibitor of Metalloproteinase-2
IGFBP-7	Insulin-Like Growth Factor-Binding Protein-
L-FABP	Liver-type Fatty Acid-Binding Protein
KIM-1	Kidney Injury Molecule-1
IL-18	Interleukin-18
HR	Hazard Ratio
CI	Confidence Interval
CCL-14	C-C Motif Chemokine Ligand-14
aOR	Adjusted Odd Ratio
MPP	Mean Perfusion Pressure
BMI	Body Mass Index
TNF	Tumor Necrosis Factor
IMV	Invasive Mechanical Ventilation
QEHB	Queen Elizabeth Hospital Birmingham
UHB	University Hospitals Birmingham NHS Foundation Trust
PICS	Prescribing Information and Communications System
WCC	White Cell Count
IQR	Interquartile Range
COPD	Chronic Obstructive Pulmonary Disease
PaO_2/FiO_2	The ratio of partial pressure of oxygen in arterial blood (PaO2) to the fraction of inspiratory oxygen concentration (FiO2)
MDRD	Modification of Diet in Renal Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
HD	Haemodialysis
CVVH	Continues Veno-Venous Haemofiltration
ELISAs	Enzyme-Linked Immunosorbent Assays
ROC	Receiver Operating Characteristic

CHAPTER 1

1. INTRODUCTION

The initial design of this PhD was aimed to evaluate the association between the peri-operative inflammation and major adverse events following major abdominal surgery. The adverse events of interest were Acute Kidney Injury (AKI) and Postoperative Pulmonary Complications (PPCs). Although we had secured the ethics for this project the pandemic occurred before the approvals required by UHB trust. Also, UHB were not approving any new research studies until studies that were already up and running have re-started. Surgery has been completely re-configured at UHB with many procedures no longer happening and the numbers are down by over 60%. We had expected that we could restart our peri-operative AKI study by early 2021, however, lately the second surge of COVID-19 has hit the UK and reached “critical” stage.

Given these unique and challenging circumstances, the time limitations of the current PhD project, and the urgent need for research relating to COVID-19, we decided to redesign our study towards a new project. This revised project aimed to assess the major adverse events associated with AKI among COVID-19 patients, with or without ARDS.

1.1 BACKGROUND

Acute kidney injury (AKI), also referred to as Acute Renal Failure (ARF), is a state where which the kidneys suddenly and severely lose their ability to filter waste and excess fluids from the blood. The history of AKI dates to ancient times, when the symptoms of the condition were described in medical texts from various civilisations (Makris and Spanou, 2016). The actual concept of ARF emerged during the First and Second World Wars, when severe traumatic injuries were commonly seen to result in kidney failure (Eknoyan, 2008). The condition was known as "war nephritis" in several publications during the First World War (Davies and Weldon, 1917). Based on studies from the Second World War and reports of the "crush kidney", a pathologist named Jean Redman Oliver made substantial contributions to the knowledge of ARF's underlying pathophysiology. He achieved this by detailing various models of both toxic and ischemic kidney injuries in animals and humans (Bywaters and Beall, 1941, Oliver et al., 1951). Homer William Smith, a renal physiologist credited for presenting the term “acute renal failure”, extensively studied the mechanisms of kidney clearance of water and solutes and played a significant role in introducing non-invasive techniques for measuring glomerular filtration rates (Giebisch, 2004).

The concept of AKI was greatly affected by the definition establishment of Chronic Kidney Disease (CKD) in a public health model (Kellum et al., 2012). This model defines CKD as evidence of renal impairment that persists for three months or longer. This suggests that renal dysfunction lasting < 3 months may be reversible and distinguished from CKD. A theoretical model of AKI development was established based on this model (Figure 1.1) (Murray et al., 2008, Kellum et al., 2012).

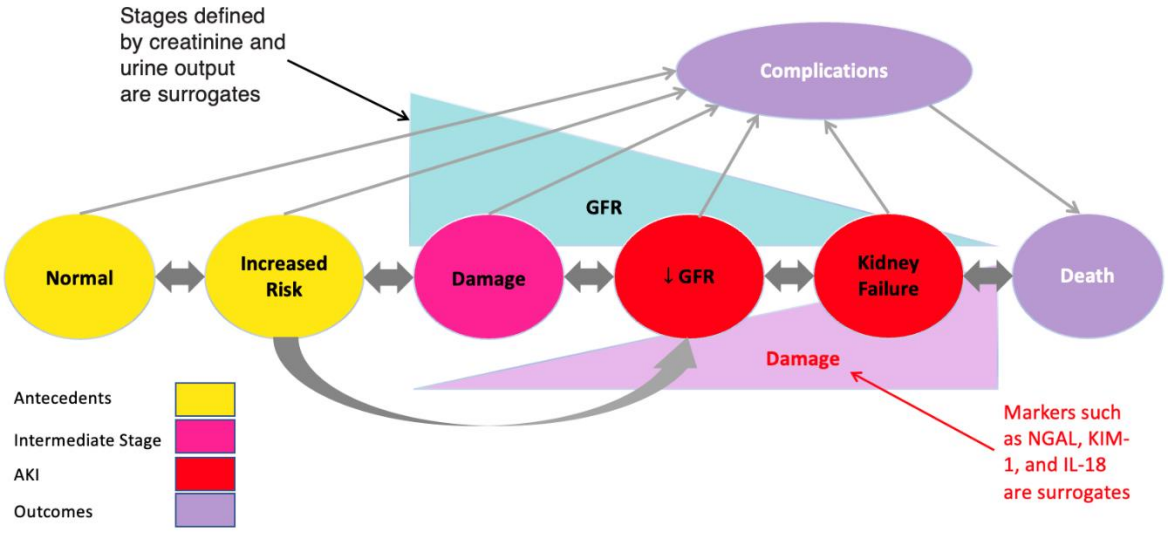


Figure 1.1. AKI conceptual model, adapted from Murray et al. (2008).

Legend: An illustration of the AKI conceptual model, the yellow colour represents the risk of AKI development, the pink colour indicates an undefined intermediate stage, the red colour indicates AKI stages, and the purple colour represent adverse outcomes to AKI.

Both AKI and CKD can progress towards the terminal phase known as End-Stage Renal Disease (ESRD), although they may initially manifest in milder forms. This idea supports the transition from ARF to AKI, as AKI is a condition that can be prevented or treated in its initial stages. Thus, it is a significant public health issue requiring additional research. The term AKI replaced ARF because it was perceived as a final-stage condition, similar to ESRD.

AKI is widely well-defined as a sudden kidney dysfunction within hours, wherein the kidney fails to sustain fluid and electrolyte balance. AKI is a spectrum, from mild impairment in kidney function to severe kidney impairment require initiating for Renal Replacement Therapy (RRT). There was until recently a lack of an agreed definition of AKI in the renal community. The Acute Dialysis Quality Initiative (ADQI) group established diagnostic and classification method for AKI in 2002 called the Risk, Injury, Failure, Loss of Function and End-stage Renal Disease (RIFLE) system (Bellomo, 2004). Later, the Acute Kidney Injury Network (AKIN) group in 2007 suggested an

adapted version of the RIFLE criteria to enhance the accuracy of AKI detection (Mehta et al., 2007). Based on the RIFLE and AKIN criteria, the Acute Kidney Injury Working Group of Kidney Disease: Improving Global Outcomes (KDIGO) presented the latest diagnosis and classification criteria for AKI, which has been adopted worldwide (Kellum et al., 2012). Accordingly, the KDIGO guidelines defined the AKI as “any of the following (Not Graded): increase in serum creatinine by ≥ 0.3 mg/dl (≥ 26.5 μmol/l) within 48 hours; or increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume < 0.5 ml/kg/h for 6 hours” (Kellum et al., 2012).

AKI is considered the most frequent complication in hospitalised patients globally, particularly critically ill patients admitted to the Intensive Care Unit (ICU) (Hoste et al., 2018). The prevalence of AKI continues to grow over time, impacting up to 22.7% of hospitalised patients and more than 50% of those admitted to the ICU (Wang et al., 2012, Minja et al., 2021). Several epidemiological investigations have demonstrated its association with elevated morbidity and mortality rates and substantial healthcare costs (Collister et al., 2017, James et al., 2020, Noble et al., 2020, Vijayan et al., 2021).

Despite the consensus on utilising alterations in serum creatinine levels and urinary output to identify AKI development and classify its severity, as well as assess kidney function recovery in multiple classification criteria, employing a composite outcome reflecting CKD progression and survival may be more effective for clinical trials investigating early interventions for AKI (Bellomo, 2004, Mehta et al., 2007, Kellum et al., 2012). The workgroup for the National Institute of Diabetes and Digestive and Kidney Diseases suggests utilising Major Adverse Kidney Event (MAKE) – a

composite of any new initiation for RRT, a drop in estimated Glomerular Filtration Rate (eGFR) to below 75% of baseline, or all-cause mortality – to evaluate progression and both short-term and long-term effects of AKI on patient outcomes (Palevsky et al., 2012). MAKE is a composite outcome increasingly recognised as a validated long-term indicator of the effects of AKI on patient-related outcomes, especially in critically ill patients (Billings and Shaw, 2014).

McKown et al. (2017) first introduced the MAKE prediction model, derived from a retrospective study utilising electronic health records to develop an exponential equation-based model. Sukmark et al. (2020) conducted a recent prospective, multicentre observational study that enrolled 5,071 Southeast Asia (SEA) patients who were treated within 17 ICUs to establish a simplified scoring system to predict 28-day MAKEs. This study indicated that out of 2,856 (56%) patients with AKI, 1,749 (61%) experienced MAKEs within 28 days after ICU admission: 414 (14.4%) had new RRT, while 1,154 (40.7%) had sustained loss of kidney function, and 1,175 (41.4%) had died. The results illustrated that a new simplified clinical score (SEA-MAKE score) offered reliable discrimination and calibration in predicting MAKEs in patients with AKI, compared to existing models such as Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores. Most studies have focused on evaluating MAKE development up to 30 days (MAKE-30) from the onset of AKI (Semler et al., 2016, Xin et al., 2022a, McKown et al., 2017). However, MAKE-30 represents a short-term endpoint that may not fully capture the long-term effects of AKI.

1.2 PATHOPHYSIOLOGY OF AKI

The kidneys are vital, life-sustaining organs that maintain the body's fluid, electrolyte, and acid–base balance. Each of the two kidneys has up to a million functioning units called nephrons, which consist of two main parts – the renal corpuscle and the renal tubule – which are responsible for urine formation throughout three processes of filtration, tubular reabsorption, and tubular secretion (Figure 1.2) (Swisher et al., 2002).

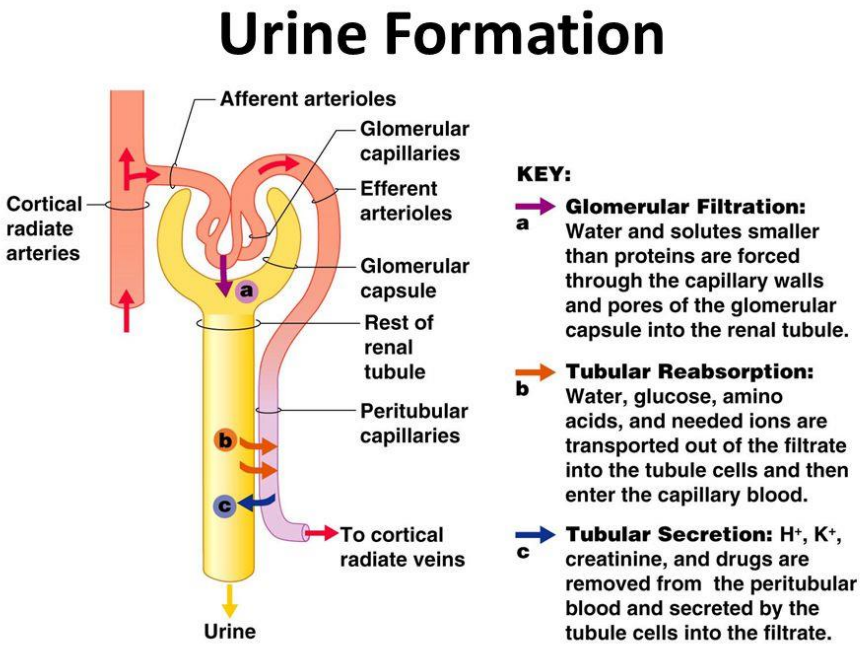


Figure 1.2. Basic physiologic mechanisms of the kidney and the processes involved in urine formation. Adapted from Karki (2017).

Initially, in glomerular filtration, blood passes via glomerular capillaries, whereas small solutes and water filter out into the glomerular capsule (Swisher et al., 2002). Most plasma proteins and blood cells do not move out during glomerular filtration. The Glomerular Filtration Rate (GFR) refers to the volume of filtrate formed, which is normally about 125 ml per minute in a healthy adult: that is, 180 litres per day (Campbell, 2006).

The kidney's primary function is to excrete waste products from the blood via urine, reabsorb nutrients, maintain pH, and regulate blood pressure and plasma osmolarity (Campbell, 2006). The permeability of the glomerular endothelium might be increased in some types of kidney disease, which would allow plasma proteins to filter out into the capsule (Swisher et al., 2002).

The kidney is supplied with approximately 1200 mL/min of blood flow, representing up to 25% of the cardiac output (Basile et al., 2012). Renal blood flow is normally controlled through mechanisms of autoregulation that maintain constant pressure and flow, along with sustaining oxygen supply that is important for a wide range of highly metabolic kidney functions. So, kidney perfusion may significantly impact any general circulation failure or isolated failure of the intrarenal circulation (Basile et al., 2012). It can also be controlled by renal artery integrity and venous outflow or Mean Arterial Pressure (MAP) (Martin, 2010). Glomerular filtration pressure and GFR can be determined by vasodilation or vasoconstriction of efferent and afferent arterioles and glomerular autoregulation, which is only functional when systolic arterial pressure is between 80 and 170 mm Hg (Basile et al., 2012). The sympathetic nervous system, renin-angiotensin-aldosterone system, and antidiuretic hormone also regulate and control renal blood flow and urine formation. Furthermore, in certain circumstances where there is a decrease in actual or effective circulating volume, prostaglandins such as PGE2 can act as vasodilators and increase both renal blood flow and GFR. This function of prostaglandins is crucial to kidney function (Martin, 2010). Administering prostaglandin inhibitors, such as Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), can result in losing this crucial function of prostaglandins. This loss may lead to severe intrarenal vasoconstriction, a reduction in eGFR, and may even trigger or exacerbate AKI (Martin, 2010).

Renal tissue oxygenation depends on the oxygen levels in the arterial blood, arterial-to-venous oxygen shunting, and the oxygen consumed by the cells (Evans et al., 2008). Some specific conditions of renal oxygenation increase the kidney's vulnerability to hypoxia and impact the pathophysiology of AKI. Most renal oxygenation is used for sodium transport, with the remaining amount allocated for other cellular activities commonly referred to as basal metabolism (Bullen et al., 2017). Ischaemia is the most common cause of AKI. It could develop for several reasons, one of which is the reduction in blood flow, although this reduction can be compensated to a certain degree through physiological adaptations. If the supply of metabolic substrates and oxygen is inadequate, it can cause cellular injury and result in dysfunction of the organ. The kidney is particularly susceptible to injury from ischemia, which can activate inflammatory processes, vasoconstriction, and damage to the endothelial cells (Bonventre, 2007). This status might be described partially through structural relationship between the renal tubules in the kidney's outer medulla and blood vessels, whereby the blood flow with ischaemia compromises its critical nephron structures. The epithelial cells cannot preserve adequate intracellular Adenosine Triphosphate (ATP) for essential processes following the decline in effective renal perfusion (Makris and Spanou, 2016). Therefore, this ATP depletion can lead to cell injury and cause cell death by necrosis or apoptosis if severe enough. Most nephron segments might be affected during an ischaemic insult. However, the most commonly injured are proximal tubular cells (Makris and Spanou, 2016).

1.3 AKI IN CRITICAL CARE SETTINGS

The AKI development in critical care settings is significantly associated with an increase in morbidity and mortality as well as healthcare costs (Harty, 2014, Jones

and Devonald, 2013). AKI can develop from various causes broadly classified into pre-renal, intrinsic renal, and post-renal factors (National Institute for Health and Care Excellence, 2023), with pre-renal conditions being the most prevalent in critical care settings (Hulse and Davies, 2015).

Critically ill patients may develop AKI due to a range of underlying causes, such as sepsis, liver failure, and cardiac failure (Ostermann and Joannidis, 2016). Within the critical care setting, sepsis is a primary catalyst for AKI, accounting for approximately 50% of cases. It dramatically elevates the risk of mortality compared to septic patients without AKI (Griffin et al., 2020b, Hamzagic et al., 2019). The pathophysiological pathway in sepsis-induced AKI includes diminished renal blood flow due to vascular dilatation, decreased systemic vascular resistance and an inflammatory cascade that leads to renal cellular injury(Dutton and Finch, 2018). This inflammatory response may cause direct damage to the kidney's structures, exacerbating the hypoperfusion injury and potentially accelerating the progression from pre-renal to intrinsic AKI (Peerapornratana et al., 2019).

Treatment with nephrotoxic antibiotics, such as vancomycin, piperacillin with tazobactam, and aminoglycosides, introduces additional risks to renal health. Accordingly, the KDIGO guidelines recommend their use only when less nephrotoxic alternatives are unavailable (Kellum et al., 2012). Particularly, aminoglycosides are implicated in the constriction of renal blood vessels and subsequent acute tubular necrosis due to their accumulation in the renal cortex (Hulse and Davies, 2015).

Acute liver failure commonly leads to AKI development due to systemic inflammation, renal hypoperfusion, or the nephrotoxic effects of paracetamol ingestion (Leventhal and Liu, 2015). Patients with liver failure and AKI are significantly

associated with worse patient outcomes and increased mortality (Griffin et al., 2020b). Several reasons can lead to renal hypoperfusion in liver failure; for instance, impaired liver function can lead to disruptions in the production of clotting factors and plasma proteins, resulting in coagulopathies and fluid shifts. Moreover, substantial blood loss from gastrointestinal bleeding due to portal venous congestion can significantly decrease circulating blood volume (Moore et al., 2013, Slack and Wendon, 2009).

1.4 ARDS AND KIDNEY DYSFUNCTION

Acute Respiratory Distress Syndrome (ARDS) is a major cause of respiratory failure in the ICU and was initially described by Ashbaugh et al. (1967). The syndrome is characterised by the sudden onset of hypoxemia, decreased lung compliance, noncardiogenic pulmonary oedema, and increased requirement for mechanical ventilation. It is often associated with various clinical conditions such as trauma, sepsis, pneumonia, and aspiration. The diagnostic criteria for ARDS were first defined during a consensus conference held between American and European experts in 1992 (Bernard et al., 1994) and subsequently updated during the Berlin consensus conference in 2012, leading to the Berlin definition (Table 1.1).

Table 1.1. ARDS Berlin definition

The Berlin definition of ARDS	
Timing	Onset within 7 days of a known clinical insult or new or worsening respiratory symptoms.
Chest imaging	Bilateral opacities on chest imaging – not fully explained by nodules, effusions, or lobar/lung collapse.
Origin of oedema	Respiratory failure that cannot be entirely attributed to fluid overload or heart failure requires thorough evaluation (such as through echocardiography) to rule out hydrostatic oedema, especially when no risk factors are present.
Oxygenation	The onset of acute hypoxemia and defined as a PaO_2/FiO_2 ratio of less than 300 mmHg while using PEEP of at least 5 cmH2O. The following PaO2/FiO2 ratios determine the severity of ARDS: - Mild ARDS: PaO2/FiO2 of 201–300 mmHg - Moderate ARDS: PaO2/FiO2 of 101–200 mmHg - Severe ARDS: PaO2/FiO2 of ≤100 mmHg

This definition modified from Ranieri et al. (2012).
Abbreviations: FiO_2: Fraction of Inspired Oxygen; PEEP: Positive End-Expiratory Pressure; PaO_2: Partial Pressure of Arterial Oxygen.

Globally, ARDS is a prevalent and severe condition in ICUs, arising from diverse clinical settings. It is associated with either direct injury to the lungs (such as aspiration of stomach contents or pneumonia caused by viruses or bacteria) or indirect injury (such as sepsis or severe trauma with shock) within a systemic process (Matthay et al., 2019, Kumar, 2007). Bellani et al. (2016a) conducted a large multicentre study that included 29,144 patients across 459 ICUs in 50 countries to understand the global impact of Severe Acute Respiratory Failure (LUNG SAFE study). This research offered significant insights, as approximately 10.4% of all those patients and 23.4% of mechanically ventilated patients developed ARDS. Furthermore, the study revealed that hospital mortality rates varied from patients with mild ARDS to those with moderate and severe ARDS (34.9%, 40% and 46.1%, respectively).

Emerging literature highlights the detrimental interaction between lung and kidney dysfunctions (Li et al., 2009, Husain-Syed et al., 2016, Cortesi, 2020). Studies in both animals and humans have investigated the pathophysiological mechanisms underlying these lung-kidney interactions, revealing several factors contributing to the adverse effects of ARDS and mechanical ventilation on kidney function. Firstly, positive-pressure ventilation diminishes preload, potentially leading to reduced cardiac output and neurohormonal activation, subsequently affecting renal blood flow and decreasing eGFR (Kuiper et al., 2005). Additionally, severe hypoxemia impairs the angiotensin II, nitric oxide, endothelin, and bradykinin pathways in the kidneys, activating the sympathetic nervous system and causing a decline in renal blood flow and eGFR. Furthermore, extreme hypoxia might also result in pulmonary arterial vasoconstriction, venous congestion, and pulmonary hypertension, contributing to kidney dysfunction (Cortesi, 2020). Finally, mechanical ventilation can induce lung injury through pulmonary overdistension (barotrauma and volutrauma) and biotrauma, promoting the release of inflammatory cytokines, exacerbating systemic inflammation, and potentially causing distant end-organ dysfunction, such as kidney dysfunction (Figure 1.3) (Husain-Syed et al., 2016).

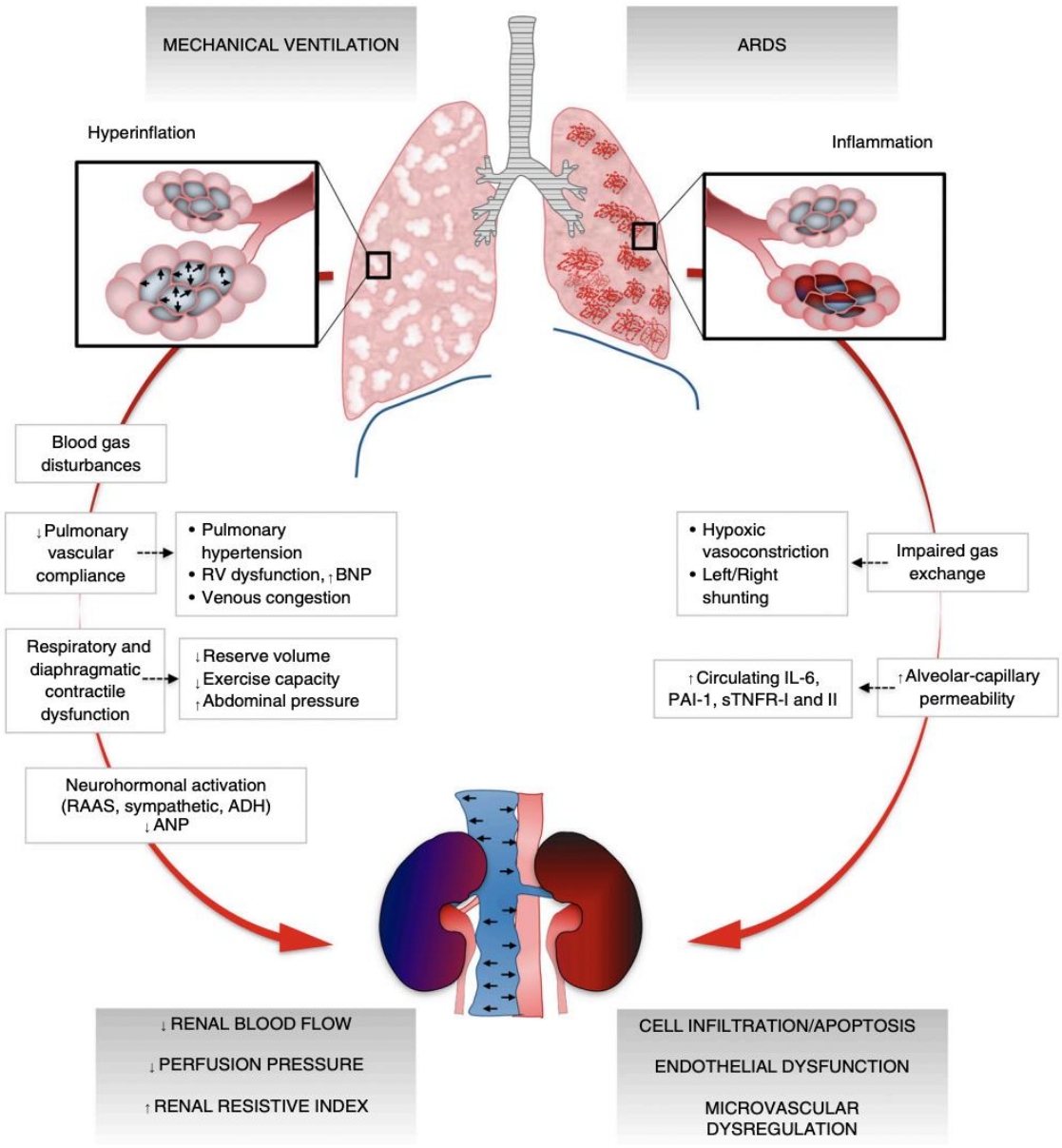


Figure 1.3. ARDS and kidney function. Adapted from Husain-Syed et al. (2016).

Legend: An illustration of the potential neurohormonal, haemodynamic, proinflammatory and proapoptotic effects of lung inflammation and hyperinflation on kidney function and their clinical features.
Abbreviations: ↓ = decrease; ↑ = increase; BNP, B-type natriuretic peptide; RV, right ventricular; ANP, A-type natriuretic peptide; PAI-1, plasminogen activator inhibitor-1; sTNFR, soluble tumour necrosis factor receptor.

Rogers et al. (2019) indicated that elevated inflammatory cytokines are associated with increased mortality in sepsis-induced ARDS. In addition, patients with AKI were more prone to experience increased inflammatory cytokines. ARDS can lead

to various complications, with AKI being one of the most common and linked to worse outcomes, such as prolonged hospital stays and increased mortality rates (Liu and Matthay, 2008, Liu et al., 2011, Mehta et al., 2002).

A secondary analysis of the LUNG SAFE study involving 1,974 mechanically ventilated ARDS patients revealed that 39% (765) experienced AKI within the first two days of ARDS (McNicholas et al., 2019). Hospital mortality rates for ARDS patients rose from 31% without AKI to 50% with mild-moderate AKI and 58% with severe AKI. Multivariate analyses demonstrated that severe and mild-moderate AKI independently contributed to increased mortality. Similarly, a study by Darmon et al. (2014a) revealed that among 1,879 ARDS patients, 44% had developed AKI and increased hospital mortality compared to patients without AKI (42.3% vs 20.2%; $p < 0.001$).

RRT, comprising Intermittent Haemodialysis (IHD) and Continuous Renal Replacement Therapy (CRRT), is a supportive treatment for AKI. It helps manage life-threatening complications linked to kidney failures, such as uraemia, hyperkalaemia, metabolic acidosis, and fluid overload, while allowing time for organ recovery (Wierstra et al., 2016). Dill et al. (2018) investigated the possibility that early RRT initiation could enhance survival rates in ARDS patients compared to late initiation. However, the study found no association between RRT initiation timing and survival benefits.

1.5 COVID-19 AND KIDNEY DYSFUNCTION

The new Coronavirus Disease (COVID-19) initially emerged in Wuhan, China, in December 2019 and rapidly expanded worldwide (Xu et al., 2020). In March 2020, the WHO announced that COVID-19 had reached pandemic status (Alvarez-Belon et

al., 2020), and by April 2023, there had been over 762 million COVID-19 cases and more than six million deaths. The pandemic of COVID-19 has posed significant challenges to the global healthcare systems. ARDS is the predominant complication among COVID-19 patients. Additional severe or life-threatening complications include sepsis, septic shock, pneumonia, arrhythmia, metabolic acidosis, acute cardiac injury, heart failure, and AKI (Baj et al., 2020).

Initial reports from China suggested that AKI was not common among patients with COVID-19 (Guan et al., 2020b, Batlle et al., 2020, Cheng et al., 2020a, Cheng et al., 2020c). However, data from Europe and the USA did not support the initial reports, as the incidence of AKI was reported to be more than 40% in ICU patients (Hirsch et al., 2020, Richardson et al., 2020). The development of AKI in COVID-19 patients has been linked to increased morbidity and in-hospital mortality, particularly in those requiring ICU care and RRT (Ng et al., 2020, Gupta et al., 2020, Carlson et al., 2021).

AKI is often a multifactorial condition rather than a distinct phenotype. Its development in the case of COVID-19 infection may arise from various factors and potential pathophysiological mechanisms leading to direct or indirect kidney injury, such as endothelial damage and local and systemic inflammatory and immune responses (Legrand et al., 2021). The role of direct viral invasion with renal tropism remains uncertain. Although some studies have detected viral particles in kidney tissue, others have not (Hassler et al., 2021, Puelles et al., 2020, Westhoff et al., 2020).

The inflammatory response to COVID-19 infection, often referred to as a "cytokine storm," is a life-threatening process that contributes to organ dysfunction. This response is characterised by elevated circulating cytokines and excessive

immune cell activation, which can result from various mechanisms, such as sepsis (Sinha et al., 2020). Three key proinflammatory cytokines of the innate immune system, including Interleukin-6 (IL-6) and Tumour Necrosis Factor-alpha (TNFα), play a significant role in cytokine storm development. While elevated levels of macrophages and monocytes have been observed in the lungs of COVID-19 patients and may contribute to the increased levels of Interleukin-1, IL-6, and TNFα in some cases, other evidence suggests that circulating cytokine levels in COVID-19 patients are often lower than those in non-COVID-19 patients with ARDS caused by alternative factors (Ragab et al., 2020, Sinha et al., 2020, Soy et al., 2020). In addition, IL-6 has been associated with AKI development, as increased IL-6 levels can stimulate renal endothelial cells to release additional proinflammatory cytokines and chemokines, leading to microvascular dysfunction (Desai et al., 2002). In a multicentre retrospective cohort study of 223 patients with COVID-19, researchers aimed to identify the prevalence of AKI and associated risk factors. They discovered that IL-6 levels were higher in AKI patients compared to those without AKI ($p < 0.001$) (Li et al., 2021). Moreover, this study identified other risk factors for AKI development, such as COVID-19 severity, increased C-Reactive Protein (CRP), d-dimer, leukocyte counts, lymphocyte counts, and ARDS and cytokine storms.

Lung and kidney interactions may contribute to AKI development in some COVID-19 patients. For example, well-established effects of respiratory failure and subsequent hypoxemia on the kidneys include increased renovascular resistance due to hypercapnia, leading to a decline in the GFR (Sharkey et al., 1998). Moreover, various factors have been recognised as being associated with AKI development in COVID-19 patients, such as obesity, older age, CKD, renal transplant recipients, invasive mechanical ventilation, vasopressor requirement, and exposure to

nephrotoxic medications (Casas-Aparicio et al., 2021, Lin et al., 2020, See et al., 2021, Geri et al., 2021, Yang et al., 2021).

1.6 DIAGNOSIS OF AKI

The widely accepted classification of AKI, established by the KDIGO work group in 2012, relies on alterations in serum creatinine levels, urine output, or both. The KDIGO workgroup defined the AKI development as "an increase in serum creatinine by ≥ 0.3 mg/dl (≥ 26.5 μmol/l) within 48 hours; or increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume < 0.5 ml/kg/h for 6 hours" (Kellum et al., 2012). This classification system further categorises AKI severity into three stages and provides criteria applicable to clinical practice and research (Table 1.2).

Table 1.2. KDIGO classification system for AKI development. Adapted from Kellum et al. (2012).

Stage	Serum creatinine level
1	Increase from baseline ≥ 0.3 mg/dL (26.5 μmol/L) within 48 hours, or 1.5 – 1.9-fold within seven days.
2	Increase from baseline ≥ 2 – 2.9-fold.
3	Increase from baseline ≥ 4.0 mg/dL (≥ 353.6 μmol/L) or ≥ 3-fold; or Initiation of renal replacement therapy.

Although the KDIGO guidelines for diagnosing and staging are associated with morbidity and mortality, their significant limitations should be noted (Mehta et al., 2015). Urine output and serum creatinine, which are surrogate indicators of GFR, do not solely indicate AKI. Additionally, GFR determined by serum creatinine might not decline until over 50% of functional nephrons have been lost in previously healthy kidneys (Sharma et al., 2014). Factors such as muscle mass, fluid therapy, muscle

injury, and tubular lumen secretion can confound serum creatinine levels (Ronco et al., 2019). Although highly sensitive to reduced GFR, urinary output lacks specificity and is susceptible to confounding factors like haemodynamic status, diuretics, and intravenous fluid therapy (Vaara et al., 2016). Consequently, urine output and serum creatinine are unsuitable for early identification of the AKI development (Pickkers et al., 2017, Waikar et al., 2012).

1.7 KIDNEY BIOMARKERS

Early detection and management of AKI are essential to prevent further damage and potentially fatal outcomes, particularly in critically ill patients (KDIGO Guidelines, 2012). Over the past decade, innovative technologies such as proteomics and genomics have identified novel biomarkers, allowing for better-informed clinical diagnosis and therapeutic decisions for those at risk of kidney dysfunction (Di Leo et al., 2018). However, determining the specific kidney biomarker based on the underlying cause and timeline of kidney injury remains unclear due to the diverse physiological and pathophysiological processes involved (Alge and Arthur, 2015). Moreover, implementation costs of new kidney biomarkers are not reimbursed in most countries, so they are mainly used in research. Consequently, AKI treatment strategies vary depending on clinical circumstances and available resources. The inclusion of novel kidney biomarkers into KDIGO criteria for AKI is under discussion (Ostermann et al., 2020a). At the 10th ADQI meeting in 2011, the potential use of biomarkers in AKI and their clinical application were discussed, revealing the need for more research and methods to implement biomarkers in clinical practice due to limited and insufficient evidence (Murray et al., 2014). Several research and clinical trials have been carried out over the last decade to discover and identify markers that might prompt early

identification of AKI development. Subsequently, various biomarkers have been identified, and their ability for early detection of AKI has been demonstrated (Murray et al., 2014, Teo and Endre, 2017, Kashani et al., 2017, Pozzoli et al., 2018). In 2019, the 23rd ADQI consensus meeting recommended using new biomarkers to prevent and manage AKI (Ostermann et al., 2020b).

1.7.1 CYSTATIN C

Cystatin C is a protein with a low molecular weight of 13.3 kDa, produced by all cells with a nucleus in the human body. This protein can be found in various biological fluids, including plasma, cerebrospinal fluid, and urine (Abrahamson et al., 1990, Abrahasom et al., 1986). Its main function is to inhibit cysteine proteases, thus making it one of the most important extracellular regulators of these enzymes (Workeneh and Mitch, 2013). Due to its low molecular weight and a positive charge at normal pH values, Cystatin C can be easily filtered by the glomeruli. It is subsequently reabsorbed and catabolised in the proximal renal tubule (Grubb, 1992, Tenstad et al., 1996). Due to its constant production rate, cystatin C concentration is determined by glomerular filtration, making it a superior marker for estimating GFR compared to serum creatinine (Kyhse-Andersen et al., 1994). Furthermore, it is less affected by factors such as gender, age, cirrhosis, and muscle mass, rendering its measurement in serum or plasma a valuable indicator of drug nephrotoxicity (Laterza et al., 2002, Shlipak et al., 2013, Taglieri et al., 2009).

Mussap et al. (2002) suggested that serum cystatin C is a more accurate GFR estimator in diabetic patients than serum creatinine, as it is susceptible to early and mild kidney function changes. However, a large cross-sectional study conducted by Knight et al. (2004a) brought up concerns regarding the reliability of serum cystatin C

as a biomarker of kidney function by identifying non-renal factors that can affect serum cystatin C levels, including smoking, corticosteroid use, male gender, obesity, older age, thyroid dysfunction, and systemic inflammation.

Variant findings have surfaced due to accumulating evidence, and the absence of standardisation in cystatin C measurement remains a concern (Ferguson and Waikar, 2012). Wan et al. (2013) examined serum cystatin C levels as an early predicting biomarker for AKI in patients with acute-on-chronic liver failure, and their results indicated that serum cystatin C level had better early predictive biomarker for AKI development (Area Under the Curve (AUC) = 0.974, sensitivity = 87.5%, specificity = 100%, $p > 0.001$) compared to creatinine (AUC = 0.526, sensitivity = 37.5%, specificity = 91.7%, $p = 0.828$), consistent with other studies by Liu et al. (2015) and Yim et al. (2015). In contrast, Gaygısız et al. (2016) investigated the ability of serum Cystatin C level to predict AKI development in ICU patients with normal creatinine levels and observed negative findings when using serum cystatin C alone for predicting the risk of AKI development, with an AUC of 0.67 and low sensitivity (63%) and specificity (66%). Consistent with the previous study, Mårtensson et al. (2016) also revealed that using plasma cystatin C alone did not improve AKI prediction in critically ill patients (AUC = 0.67, sensitivity = 55%, specificity = 76%). Recent findings by Pei et al. (2022) suggest that combining serum creatinine and cystatin C might enhance the diagnostic efficiency of AKI.

1.7.2 NGAL

Neutrophil Gelatinase-Associated Lipocalin (NGAL), also known as Lipocalin-2 or Siderocalin, is a 25-kDa protein initially identified in neutrophil granules (Kjeldsen et al., 1993). It is commonly expressed in various human tissues, including bone

marrow, lung, liver, and kidney (Cowland and Borregaard, 1997). NGAL is released extensively from neutrophils during inflammation and from kidney tubular epithelial cells under any stress conditions such as ischemic kidney injury (Mishra et al., 2003). *In vivo* studies suggest that urinary NGAL primarily originates from the kidneys' thick ascending limb and collecting ducts, while *in vitro* findings indicate that proximal tubule cells may also secrete NGAL in response to ATP reduction (Mishra et al., 2003, Mori et al., 2005). As a result, increased urine NGAL levels could indicate reduced absorption of filtered NGAL due to proximal tubule injury or dysfunction and enhanced NGAL release from collecting ducts and the thick ascending limb (Paragas et al., 2011).

NGAL has emerged as a widely investigated marker of AKI development in the past decade. NGAL is filtered through the glomeruli and predominantly reabsorbed in the proximal tubules. Consequently, reduced tubular reabsorption leads to increased urinary NGAL within 3 hours to 5 days from the initial kidney injury (Mishra et al., 2005, Parikh et al., 2011). Moreover, a reduced GFR may decrease kidney clearance of NGAL, resulting in its accumulation in the systemic circulation (Grigoryev et al., 2008). Thus, measuring NGAL concentrations in urine or plasma could enhance early AKI detection in critically ill patients.

It is essential to recognise that Systemic Inflammatory Response Syndrome (SIRS) and sepsis can influence NGAL concentrations and AKI diagnostic accuracy (Md Ralib et al., 2017, Schrezenmeier et al., 2017). Furthermore, inflammation presents a challenge when using NGAL alone as an AKI biomarker, especially in ICU patients with sepsis (Mårtensson and Bellomo, 2014). However, NGAL has shown

potential as an early predictive marker for AKI development after cardiac surgery (Ho et al., 2015).

Haase et al. (2009) conducted a meta-analysis with 2,538 patients to assess the diagnostic and prognostic accuracy of NGAL levels for early AKI prediction (within 7 days). The study demonstrated comparable AUC values for urinary (0.837) and serum/plasma NGAL (0.775) in predicting AKI, with a slightly higher cut-off value for urinary NGAL (179.2 ng/mL vs 193.2 ng/mL). In addition, age was recognised as an effective modifier of NGAL value, with superior predictive capacity in children (AUC = 0.930) compared to adults (AUC = 0.782). NGAL concentration also effectively predicts mortality (AUC = 0.706) and the need for RRT (AUC = 0.782). These findings aligned with a recent meta-analysis carried out by Albert et al. (2020).

Komaru et al. (2020) examined urinary NGAL levels in 17 ICU patients with COVID-19 and respiratory failure, finding that urinary NGAL concentrations were significantly elevated in patients with AKI. The AUC of urinary NGAL levels for AKI diagnosis at ICU admission was 0.84, with an optimal cut-off value of 73 ng/mL, a specificity of 86% and a sensitivity of 70%. Furthermore, higher urinary NGAL levels at ICU admission correlated with longer ICU stays ($p < 0.01$) and mechanical ventilation durations ($p < 0.01$), potentially reflecting the impact of AKI development. Nonetheless, elevated NGAL concentrations have also been observed in ventilator-associated lung injury (Xiao and Chen, 2017).

1.7.3 TIMP-2 and IGFBP-7

Tissue Inhibitor of Metalloproteinase-2 (TIMP-2) and Insulin-Like Growth Factor-Binding Protein-7 (IGFBP-7) are proteins involved in cell-cycle arrest, specifically in the G1 phase. These proteins are expressed and secreted through

kidney tubular cells through the initial phases of cell stress or injury initiated by different factors such as ischemia, sepsis, and toxins. Kidney tubular cells generate and release TIMP-2 and IGFBP-7 in response to cellular stress or damage. TIMP-2 prompts the expression of p27, while IGFBP-7 directly upregulates p21 and p53. Subsequently, these p proteins stop the influence of cyclin-dependent protein kinase complexes on cell cycle progression, leading to a temporary G1 cell cycle arrest. This allows the cells to repair damaged DNA and recover function after initial cellular stress, potentially preserving energy balance and preventing more DNA damage and division (Wang et al., 2016, Kashani et al., 2013). Nonetheless, prolonged cell cycle arrest can lead to a senescent cell phenotype and cause fibrosis (Figure 1.4).

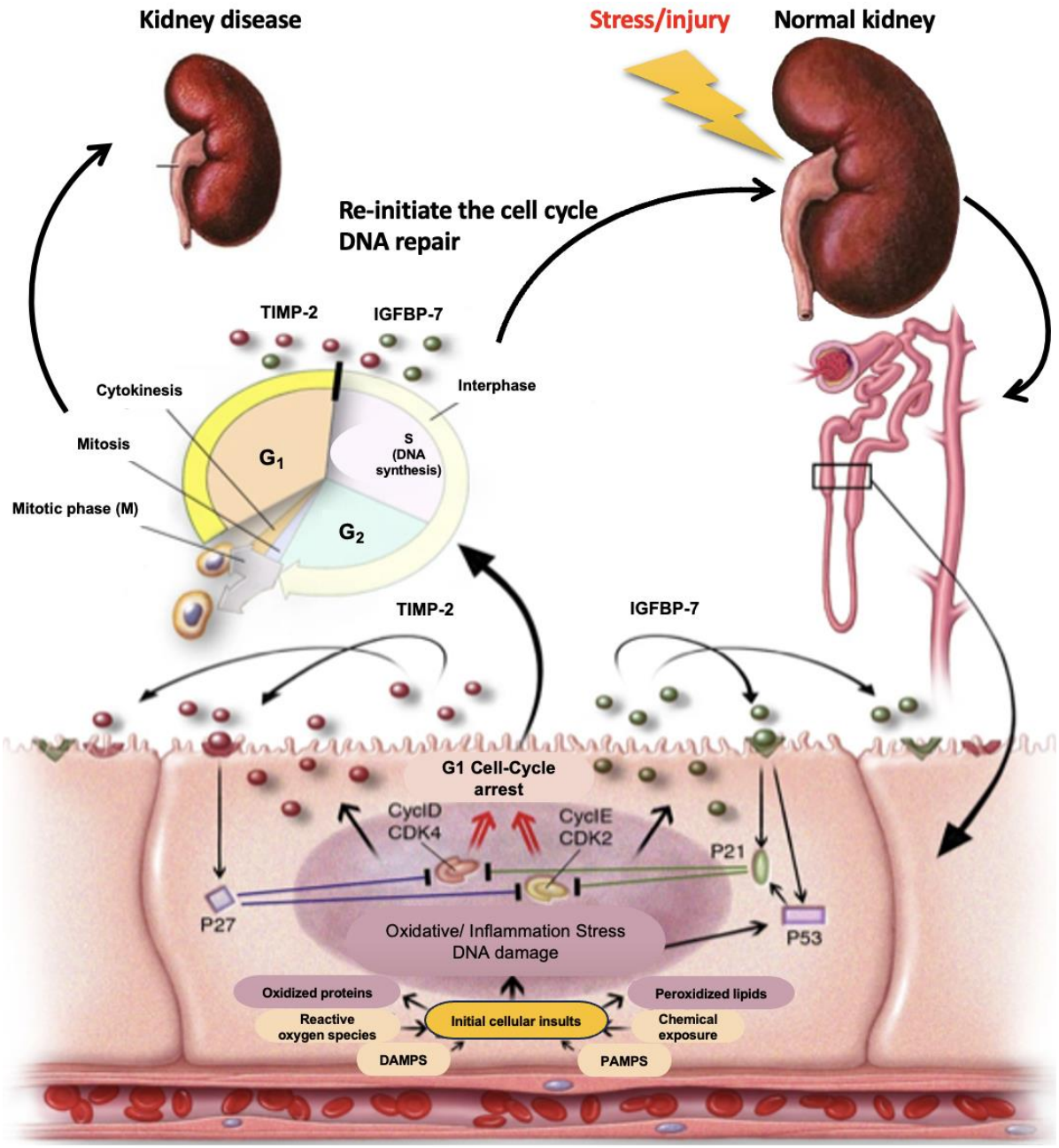


Figure 1.4. Proposed mechanistic involvement of TIMP-2 and IGFBP-7 in AKI development. Adapted from Kashani et al. (2013).

Legend: Kidney tubular cells generate and release TIMP-2 and IGFBP-7 in response to cellular stress or damage. TIMP-2 prompts the expression of p27, while IGFBP-7 directly upregulates p21 and p53. Subsequently, these p proteins stop the influence of cyclin D/CDK4 and cyclin E/CDK2 on cell cycle progression, leading to a temporary G1 cell cycle arrest. This allows damaged DNA to be repaired by the cells and recover function after initial cellular stress, potentially preserving energy balance and preventing more DNA damage and division. Nonetheless, prolonged cell cycle arrest can lead to a senescent cell phenotype and cause fibrosis.

Therefore, cell cycle arrest is linked to a higher risk of AKI development (Andrade et al., 2018, Yang et al., 2010). AKI involves complex cellular and molecular pathways, including cell cycle, inflammation, immunity, and apoptosis (Kashani et al., 2013). TIMP-2 and IGFBP-7 can be signs of stress in the kidney epithelium or the shutdown of any functional activity. However, the organ might recover without permanent injury if the relevant cause ends (Di Leo et al., 2018).

A multicentre cohort study (Sapphire study) was carried out in the discovery and the validated phases (Kashani et al., 2013). First, in the discovery phase, a total of 522 ICU patients with different conditions (such as trauma, sepsis, shock, and major surgery) and over 300 biomarkers from the blood and urine samples collected within 18 hours from enrolment (including cystatin C, NGAL, Liver-type Fatty Acid-Binding Protein (L-FABP), Kidney Injury Molecule-1 (KIM-1), and Interleukin-18 (IL-18)) were investigated to discover the potential markers for AKI development. This phase showed that urinary TIMP-2 and IGFBP-7 were the top two novel biomarkers for AKI, both inducers of G1 cell cycle arrest. Subsequently, 728 critically ill adult patients were analysed during the validation phase, revealing that urinary [TIMP-2]*[IGFBP-7] demonstrated the highest performance, with an AUC of 0.80. This performance was notably superior to all previously identified biomarkers for predicting AKI development ($p < 0.002$). Moreover, urinary TIMP-2 and IGFBP7 demonstrated stability across various clinical conditions, substantially enhancing the risk stratification (Kellum and Chawla, 2016).

In the Opal study, Hoste et al. (2014) conducted a derivation and validation study on 154 ICU patients, which aimed to validate the diagnostic precision and clinical impact of two distinct cut-off values (0.3 and 2.0 $[ng/mL]^2/1000$) of [TIMP-2]*[IGFBP7]

from the Sapphire study. This study replicated the findings of the Sapphire study, showing high sensitivity (89%) for the cut-off value of 0.3 $(ng/mL)^2/1000$, and high specificity (95%) for the cut-off value of 2.0 $(ng/mL)^2/1000$. Bihorac et al. (2014) examined 420 ICU patients in the Topaz study to validate the lower cut-off value (0.3 $(ng/mL)^2/1000$) for risk assessment of AKI. The patients with urinary [TIMP-2]*[IGFBP7] values > 0.3 faced a seven-fold increased risk for AKI development (95% CI, 4–22) compared with those with values ≤ 0.3.

The NephroCheck® test is an advanced point of care diagnostic tool designed to identify kidney stress before any significant damage happens. It is measuring the concentration of both TIMP-2 and IGFBP7 biomarkers in the urine. The results of these biomarkers are intended to be used alongside clinical assessment as a tool to evaluate the risk of AKI development in ICU patients within 12 hours of patient assessment (Kashani et al., 2013). Three major studies (the Sapphire, Opal, and Topaz studies) were conducted to detect and validate the ability of [TIMP-2]*[IGFBP-7] to pre-diagnose AKI before the clinical application of NephroCheck® (Kashani et al., 2013, Kellum and Chawla, 2016, Hoste et al., 2014, Bihorac et al., 2014). Subsequently, the US FDA granted approval for the marketing of NephroCheck® (developed by Astute Medical), which is used to measure the levels of TIMP-2 and IGFBP7 markers in urine samples for predicting the risk of developing moderate to severe AKI in ICU patients (Vijayan et al., 2016b).

The TIMP-2 and IGFBP-7 biomarkers also help predict the risk for short-term adverse outcomes linked to AKI, particularly within 30 days from hospital discharge. The Sapphire study findings demonstrated that the risk of MAKE at 30 days was significantly increased among patients who had urinary [TIMP-2]*[IGFBP7] above 0.3

ng/mL^2/1000 (samples collected within 18 hours from enrolment), and this risk was even higher in those with urinary [TIMP-2]*[IGFBP7] above 2 ng/mL^2/1000 (Kashani et al., 2013). A secondary analysis of the Sapphire study has also indicated that increased urinary [TIMP-2]*[IGFBP7] levels were related to adverse long-term outcomes in patients with AKI (Koyner et al., 2015). AKI patients with urinary [TIMP-2]*[IGFBP7] levels above 0.3 but below 2.0 had a considerably higher risk of long-term RRT or death (within 180 days after enrolment) (Hazard Ratio (HR) = 1.44; 95% Confidence Interval (CI)= 1.00 – 2.06; p = 0.05) compared to those with levels under 0.3, and the risk was even greater for patients with levels above 2.0 (HR, 2.16; 95% CI, 1.32 to 3.53; p = 0.002).

Gocze et al. (2015) also revealed that [TIMP-2]*[IGFBP-7] is a more specific, sensitive, and highly predictive early biomarker for AKI in adult patients following surgeries. These biomarkers may also predict renal recovery and long-term outcomes (within 180 days) following AKI development (Dewitte et al., 2015, Koyner et al., 2015). Compared to other biomarkers like cystatin C, NGAL, L-FABP, KIM-1, and IL-18, TIMP-2 and IGFBP7 demonstrated better performance in terms of accuracy and stability, even among patients with significant comorbidities (Heung et al., 2016). In contrast to earlier findings, Bell et al. (2015) revealed that TIMP-2 and IGFBP-7 could not predict the development of AKI within 12 to 48 hours and were strongly influenced by pre-existing comorbidities, such as diabetes.

1.7.4 CCL-14:

C-C Motif Chemokine Ligand-14 (CCL-14), a small-molecule chemokine, was initially identified for its role in leukocyte chemotaxis and involvement in damaged tissue and healing processes (Detheux et al., 2000). CCL-14 demonstrated a lower

binding affinity for chemokine receptors CCR3 and a high affinity for CCR1 and CCR5 (Detheux et al., 2000).

CCL-14 is crucial for macrophage and monocyte recruitment and has been linked to pro-inflammatory chemotaxis in a range of illnesses, including multiple sclerosis, rheumatoid arthritis, and lupus (Vyshkina et al., 2008, Rump et al., 2017). Understanding of CCL-14's function and role in AKI is limited due to the absence of CCL-14 expression in rats and mice, so these animals cannot be employed in pre-clinical models. However, the potential involvement of CCL-14 in AKI can be suggested based on the primary role of macrophage recruitment and polarisation in the kidney tissue injury development of persistent kidney dysfunction (Figure 1.5) (Meng et al., 2015). Furthermore, CCL-14 has been identified as an inflammatory marker predicting the risk of developing ESRD in diabetic individuals (Niewczas et al., 2019).

The severity of AKI and the period of kidney impairment impact patients' short- and long-term outcomes (Koyner et al., 2015, Mehta et al., 2018, Perinel et al., 2015). Accordingly, those with a renal impairment that improves within 3 to 7 days have better outcomes than those with persistent AKI, who commonly need RRT and are at a significantly higher risk of developing CKD (Kellum et al., 2017, Chawla et al., 2017).

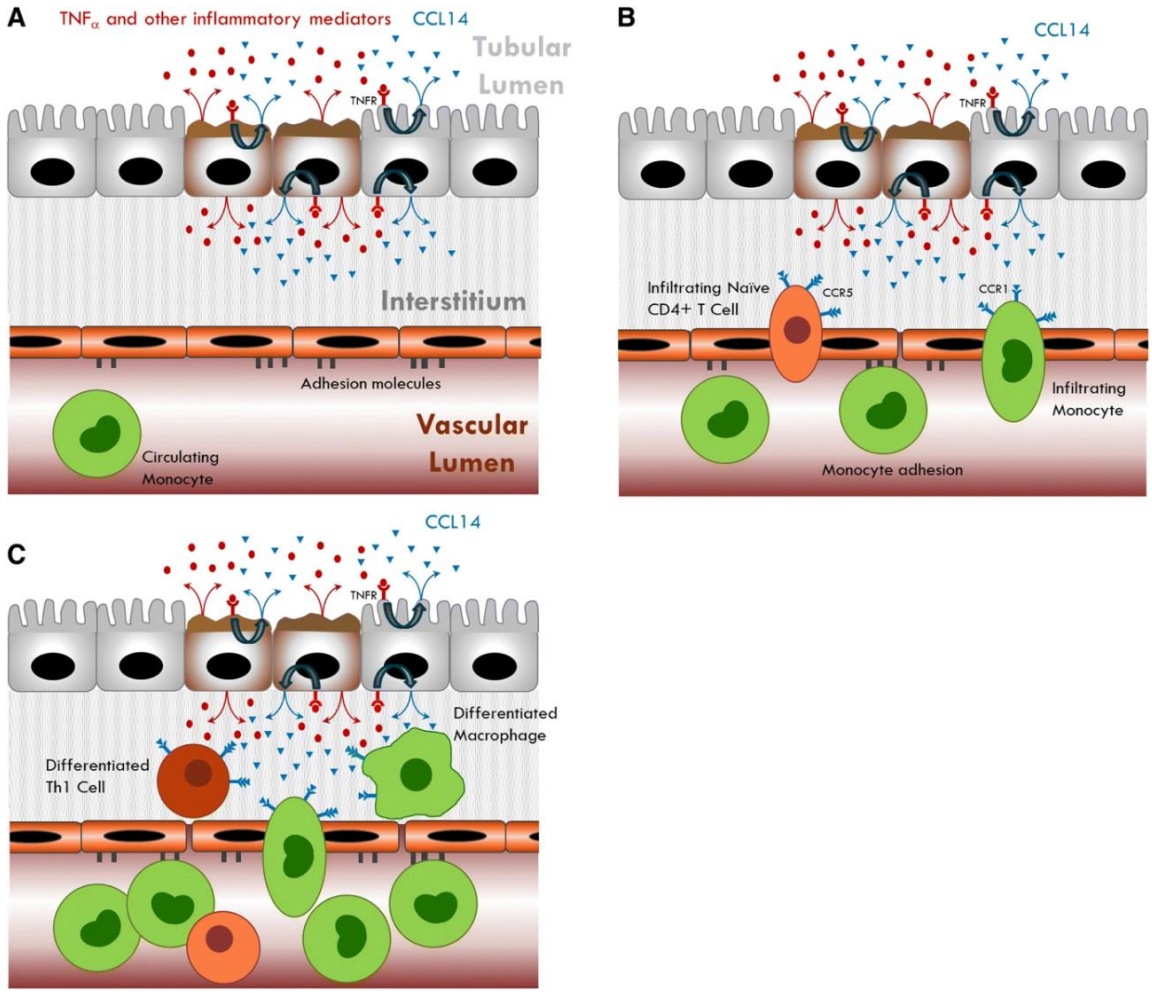


Figure 1.5. Proposed mechanism of CCL14. Adapted from Hoste et al. (2020).

Legend: A. Damaged epithelium releases TNFα and other inflammatory mediators that interact with TNF receptors and induce tubular epithelial cells to release CCL14. **B.** CCL14 binding to CCR1 and CCR5 receptors on monocytes and T cells induces chemotaxis towards the site of injury. **C.** Naïve T cells differentiate into proinflammatory Th1 cells and monocytes differentiate into macrophages.

Hoste et al. (2020) recently conducted an international multi-centre observational study (the RUBY study) to assess new potential biomarkers to predict persistent severe AKI (AKI stage 3 lasting ≥ 72 hours). Among 337 critically ill adult patients, 33% (n = 110) developed persistent AKI stage 3, of whom 56 (51%) received RRT. Among all evaluated biomarkers, which included plasma cystatin C, NGAL, [TIMP-2]*[IGFBP-7], Proenkephalin 119-159, L-FABP, KIM-1, and chitinase-3-like protein 1 (CHI3L1), CCL-14 proved to be the most predictive for persistent AKI stage 3, with an AUC of 0.83 (95% CI, 0.78–0.87). The RUBY study's findings were

externally validated by Bagshaw et al. (2021), who conducted a secondary analysis of the SAPPHIRE study. Of 195 patients with AKI, 14% (n = 28) developed persistent severe AKI, 15 had AKI stage 3 ≥ 72 h, 12 received RRT, and one died before 72 hours. The urinary CCL-14 levels indicated a good prediction for persistent severe AKI with an AUC of 0.81 (95% CI, 0.72-0.89), consistent with RUBY study findings. These findings support the reliability of CCL-14 in predicting persistent AKI.

In 2022, a secondary analysis of the RUBY Study was conducted to identify two cut-offs for predicting persistent severe AKI using a clinical assay (Koyner et al., 2022). A 13 ng/ml cut-off value for urinary CCL14 was determined to achieve 93% specificity (95% CI, 89% – 96%), while a 1.3 ng/ml was set for 91% sensitivity (95% CI, 84% – 96%). Moreover, the study demonstrated that patients with urinary CCL-14 levels ranging from 1.3 to 13 ng/ml had an elevated risk of persistent severe AKI development (adjusted Odd Ratio (aOR)= 3.82; 95% CI= 1.73-9.12; p= 0.001) compared to those with levels ≤ 1.3 ng/ml, and even greater risk in patients with urinary CCL-14 levels > 13 ng/ml (aOR = 10.4; 95% CI, 3.89 – 29.9; p < 0.001).

In a recent single-centre observational study, Massoth et al. (2023) evaluated the performance of biomarkers (including L-FABP, KIM-1, and CCL-14) for predicting persistent AKI and MAKEs at 90 days (MAKE-90) in 100 patients undergoing cardiac surgery. Among 37 (37%) patients who had developed persistent AKI, 36 had MAKE-90, of whom five patients were on RRT, 15 were dead, and 16 had persistent renal dysfunction. Of the three biomarkers evaluated, urinary CCL-14 was the best predictor for persistent AKI, with an AUC of 0.93 (95% CI, 0.88 – 0.97; p < .001) and MAKE-90 with an AUC of 0.897 (95% CI, 0.83 – 0.96; p < 0.001).

1.8 PREVENTION AND TREATMENT

According to the KDIGO clinical practice guidelines and care bundles, treatment options for AKI are mainly supportive and limited (Khwaja, 2012). The primary strategies for preventing and managing established AKI involve addressing the cause and maintaining homeostasis, facilitating recovery (Bellomo et al., 2012). Promptly recognizing patients at higher risk of AKI is crucial for effective prevention and treatment. Risk factors can be categorized into patient-related factors (e.g., male gender, older age, obesity, CKD, anaemia, sepsis, cardiovascular and pulmonary diseases, hepatobiliary disease, diabetes mellitus, cancer, steroid use, increased intraabdominal pressure, and ICU admission) or procedure-related factors (e.g., potential hypovolemia, nephrotoxic drug use, contrast dye administration, and emergency or major surgery) (Goren and Matot, 2015). The lack of interventions for AKI treatment is one of the challenges in managing critically ill patients (Hobson et al., 2015). Initial clinical management of AKI should focus on haemodynamic stabilization, prompt detection of AKI-related complications, determining underlying causes, and appropriate treatment (Moore et al., 2018).

Haemodynamic stabilization is crucial in AKI cases due to impaired autoregulation mechanisms (Ostermann et al., 2019). Proper kidney function depends on regulating renal venous pressure and renal blood flow. In healthy individuals without systemic hypertension, renal blood flow is autoregulated at Mean Perfusion Pressure (MPP) between 60 and 100 mmHg (Loutzenhiser et al., 2006). Critical illness may compromise these autoregulation mechanisms. Elevated central venous pressure and the resulting increase in backward pressure can negatively impact

kidney function, primarily through kidney congestion, increased intrarenal pressure, and reduced GFR (Firth et al., 1988, Winton, 1931, Maxwell et al., 1950).

A retrospective analysis showed that MPP below 60 mmHg was associated with an increased risk of AKI progression (Ostermann et al., 2017). Various management strategies during surgery can help reduce and prevent AKI incidence postoperatively. Preventing tissue hypoperfusion during the intraoperative period is a primary haemodynamic goal to avoid organ hypoxia and AKI development. A study involving 5,127 patients undergoing noncardiac surgery found that AKI risk increased when the mean arterial pressure (MAP) was below 60 mmHg for more than 20 minutes or below 55 mmHg for more than 10 minutes (Sun et al., 2015). Thus, it is recommended to maintain MAP values at > 60–65 mmHg (> 75 mmHg in patients with chronic arterial hypertension) (Leone et al., 2015, Joannidis et al., 2010).

Drug nephrotoxicity is one of the most common causes of AKI development in critically ill patients, contributing to as much as 40% of AKI cases and even up to 60% in elderly patients (Perazella, 2012, Morales-Alvarez, 2020, Bentley et al., 2010). Drugs can induce nephrotoxicity directly through obstructive nephropathy, interstitial nephritis, or glomerular or tubular damage, or indirectly by decreasing renal blood flow (Pannu and Nadim, 2008).

Potentially nephrotoxic drugs should be limited or avoided, and doses should be adjusted based on kidney function to prevent underdosing or side effects (Moore et al., 2018, Meersch et al., 2017). Prompt administration of antibiotics is crucial for septic patients (Bagshaw et al., 2009). Patients with altered systemic and renal haemodynamics or fluid loss are at high risk of developing prerenal AKI if exposed to high-dose systemic vasoconstrictors, NSAIDs, calcineurin inhibitors, or renin-

angiotensin-aldosterone system blockers, as these can reduce glomerular pressure and increase the risk of acute tubular injury (Perazella, 2012). In AKI patient management, it is recommended to promptly identify and treat additional complications, such as anaemia, metabolic acidosis, hyperkalaemia, and fluid overload, and initiate stress-ulcer prophylaxis to prevent infection (Khwaja, 2012).

The main goal of fluid therapy is to correct intravascular hypovolemia while avoiding fluid overload and associated complications, such as onset or worsening of AKI (Ostermann et al., 2019). The association between elevated CVP, renal venous congestion and AKI development has been reported in different ICU cohorts, particularly those with congestive heart failure (Gambardella et al., 2016, Legrand et al., 2013).

A randomised study of 1000 patients with ARDS found that fluid-restrictive strategies were safe (Wiedemann et al., 2006). However, fluid-restrictive management during major elective abdominal surgeries increases the risk of AKI development (Myles et al., 2018). The role of fluid restriction in established AKI remains unclear and may depend on intravascular volume status. A pilot trial comparing restrictive fluid strategies to usual care in critically ill AKI patients demonstrated that restrictive fluid intake led to less need for RRT and reduced adverse effects incidence (Vaara et al., 2021). These findings aligned with Hjortrup et al. (2016), who observed that restrictive fluid strategies were associated with less AKI progression following initial fluid resuscitation in septic shock patients. However, two subsequent trials employing similar strategies did not replicate this result (Macdonald et al., 2018, Corl et al., 2019).

1.9 CONCLUSION

AKI is a growing concern associated with major adverse outcomes in critically ill patients, such as CKD progression, ESRD, and mortality. AKI is often a multifactorial condition rather than a distinct phenotype. AKI in the context of COVID-19 infection and ARDS may develop from different factors and potential pathophysiological mechanisms leading to direct or indirect kidney injury, such as endothelial injury, and local and systemic inflammatory and immune responses. Various novel biomarkers involved in different pathophysiological pathways following kidney injury show their ability to enhance diagnostic accuracy, risk stratification, and prognosis for patients with AKI.

Over time, studies have highlighted the effect of ARDS on kidney function and patient-related outcomes during ICU admission. However, this focus has been predominantly on short-term outcomes. There is limited evidence investigating long-term outcomes such as MAKE for up to 365 days (MAKE-365) after the onset of AKI in ICU patients with ARDS. This is indeed the gap that our research aims to address. Early identifying those patients at risk of MAKE-365 will enable clinicians to monitor signs of deteriorations and investigate interventions that could potentially prevent these long-term adverse outcomes related to AKI development. Further investigation is needed, although this area is still promising and could enhance patient care and outcomes.

1.10 HYPOTHESES

Three main hypotheses were tested in this thesis:

- First, that COVID-19 patients with ARDS would have a higher incidence of AKI than those without ARDS.
- Second, that non-COVID-19 ARDS patients would have a higher incidence of MAKE-365 than COVID-19 ARDS patients, and this difference could be predicted by identifiable clinical factors on ICU admission.
- Third, that novel kidney biomarkers would accurately predict MAKE-365 risk in ICU patients with ARDS.

1.11 AIMS

Aims for the first hypothesis:

- To summarise and evaluate evidence of AKI development in COVID-19 patients.
- To analyse AKI incidence and associated risk factors, the need for RRT, and mortality rates in COVID-19 patients with and without ARDS

Aim for the second hypothesis:

- To identify the incidence of MAKE-365 in non-COVID-19 and COVID-19 ARDS patients.

Aim for the third hypothesis:

- To assess the relationships between novel kidney biomarkers (including plasma Cystatin C, urinary NGAL, Urinary [TIMP-2]*[IGFBP-7], and urinary CCL-14) and MAKE-365 in ICU patients who developed ARDS during their ICU stay.

1.12 OBJECTIVES

The following objective was set to achieve the aims of the first hypothesis:

- To conduct a comprehensive systematic review on AKI development in COVID-19 patients with and without ARDS.

The objective to achieve the aim of the second hypothesis:

- To conduct a retrospective observational study comparing MAKE-365 incidence in COVID-19 and non-COVID-19 ARDS patients and identify clinical risk factors for MAKE-365 development in those patients.

The objective to achieve the aim of the third hypothesis:

- To conduct a secondary analysis on the prediction of MAKE-365 by using novel kidney biomarkers in ICU patients with and without ARDS.

CHAPTER 2

2 INCIDENCE AND RISK FACTORS OF ACUTE KIDNEY INJURY IN COVID-19 PATIENTS WITH AND WITHOUT ACUTE RESPIRATORY DISTRESS SYNDROME: A SYSTEMATIC REVIEW

2.1 INTRODUCTION

The COVID-19 pandemic has raised significant concerns about its potential impact on various organ systems, including the lungs and kidneys. There is increasing interest in assessing AKI development in COVID-19 patients. Despite this interest, limited studies have focused specifically on patients with COVID-19 and ARDS. This systematic review was performed to assess the incidence and risk factors of AKI, the need for RRT, and the mortality rate among COVID-19 patients with and without ARDS from the first wave of COVID-19.

This chapter has also been published in full in the Renal Failure Journal under the title **"Incidence and risk factors of acute kidney injury in COVID-19 patients with and without acute respiratory distress syndrome (ARDS) during the first wave of COVID-19: a systematic review and Meta-Analysis"** (Alenezi et al., 2021) (see Appendix 7.1). The paper is presented in full, below, and author contributions, as published, are given.

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Authors' contributions:

F.K.A., D.R.T., and J.M.P. conceived and planned the study. F.K.A. performed data analysis and visualisation and wrote the manuscript. F.K.A. and M.A.A. performed abstract screening, full-text screening and quality assessment. F.K.A. and R.M. planned and performed the searching strategy and data synthesis. M.N.B. and D.P. revised the manuscript.

2.2 ABSTRACT

Background: Acute kidney injury (AKI) is common among patients with COVID-19. However, AKI incidence may increase when COVID-19 patients develop acute respiratory distress syndrome (ARDS). Thus, this systematic review and meta-analysis aimed to assess the incidence and risk factors of AKI, need for renal replacement therapy (RRT), and mortality rate among COVID-19 patients with and without ARDS from the first wave of COVID-19.

Methods: The databases MEDLINE and EMBASE were searched using relevant keywords. Only articles available in English published between December 1, 2019, and November 1, 2020, were included. Studies that included AKI in COVID-19 patients with or without ARDS were included. Meta-analyses were conducted using random-effects models.

Results: Out of 618 studies identified and screened, 31 studies met the inclusion criteria. A total of 27500 patients with confirmed COVID-19 were included. The overall incidence of AKI in patients with COVID-19 was 26% (95% CI=19% to 33%). The incidence of AKI was significantly higher among COVID-19 patients with ARDS than COVID-19 patients without ARDS (59% vs. 6%, P< 0.001). Comparing ARDS with non-ARDS COVID-19 cohorts, the need for RRT was also higher in ARDS cohorts (20% vs. 1%). The mortality among COVID-19 patients with AKI was significantly higher (Risk ratio= 4.46; 95% CI= 3.31-6; P<0.00001) than patients without AKI.

Conclusion: This study shows that ARDS development in COVID-19-patients leads to a higher incidence of AKI and increased mortality rate. Therefore, healthcare providers should be aware of kidney dysfunction, especially among elderly patients with multiple comorbidities. Early kidney function assessment and treatments are vital in COVID-19 patients with ARDS.

2.3 BACKGROUND

In December 2019, a novel coronavirus disease (COVID-19), was identified in Wuhan, China, which has spread quickly worldwide (Xu et al., 2020). On March 11, 2020, the World Health Organization declared COVID-19 as a pandemic (Alvarez-Belon et al., 2020). At the time of writing this review, over 32.7 million COVID-19 cases and 991000 deaths have been reported. This rapid spread of COVID-19 across the world brought many challenges to global health care systems. COVID-19 leads to a wide range of clinical manifestations from asymptomatic, mild, moderate to severe health conditions. Symptomatic patients usually present with fever, dry cough, shortness of breath, myalgia or fatigue (Baj et al., 2020). COVID-19 is of clustering onset and mostly affects the respiratory system, with some patients rapidly progressing to acute respiratory distress syndrome (ARDS); these patients frequently require admission to the intensive care unit (ICU) (Grasselli et al., 2020). Furthermore, it has been demonstrated that severe cases are mostly among the elderly and those with an underlying disease, which may progress to respiratory failure and increased risk of mortality (Grasselli et al., 2020).

A growing body of literature has exhibited that there are three potential mechanisms through which the kidney becomes involved in COVID-19 disease: cytokine-induced damage, systemic effects, and organ crosstalk (Ronco and Reis, 2020). These mechanisms are interrelated and have important implications for extracorporeal therapy (Ronco and Reis, 2020). Several risk-factors may contribute to developing acute kidney injury (AKI) in severe cases; for example, most COVID-19 patients with AKI are older.

Furthermore, they have comorbidities such as diabetes mellitus or hypertension, which are a well-known to associate with kidney vulnerability (Gabarre et al., 2020). ARDS has been identified as one of the prominent conditions that could lead to AKI development; this is also one of the primary reasons for admission in individuals with severe COVID-19 (Grasselli et al., 2020, Guan et al., 2020a, Huang et al., 2020). Additionally, some factors were associated with AKI development in patients with ARDS, such as impairment of gas exchange and severe hypoxemia (Darmon et al., 2009b).

Early reports from China suggested that the prevalence of AKI among patients with COVID-19 was low (Gabarre et al., 2020). Guan et al studied 1,099 Chinese patients with confirmed COVID-19; 93.6% of those patients were hospitalised, but only 5.3% of those were admitted to the ICU (Guan et al., 2020a). Across the hospital cohort, 3.4% developed ARDS and only 0.5% developed AKI. Notwithstanding, AKI is mostly common in critically ill patients with COVID-19, affecting 20-40% of patients admitted to ICU (Izzedine and Jhaveri, 2020). It is deemed a marker of disease severity and an adverse prognostic factor of survival (Izzedine and Jhaveri, 2020). A multicentre retrospective study from Wuhan investigated 239 critically ill COVID-19 patients and reported that the most common complications among those patients were ARDS, acute cardiac injury, and AKI (68.6%, 43.1%, and 49.8%, respectively) (Xu et al., 2020). To date, most studies have revealed the incidence of AKI and ARDS in COVID-19 patients. However, none of these studies has compared AKI incidence in COVID-19 patients with and without ARDS. Therefore, this systematic review aimed to assess the incidence and risk factors of AKI among COVID-19 patients with and without ARDS. We also aimed to assess the necessity of renal replacement therapy (RRT) in addition to mortality rate.

2.4 MATERIALS AND METHODS

The protocol of this review has been registered prospectively in the international registry of systematic reviews (PROSPERO) with registration number CRD42020219460, complete protocol is found in Appendix 7.2. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) guideline was used to report this systematic review and meta-analysis (Moher et al., 2009). The PRISMA checklist is provided in Appendix 7.3.

A comprehensive literature search was performed by searching MEDLINE and EMBASE databases via the Ovid portal to select studies that met the inclusion criteria. The search terms and strategy used were; (Adult*) AND (“Novel coronavirus.ti,ab.” OR “New coronavirus.ti,ab.” OR “Coronavirus 2019.ti,ab.” OR “COVID-19.ti,ab.” OR “SARS-CoV-2.ti,ab.”) AND (“hospitalisation.ti,ab.” OR “hospitalization.ti,ab.” OR “oxygen therapy.ti,ab.” OR “ventilation.ti,ab.” OR “mechanical ventilation.ti,ab.” OR “Positive Pressure Ventilation.ti,ab.” OR “renal dialysis.ti,ab.” OR “renal replacement therapy.ti,ab.” OR “RRT.ti,ab”). AND (“acute kidney injury.ti,ab.” OR “AKI.ti,ab.” OR “acute renal injury.ti,ab.” OR “acute kidney insufficiency.ti,ab.” OR “acute renal insufficiency.ti,ab.” OR “acute kidney failure.ti,ab.” OR “acute renal failure.ti,ab.” OR “respiratory distress syndrome.ti,ab.” OR “respiratory failure.ti,ab.”). The search was limited to original research published between December 1, 2019 and November 1, 2020 with full text available in English.

2.4.1 Study Selection:

Two authors independently screened the abstracts, and any disagreements were resolved by consensus or by a third reviewer. The studies were initially screened by title and abstract to assess articles for relevance. The following populations were excluded: paediatric, end-stage kidney disease, kidney transplant, pregnant, or patients who have cancer. Additionally, case reports, reviews, and case series with less than ten patients were excluded. The full texts for the remaining studies were assessed for the following inclusion criteria: observational cohort studies, cross-sectional studies, and case series, with extractable quantitative data on patient demographics and data on AKI, ARDS, need for RRT, and mortality rate. Retrieved full-texts were independently assessed for eligibility by two authors, and disagreements resolved through consensus.

2.4.2 Data Extraction and Quality Assessment:

The following information was extracted from each included study: authors' names, study sites, study design, sample size, cohort demographics (age and sex), the prevalence of comorbidities, and ICU admission. All clinical information related to AKI incidence, ARDS, need for RRT, and mortality rate were extracted. The primary outcome was the incidence of AKI in COVID-19 patients with and without ARDS. The secondary outcomes were the need for RRT and the mortality rate of COVID-19 patients with AKI and ARDS as well as AKI without ARDS. All studies were qualitatively evaluated based on the National Institute of Health (NIH) quality assessment tools for observational cohort/ cross-sectional studies and case series studies with the quality classified as good, fair

and poor. Two independent reviewers assessed quality of included studies (FA and MAA). Disagreement was resolved through discussion.

2.4.3 Data Synthesis and Analysis:

Random-effects meta-analyses were performed to obtain pooled incidence, Risk Ratio (RR) estimates, and 95% confidence intervals (CIs) for categorical variables. The Metan and Metaprop command tools were used to analyse the incidence of AKI (Nyaga et al., 2014). After the initial analysis, heterogeneity in incidence and mortality outcomes were investigated. All analyses were performed using Stata 16 and Revman 5 (Cochrane). A funnel plots were used to assess publication bias.

2.5 RESULTS

2.5.1 Study selection:

A total of 618 abstracts were obtained and screened, of which 63 full-text articles were assessed for eligibility and 31 met the inclusion criteria (Figure 2.1 shows the PRISMA flow diagram). Only two studies were cross-sectional in design (Yu et al., 2020, Gasparini et al., 2021), fifteen studies were cohort studies (Aggarwal et al., 2020, Chen et al., 2020a, Chen et al., 2020b, Cheng et al., 2020b, Cui et al., 2020, El Aidaoui et al., 2020, Fisher et al., 2020, Fominskiy et al., 2020, Grimaldi et al., 2020a, Hong et al., 2020, Okoh et al., 2020, Qian et al., 2020, Russo et al., 2020, Zahid et al., 2020, Zhou et al., 2020a), and fourteen studies were case series (Arentz et al., 2020, Argenziano et al., 2020, Ch et al., 2020, Cheng et al., 2020a, Guan et al., 2020a, Hirsch et al., 2020, Huang

et al., 2020, Pei et al., 2020, Richardson et al., 2020, Suleyman et al., 2020, Yang et al., 2020, Zangrillo et al., 2020a, Zheng et al., 2020, Zhou et al., 2020b).

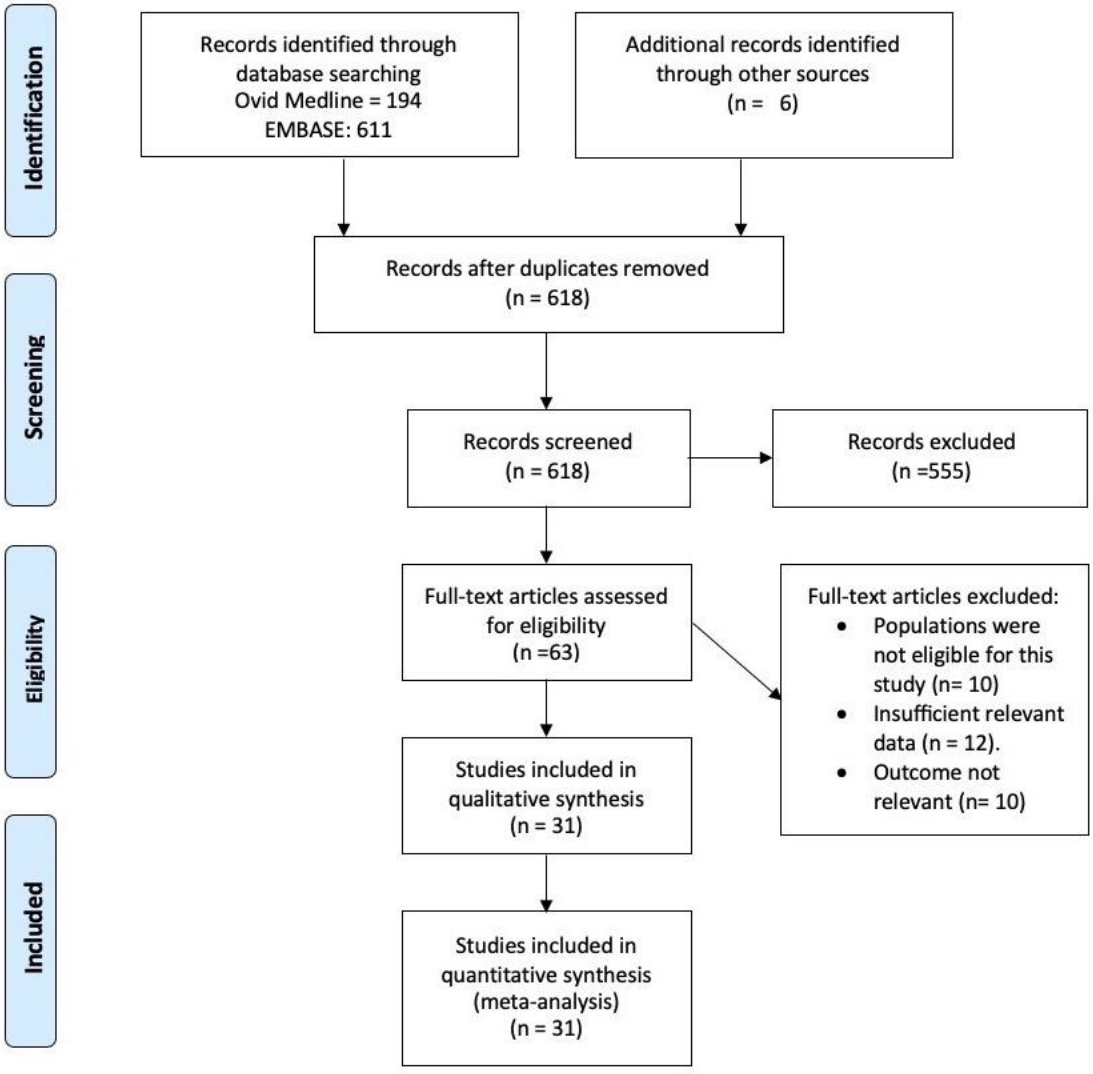


Figure 2.1. PRISMA flow diagram of included studies.

2.5.2 Study characteristics:

The included studies covered 27500 patients from hospitals in China, United States (US), United Kingdom (UK), Morocco, Italy, France, and Belgium. All studies included hospitalised patients, except Guan et al. (2020a), who included both inpatients and outpatients. Seven studies included only patients admitted to the ICU. All included studies reported the incidence of AKI and mortality rate; twenty-four studies reported the need for RRT; twenty-one studies reported the development of ARDS in COVID-19 patients.

The majority of patients were male (55.9%, 15378/27500). Twenty-one per cent (5934/27500) were admitted to the ICU, and 16.8% of all patients (4617/27128) died. The most common comorbidities reported were hypertension (40%) and diabetes (26%). 5.8% of patients had evidence of chronic kidney disease (CKD) at baseline. Two studies from United States (Suleyman et al., 2020, Arentz et al., 2020) and one from Italy (Russo et al., 2020) reported CKD prevalence between 28.6% to 47.6% (See Table 2.1).

Table 2.1. Characteristics of the included studies in patients with COVID-19.

Study name	Country	Study design	N	Demographics		Comorbidities (%)			
				Mean/median age (years)	Male (%)	Hypertension	Diabetes	CKD	Obesity
Aggarwal et al. (2020)	US	Single-centre, retrospective cohort study	16	67 (38-95)	12 (75)	9 (57)	5 (31)	6 (38)	8 (50)
Arentz et al. (2020)	US	Single-centre, retrospective case series	21	70 (43-92)	11 (52)	—	7 (33.3)	10 (47.6)	—
Argenziano et al. (2020)	US	Single-centre, retrospective case series	1000	63 (50-75)	596 (59.6)	601 (60.1)	372 (37.2)	137 (13.7)	52/841 (48.3)
Ch et al. (2020)	US	Multicentre, Retrospective case series	300	58.2 ± 12.6	182 (60.7)	200 (66.7)	134 (44.7)	39 (13)	163 (54)
Chen, Bai et al. (2020)	China	Multicentre, Retrospective Cohort study	3309	62 (49-69)	1642 (49.62)	988 (29.9)	464 (14)	57 (1.7)	—
Chen, Liu et al. (2020)	China	Multicentre, Retrospective Cohort study	792	55 (36-68)	432 (55)	215 (27)	142 (18)	26 (3.3)	—
Cheng et al. (2020) a	China	Single-centre, retrospective cohort study	1392	63 (50-71)	711 (51)	499 (36)	241 (17)	21 (1.5)	—
Cheng et al. (2020) b	China	Single-centre, Prospective case series	701	63 (50-71)	367 (52.4)	233 (33.4)	100 (14.3)	14 (2)	—
Cui et al. (2020)	China	Multicentre, Retrospective cohort study	116	59	66 (56.9)	38 (32.27)	28 (24.1)	5 (4.3)	—
El Aidaoui et al. (2020)	Morocco	Single-centre, retrospective cohort study	134	53 (36-64)	73 (54.5)	36 (26.9)	19 (14.2)	3 (2.2)	—
Fisher et al. (2020)	US	Multicentre, Retrospective cohort study	3345	64.4 ± 16.4	1776 (53.1)	—	906 (27.1)	409 (12.1)	1351 (42.9)
Fominskiy et al. (2020)	Italy	Single-centre, Prospective cohort study	99	61	83 (83.8)	34 (52.9)	12 (13.6)	5 (5)	22 (22.2)
Gasparini et al. (2020)	UK	Multicentre, Retrospective cross-sectional study	372	59 (51-65)	269 (72)	—	—	—	—
Grimaldi et al. (2020)	France /Belgium	Multicentre, Retrospective cohort study	415	64 ± 10	321 (77)	235 (57)	—	33 (7.9)	—
Guan et al. (2020)	China	Multicentre, Retrospective case series	1099	47 (35-58)	640 (58.2)	165 (15)	81 (7.4)	8 (0.7)	—
Hirsch et al. (2020)	US	Multicentre, Retrospective case series	5449	64 (52-75)	3317 (60.9)	3037(55.7)	1797 (33)	—	1475 (27.1)

Hong et al. (2020)	China	Single-centre, retrospective cohort study	98	55.4 ± 17.1	38 (38.8)	30 (30.6)	9 (9.2)	—	—
Huang et al. (2020)	China	Single-centre, Prospective case series	41	49 (41-58)	30 (73.2)	6 (15)	8 (20)	—	—
Okoh et al. (2020)	US	Single-centre, retrospective cohort study	251	62 (49-74)	129 (51)	175 (70)	115 (46)	46 (18)	120 (48)
Pei et al. (2020)	China	Single-centre, retrospective case series	333	56.3 ± 13.4	182 (54.7)	107 (32.2)	76 (22.9)	—	—
Qian et al. (2020)	China	Single-centre, retrospective cohort study	37	55 (48-68)	26 (68.4)	14 (36.8)	8 (21.1)	1 (2.7)	—
Richardson et al. (2020)	US	Multicentre, Retrospective case series	5700	63 (52-75)	3437 (60.3)	3026 (56.6)	1808 (33.8)	268 (4.7)	1737 (41.7)
Russo et al. (2020)	Italy	Single-centre, retrospective cohort study	777	70 ± 16	59 (7.6)	385 (49.5)	123 (15.8)	222 (28.6)	—
Suleyman et al. (2020)	US	Single-centre, retrospective case series	463	57.5 ± 16.8	204 (44)	295 (63.7)	178 (38.4)	182 (39.3)	262 (57.6)
Yang et al. (2020)	China	Single-centre, retrospective case series	52	59.7 ± 13.3	35 (67)	—	9 (17)	—	—
Yu et al. (2020)	China	Multicentre, Prospective cross-sectional study	226	64 (57-70)	139 (61.5)	96 (42.5)	47 (20.8)	—	—
Zahid et al. (2020)	US	Single-centre, retrospective cohort study	469	66 (55-75)	268 (57.1)	232 (68.6)	219 (46.7)	50 (11)	—
Zangrillo et al. (2020)	Italy	Single-centre, retrospective case series	73	61 (54-69)	61 (83.6)	39 (52.9)	10 (13.6)	—	—
Zheng et al. (2020)	China	Single-centre, retrospective case series	34	66 (58-76)	23 (67.6)	22 (64.7)	8 (23.5)	2 (5.9)	—
Zhou, Yang et al. (2020)	china	Multicentre, Retrospective case series	195	66 (56-76)	130 (66.7)	89 (45.6)	55 (28.2)	—	—
Zhou, Yu et al. (2020)	China	Multicentre, Retrospective Cohort study	191	56 (46-67)	119 (62)	58 (30)	36 (19)	2 (1)	—

Values are median (IQR), mean (SD) or number (proportion).
N: number; CKD: Chronic kidney disease.

Definitions of AKI and ARDS were consistent among the included studies, and the same definitions were used in this review. AKI was defined based on the Kidney Disease: Improving Global Outcomes criteria (KDIGO) (Kellum et al., 2012) and ARDS was defined based on Berlin definition (Ranieri et al., 2012).

2.5.3 Quality Assessment and Risk of Bias:

As the studies were case-series and cohort/ cross-sectional studies, all included articles were evaluated using the NIH quality assessment tools. Domains 5 of the NIH quality assessment tool of case series and also the domain 5, 8, and 12 of the NIH quality assessment tool of observational cohort/ cross-sectional studies were not applicable as they relate to the intervention, power calculation, exposure measure overtime and blinding of outcome assessment and these were not applicable to the included studies (Appendix 7.4). Out of the 31 studies, 27 were judged as good quality, 3 as fair (Aggarwal et al., 2020, Cui et al., 2020, Zahid et al., 2020) and 1 as poor quality (Hong et al., 2020). A funnel plot did not indicate major publication bias (Figure 2.2).

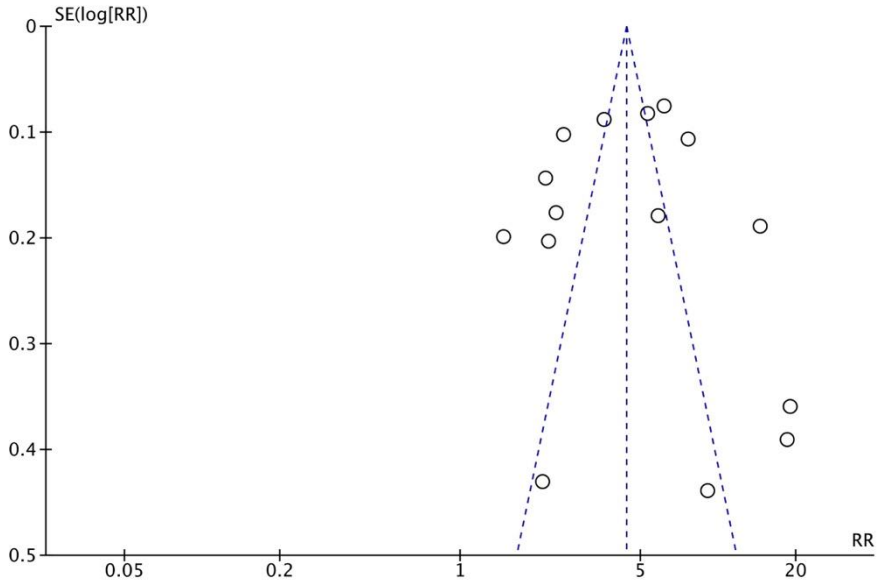


Figure 2.2. Funnel plot for detection of publication bias.

2.5.4 Results of individual studies:

Across all 31 studies, a total of 27500 patients were included in this review. Overall pooled AKI incidence was 26% (95% CI= 19-33). Across eight studies that only included COVID-19 patients admitted to the ICU (n=1540), AKI incidence was 50% (95% CI= 35-65) (Ch et al., 2020, Fominskiy et al., 2020, Grimaldi et al., 2020a, Yu et al., 2020, Zangrillo et al., 2020a, Zheng et al., 2020, Arentz et al., 2020, Gasparini et al., 2021). Only three studies included hospitalised patients who were not admitted to the ICU, across which the pooled AKI incidence was only 25% (95% CI= 21-29) (Russo et al., 2020, Yang et al., 2020, Zahid et al., 2020). In table 2.2, the overall study outcomes are reported.

Table 2.2. Outcomes of the included studies in patients with COVID-19.

				Incidence			Mortality			
Study name	**Country**	**N**	**Admitted to ICU**	**AKI**	**ARDS**	**Need for RRT**	**Overall mortality**	**AKI**	**ARDS**	**RRT**
Aggarwal et al. (2020)	US	16	8 (50)	11 (69)	5 (31)	__	3 (19)	__	__	__
Arentz et al. (2020)	US	21	__	4 (19.1)	20 (95.2)	__	11 (52.4)	__	__	__
Argenziano et al. (2020)	US	1000	236 (23.6)	288/850 (33.9)	299/850 (35.2)	117/850 (13.8)	211 (21.1)	__	__	__
Ch et al. (2020)	US	300	300 (100)	230 (76.7)	275 (91.7)	133 (44.3)	157(52.3)	138 (60)	155 (56.4)	82 (61.7)
Chen, Bai et al. (2020)	China	3309	1036 (31.3)	401 (12.1)	1325 (40)	__	307 (9.3)	__	__	__
Chen, Liu et al. (2020)	China	792	94 (12)	46 (6)	104 (13)	11 (1.4)	68 (8.6)	32 (69.6)	61 (58.6)	11 (100)
Cheng et al. (2020) a	China	1392	140 (10)	99(7)	__	__	199 (14)	71 (71.7)	__	__
Cheng et al. (2020) b	China	701	73 (10.4)	36 (5.1)	__	__	113 (16.1)	__	__	__
Cui et al. (2020)	China	116	NA	21 (18.1)	__	__	18 (15.5)	12 (57.1)	__	__
El Aidaoui et al. (2020)	Morocco	134	45 (33.6)	8 (6)	13 (9.7)	8 (6)	14 (10.4)	8 (100)	4 (30.8)	__
Fisher et al. (2020)	US	3345	438 (13.1)	1903 (56.9)	__	164 (4.9)	775 (23.2)	641 (33.7)	__	__
Fominskiy et al. (2020)	Italy	99	99 (100)	72 (72.7)	__	17 (17.7)	33 (33.3)	28 (38.9)	__	9 (52.9)
Gasparini et al. (2021)	UK	372	372 (100)	168 (45)	__	121 (32.5)	139 (37)	81 (48)	__	__
Grimaldi et al. (2020)	France /Belgium	415	415 (100)	231 (56)	415 (100)	82 (19.76)	166 (40)	121 (52.4)	166 (40)	49 (59.7)
Guan et al. (2020)	China	1099	33 (16.2)	6 (0.5)	37 (3.4)	9 (0.8)	15 (1.4)	__	__	__
Hirsch et al. (2020)	US	5449	1395 (25.6)	1993 (36.6)	__	285 (5.2)	888 (16.3)	694 (34.8)	__	157 (55.1)

Hong et al. (2020)	China	98	13 (13.3)	9 (9.2)	18 (18.4)	3 (3.1)	5 (5.1)	__	__	__
Huang et al. (2020)	China	41	13 (32)	3 (7)	12 (29)	3 (7)	6 (14.6)	__	__	__
Okoh et al. (2020)	US	251	82 (33)	52 (21)	82 (33)	52 (21)	97 (38.6)	__	__	__
Pei et al. (2020)	China	333	189 (56.8)	35 (10.5)	__	6 (1.8)	29 (8.7)	20 (57.1)	__	__
Qian et al. (2020)	China	37	37 100)	8 (21.6)	11 (29.7)	3 (8.1)	1 (2.7)	__	__	__
Richardson et al. (2020)	US	5700	373 (6.5)	1370 (24)	__	225 (3.9)	553 (9.7)	347 (25.3)	__	78 (34.7)
Russo et al. (2020)	Italy	777	__	176 (22.6)	__	21 (2.8)	275 (35)	111 (63.1)	__	__
Suleyman et al. (2020)	US	463	141 (39.7)	159/355 (44)	111/355 (31.3)	25/355 (7)	72 (16)	__	__	__
Yang et al. (2020)	China	52	__	15 (29)	35 (67)	9 (17)	32 (61·5)	12 (80)	26 (74.3)	8 (88.9)
Yu et al. (2020)	China	226	226 (100)	57 (25.2)	161 (71.2)	24 (10.6)	87 (38.5)	__	__	__
Zahid et al. (2020)	US	469	__	128 (27.3)	206 (44)	22 (4.7)	188 (40.1)	91 (71.1)	__	18 (81.8)
Zangrillo et al. (2020)	Italy	73	73 (100)	55 (75.3)	73 (100)	16 (21.9)	19 (26)	__	19 (26)	__
Zheng et al. (2020)	China	34	34 (100)	7 (20.6)	33 (97.1)	5 (14.7)	0(0)	__	__	__
Zhou, Yang et al. (2020)	china	195	19 (9.8)	58 (29.7)	162 (83.1)	26 (13.3)	82 (42)	__	__	__
Zhou, Yu et al. (2020)	China	191	50 (26)	28 (15)	59 (31)	10 (5)	54 (28.3)	27 (96)	50 (84.7)	10 (100)

Values are numbers (proportion).
N, number; ICU, Intensive care unit; AKI, Acute Kidney Injury; ARDS, Acute respiratory distress syndrome; RRT, Renal Replacement Therapy.

The majority (68.6%) of patients admitted to ICU had ARDS (Ch et al., 2020, Fominskiy et al., 2020, Gasparini et al., 2021, Grimaldi et al., 2020a, Qian et al., 2020, Yu et al., 2020, Zangrillo et al., 2020a, Zheng et al., 2020). Suleyman et al. (2020) carried out a case series of 463 consecutive patients with COVID-19. The mean age was 57.5±16.8 years and the majority female (55.9%), and African American (72.1%). The most common comorbidities in this cohort included hypertension (63.7%), CKD (39.3%), and diabetes (38.4%). Of these patients, 355 required hospital admission; 214 were treated in the general practice unit and 141 required ICU management. The AKI incidence was significantly higher among patients in the ICU than patients in the general practice unit (69.5% vs 28.5%. P <0.001). In the UK, Gasparini et al. (2021) conducted a multicentre observational study, aiming to examine the association between acute and chronic kidney disease with clinical outcomes in 372 patients with COVID-19 and admitted to ICU. The median age of this cohort was 59 (51-65) years. Most them were male (72%) and the majority of patients were from a Black, Asian and minority ethnic (BAME) background (76%). Most patients (91%) required mechanical ventilation. A total of 168 patients (45%) developed AKI and had a high mortality rate (48%) (95% CI= 41-56).

2.5.4.1 AKI incidence rate in non-ARDS COVID-19 patients:

After excluding all studies that reported the presence of ARDS among their cohorts, the pooled AKI incidence across eight studies with a total of 18185 patients, was 23% (95% CI= 13-35) (Richardson et al., 2020, Hirsch et al., 2020, Fisher et al., 2020, Cui et al., 2020, Cheng et al., 2020b, Cheng et al., 2020a, Russo et al., 2020, Pei et al., 2020, Gasparini et al., 2021). There was a high rate of comorbidities in these cohorts

including hypertension (42%) (95% CI= 35-49) (Russo et al., 2020, Pei et al., 2020, Hirsch et al., 2020, Cui et al., 2020, Cheng et al., 2020b, Cheng et al., 2020a, Richardson et al., 2020), obesity (33%) (95% CI= 26-40) (Hirsch et al., 2020, Fisher et al., 2020, Richardson et al., 2020), and diabetes (23%) (95% CI= 18-28) (Russo et al., 2020, Pei et al., 2020, Hirsch et al., 2020, Fisher et al., 2020, Cui et al., 2020, Cheng et al., 2020b, Cheng et al., 2020a).

Hirsch et al. (2020) and Richardson et al. (2020) studied 11149 hospitalised COVID-19 patients with a mean age of 63.5 (52-75) years. Both cohorts had a high prevalence of hypertension (55.7%-56.6%) and obesity (27.1%- 41.7%). Both studies reported a high incidence of AKI (24%-36.6%) and a high mortality rate in those patients who developed AKI (25.3%- 35%).

Furthermore, Cheng et al. (2020b) studied 1392 COVID-19 patients retrospectively, aiming to assess AKI incidence. The median age of this cohort was 63 years, and they had fewer comorbidities compared to previous studies: hypertension (36%), diabetes (17%) and CKD (1.5%). Only 7% (99 patients) of this cohort developed AKI, and no patient needed RRT. Later, the same authors conducted a prospective cohort study on 701 COVID-19 patients (Cheng et al., 2020a). The median age was 63 years, and 33.4% of those patients had hypertension, 17% had diabetes, and only 2% had CKD. The incidence of AKI among those patients was 5.1%, and the overall mortality was 16.1%.

2.5.4.2 AKI incidence rate in ARDS COVID-19 patients:

Twenty-two studies included COVID-19 patients with ARDS. While these cohorts included >90% of patients with ARDS, the pooled AKI incidence was 67% (95% CI= 57-76) (Zheng et al., 2020, Zangrillo et al., 2020a, Zahid et al., 2020, Grimaldi et al., 2020a, Fominskiy et al., 2020, Ch et al., 2020).

Grimaldi et al. (2020a) examined 415 COVID-19 patients with moderate-to-severe ARDS who were invasively ventilated and treated with different antiviral strategies. Patients were aged between 50 and 70 years. Most were males (n = 321, 77%) with mean Body Mass Index (BMI) (30 ± 5 kg/m2), and hypertension was the most frequent comorbidity among the cohort (n = 235 patients; 57%). The findings of this study showed that 56% of patients developed AKI. However, these findings might be affected by the different antiviral therapies being used. Zangrillo et al. (2020a) also assessed 73 COVID-19 patients with ARDS; they were mostly male (83.6%) with a median age of 61 years. The authors revealed that 75.3% of the population developed AKI. The most frequent comorbidities were hypertension (52.9%), obesity (>25%) and diabetes (13.6%). Fominskiy et al. (2020) studied 99 confirmed COVID-19 patients who were admitted to ICU and invasively ventilated. The aim was to assess the clinical characteristics, predictors of AKI, and RRT need. The median age was 61 years, and the most frequent comorbidities were hypertension (52.9%) and obesity (22.2%). Since all patients were invasively ventilated, it is likely that a substantial proportion of these patients had ARDS. A total of 72.7% of those patients developed AKI.

Ch et al. (2020) studied 300 COVID-19 patients admitted to the ICU with a mean age (+SD) of 58.2±12.6 years. The majority (91.7%) of participants had ARDS, and 76.7% of patients presented either with AKI on admission or developed AKI during the course of illness. Increasing age (RR: 1.02; 95% CI= 1.01-1.03)) and male sex (48.4% vs. 23.8%; RR: 1.68; 95% CI= 1.2-2.3) were also risk factors for presentation with AKI. Both Arentz et al. (2020) and Zheng et al. (2020) carried out similar case series that included 55 participants to assess the clinical characteristics and outcomes of confirmed COVID-19 patients admitted to the ICU. The mean age was between 66 to 70 years. Although the majority (96.36%) of participants in both studies had ARDS, AKI incidence was ranged from 19.1% to 20.6%. The most common comorbidities reported by Arentz et al. (2020) were CKD (47.6%) and congestive heart failure (42.9%), and most frequent comorbidity reported by Zheng et al. (2020) was hypertension (64.7%).

2.5.4.3 Need for RRT:

Twenty-five studies reported the need for RRT and only 6% of all patients required RRT (Table 2). After analysing the studies that reported patients with ARDS, we found that 10% of patients required RRT across nineteen studies. Nevertheless, the need for RRT was only 5% among studies which did not report ARDS incidence (Russo et al., 2020, Richardson et al., 2020, Pei et al., 2020, Hirsch et al., 2020, Gasparini et al., 2021, Fisher et al., 2020). A higher incidence of AKI (76.7%) and need for RRT (44.3%) were reported by Ch et al. (2020) who only included patients who were admitted to the ICU, of which >90% developed ARDS.

2.5.4.4 Mortality:

The overall mortality across all cohorts was 16.9%. However, the mortality was higher (38.7%) when the studies enrolled only COVID-19 patients admitted to the ICU (Zheng et al., 2020, Zangrillo et al., 2020a, Yu et al., 2020, Qian et al., 2020, Grimaldi et al., 2020a, Gasparini et al., 2021, Fominskiy et al., 2020, Ch et al., 2020). Mortality rate was significantly higher among cohorts comprising >90% of ARDS patients. For instance, ARDS patients comprised >90% of cohorts studied by both Ch et al. (2020) and Arentz et al. (2020), and the mortality was 52.3% and 52.4%, respectively. AKI mortality was reported across eighteen studies. Across eight studies that included patients with ARDS, AKI mortality was 60.3% (range, 52.4%-100%) (Zhou et al., 2020a, Zangrillo et al., 2020a, Yu et al., 2020, Grimaldi et al., 2020a, Fominskiy et al., 2020, El Aidaoui et al., 2020, Chen et al., 2020b, Ch et al., 2020). The remaining eight studies did not report ARDS incidence and revealed that AKI mortality was 34.2% (range, 25.3%-63%) (Russo et al., 2020, Richardson et al., 2020, Pei et al., 2020, Hirsch et al., 2020, Gasparini et al., 2021, Fisher et al., 2020, Cui et al., 2020, Cheng et al., 2020b).

2.5.5 Synthesis of results:

A total of 27500 patients from 31 studies were included in the meta-analysis of AKI incidence amongst all COVID-19 cohorts. By using a random-effects model, the pooled incidence of AKI was 26% (95% CI= 19-33; I^2= 99.38%; P< 0.001; Figure 2.3).

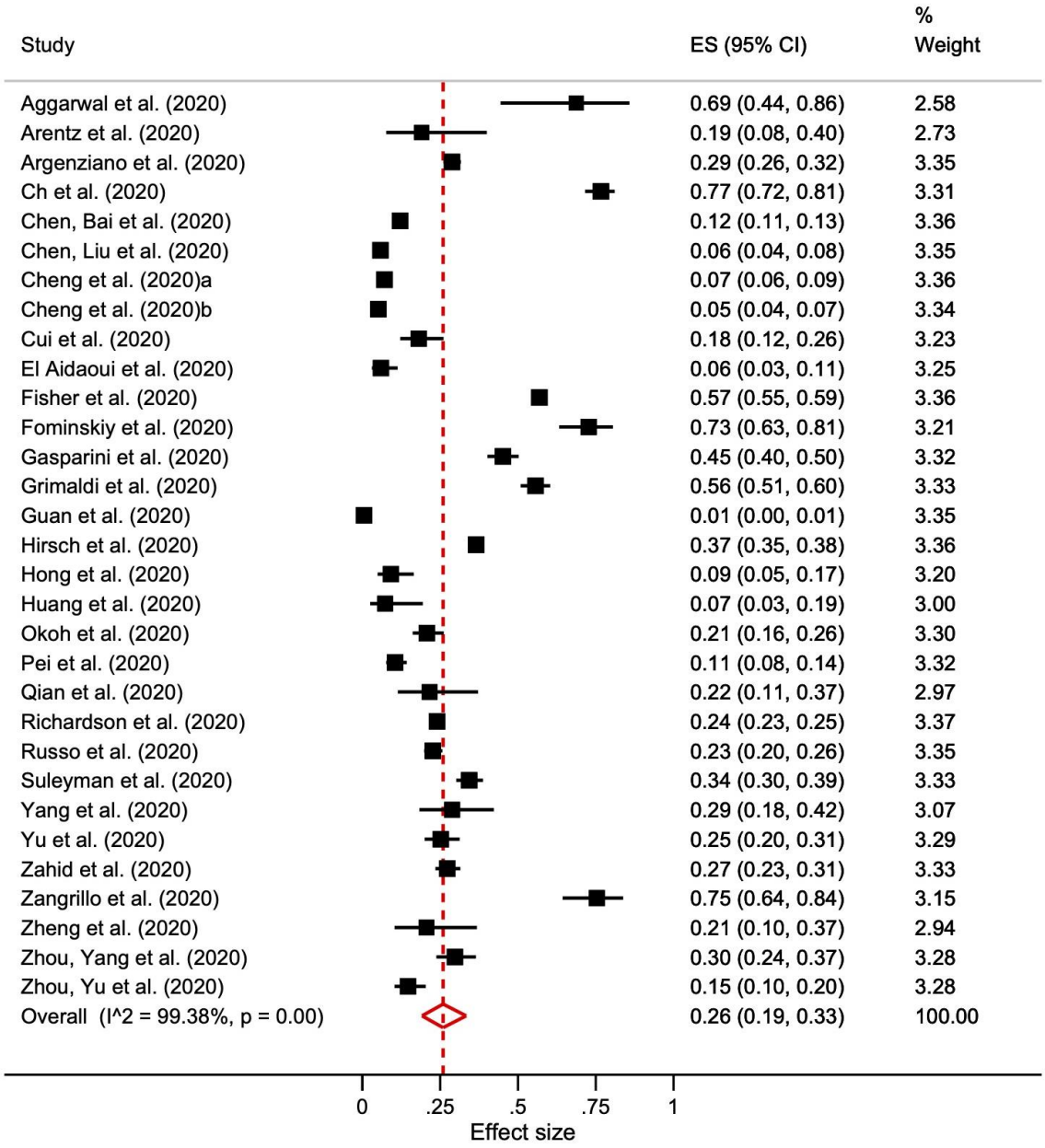


Figure 2.3. Forest plot of pooled AKI incidence in overall cohorts.

A total of 808 COVID-19-ARDS patients from five studies were included. The pooled incidence of AKI in ARDS patients was 59% (95% CI= 46-71; I^2= 90.26%; P< 0.001; Figure 2.4. A). A total of 174 COVID-19 patients without ARDS were included from three studies. The pooled incidence of AKI in this population was 6% (95% CI= 0-31; I^2 = 93.30%; P< 0.001; Figure 2.4 B).

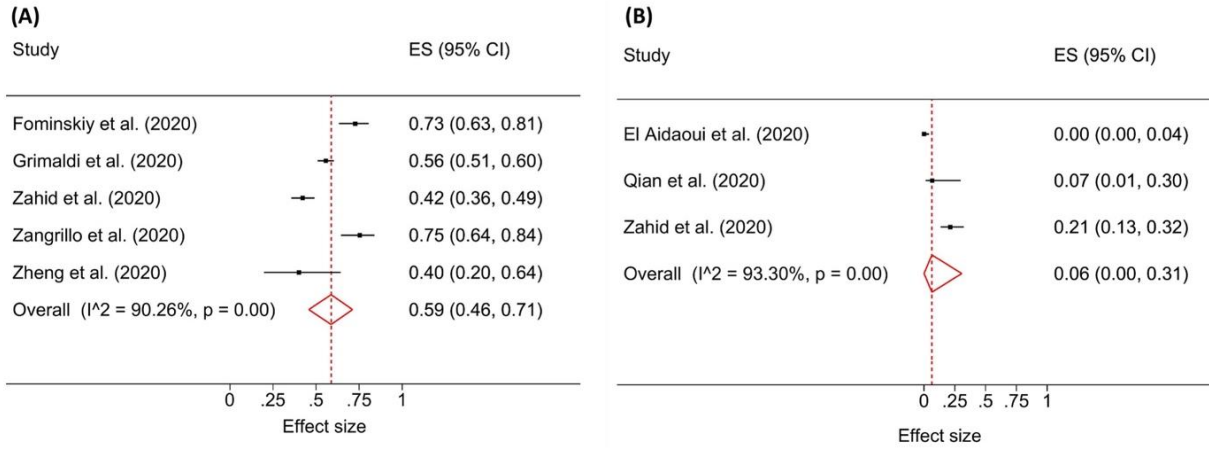


Figure 2.4. Forest plot of the pooled AKI incidence showing the increased rate in ARDS (A) compared to non-ARDS (B) cohorts.

The pooled need for RRT was assessed on a total of 590 ARDS patients from four studies and 174 non-ARDS patients from three studies. In ARDS patients, the pooled need for RRT was 20% (95% CI= 17- 23; I^2 = 0; P= 0.84; Figure 2.5 A) and only 1% (95% CI= 0- 5; I^2 = 56.41%; P= 0.10; Figure 2.5 B) in non-ARDS patients.

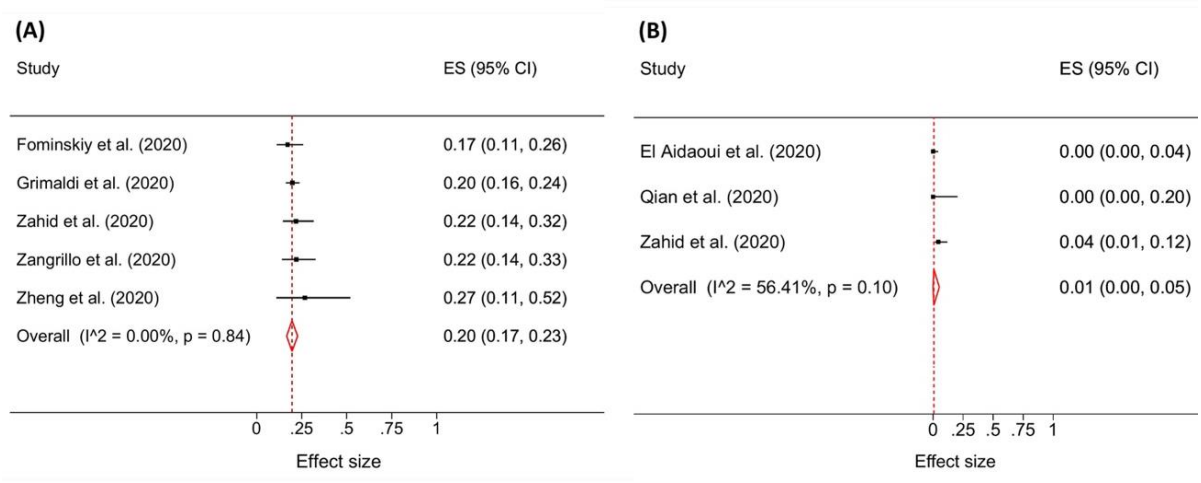


Figure 2.5. Forest plot demonstrating the need for RRT in ARDS (A) compared with non-ARDS (B) COVID-19 cohort.

The AKI mortality was analysed based on the data of 19,888 patients available from 16 studies. Development of AKI was associated with significantly higher mortality among COVID-19 patients, with RR of 4.46 (95% CI= 3.31- 6; I^2= 95%; P < 0.00001; Figure 2.6) in a random-effects model.

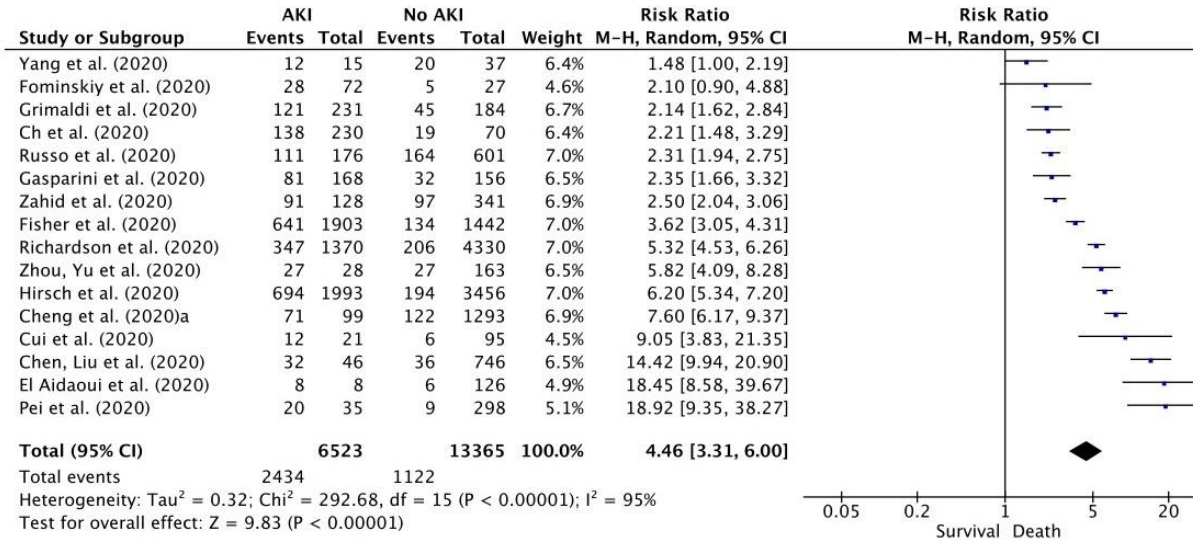


Figure 2.6. Forest plot for mortality risk among patients with AKI associated with COVID-19.

2.6 DISCUSSION

To the authors' knowledge, this is the first systematic review to assess and compare the incidence of AKI between COVID-19 patients with and without ARDS. Based on the literature, the incidence of AKI in ARDS patients prior to the emergence of COVID-19 was approximately 35-50%, and was associated with a high mortality rate which significantly increased by almost two-fold in the ICU (Cooke et al., 2008, Darmon et al., 2014b). For instance, a retrospective study examined a cohort of 634 ARDS patients and revealed an AKI incidence rate of 68.3% after ARDS onset (Panitchote et al., 2019a). However, AKI incidence may increase significantly in COVID-19 patients after the onset of ARDS, suggesting lung-kidney crosstalk as the dominant cause of kidney injury (Ahmed et al., 2020).

This review shows that most of the included studies reported a higher incidence of AKI in COVID-19 patients who developed ARDS. Across all cohorts with confirmed COVID-19 infection from China, US, UK, Morocco, Italy, France, and Belgium, we identified a wide range of AKI incidence which ranged from 0.5% to 76.7%. However, this may reflect the variety of disease severity thresholds for hospitalisation over the world and potential differences in clinical practice for monitoring kidney dysfunction.

Our findings show that COVID-19 patients admitted to the ICU had a higher incidence of AKI; however, most (68.6%) of those patients also had ARDS. This finding is consistent with that of Xu et al. (2020) who studied 239 critically ill COVID-19 patients admitted to the ICU and found that 49.8% of those patients developed AKI, and 68.6% had ARDS.

We identified that a high AKI incidence was most commonly reported when > 90% of patients in the cohort had ARDS (Arentz et al., 2020, Ch et al., 2020, Grimaldi et al., 2020a, Zangrillo et al., 2020a, Zheng et al., 2020, Zhou et al., 2020b, Fominskiy et al., 2020). Additionally, this meta-analysis comparing ARDS with non-ARDS COVID-19 cohorts revealed that AKI incidence was significantly higher among COVID-19 patients with ARDS (59% vs 6%, P< 0.001). These findings are consistent with a multicentre study conducted in nine ICUs located in Europe, which found that 50% of COVID-19 patients with ARDS developed AKI (Chaibi et al., 2020).

Although some studies did not enrol COVID-19 patients with ARDS, a few studies demonstrated a high incidence of AKI that ranged from 5.1% to 56.9% (Cheng et al., 2020a, Cheng et al., 2020b, Fisher et al., 2020, Gasparini et al., 2021, Hirsch et al., 2020, Pei et al., 2020, Richardson et al., 2020, Russo et al., 2020). Based on the literature, patients with a history of CKD are more likely to have comorbidities that have been identified as risk factors for poor outcomes, such as older age, hypertension, diabetes mellitus, cardiovascular disease, and this may be explained our findings (Portolés et al., 2020). Additionally, Nadim et al. (2020) suggested that the advanced age, CKD, and high prevalence of other comorbidities (e.g., hypertension, diabetes, obesity, and heart failure) are all linked to worse outcomes and are risk factors for the development of AKI in patients with COVID-19.

The metabolic syndrome is a cluster of risk factors (diabetes mellitus, hypertension, obesity) for developing cardiovascular disease and kidney abnormalities (Locatelli et al., 2006). The consequences of the metabolic syndrome on kidney functions in COVID-19 patients are poorly descried. Lohia et al. (2021) investigated

the association between metabolic syndrome and severe disease outcomes among 1871 patients with confirmed COVID-19 diagnosis. Author found that patients with metabolic syndrome had significantly increased in the ICU admission (odds ratio [OR], 1.68; 95% CI, 1.36-2.08; P < .001), and need for mechanical ventilation (OR, 1.90; 95% CI, 1.52-2.37; P < .001), and mortality rate (OR, 1.40; 95% CI, 1.11-1.75; P = .004). Patients with CKD were higher in metabolic syndrome cohort compared to none-metabolic syndrome cohort (14.7% vs 9%; P < .001). Metabolic syndrome cohort may be at higher risk of developing AKI if they contract COVID-19, and this risk may be by background CKD. Chen et al. (2004) recruited >6000 participants to examine the association between the metabolic syndrome and kidney impairment, and they found that the multivariate-adjusted risk for both CKD (defined as a GFR of <60 ml/min per 1.73 m2) and microalbuminuria was significantly higher in those with the metabolic syndrome compared to participants without metabolic syndrome (Odds ratio 2.60, 95% CI= 1.68-4.03 and 1.89, CI 1.34- 2.67, respectively). Also, they revealed that risk increased progressively with the number of the metabolic syndrome's components observed in each patient.

A meta-analysis comparing ARDS with non-ARDS COVID-19 cohorts showed the need for RRT was also higher in ARDS cohorts (20% vs 1%). Across all studies which reported the need for RRT, we observed a higher need for RRT among patients with a high incidence of AKI as reported by Ch et al. (2020) and Fominskiy et al. (2020). However, it is unclear from these studies whether RRT was used to treat fluid overload, end-stage kidney disease or patients with AKI alone.

The mortality rate was significantly increased in critically ill patients if they had a high incidence of AKI or ARDS (Grimaldi et al., 2020a, Ch et al., 2020). In our meta-analysis, the overall mortality among patients with AKI was significantly higher than those without AKI ($P < 0.00001$). In both Ch et al. (2020) and Arentz et al. (2020), AKI and ARDS development were associated with a high mortality rate. Ch et al. (2020) found that the AKI incidence was associated with a 25% increased risk of death (RR: 1.25; 95% CI: (1.02, 1.52)). These findings are consistent with previously published research, which found that severe AKI in patients with COVID-19 is associated with a high mortality rate (Ali et al., 2020). Additionally, in the population of Ch et al. (2020) high rates of comorbidities such as obesity (85.7% with BMI >25) and hypertension (66.7%) were also linked with increased mortality rate. Both Gasparini et al. (2021) and Fominskiy et al. (2020) also found that patients with AKI had a higher mortality rate compared to patients without AKI. A possible explanation for the higher mortality rate in the previous two studies is that each study recruited >90% critically ill individuals who were invasively ventilated in ICU.

The main limitation of this study is that most of the selected studies were of retrospective design, making them susceptible to selection bias. There was limited data on AKI patients' characteristics among included studies, such as urine output status, the need for RRT and the grade of AKI. This information is essential to define the severity and recoverability of AKI. Moreover, most cohorts were from China and the United States, and a small amount from Africa and Europe, which does reduce the generalization to other countries. The heterogeneity between studies was high; consequently, most of the analyses were interpreted based on a random-effects model. Furthermore, given the rapid, constant expansion of COVID-19 research,

several studies had limitations in their description of details and relatively short periods of follow-up. Finally, we cannot be certain that all relevant studies were captured, despite a detailed, comprehensive search strategy.

2.7 CONCLUSION

A higher incidence of AKI was most common among COVID-19 cohorts admitted to the ICU and was associated with the development of ARDS. Also, increased age, male sex, and pre-existing comorbidities (e.g., hypertension, diabetes, obesity, and CKD) were associated with significantly worse outcomes, which may be considered risk factors for developing AKI and increased mortality among COVID-19 patients. Therefore, healthcare providers should be aware of kidney dysfunction among those patients, especially those who are elderly with multiple comorbidities. This may ultimately lead to using appropriate diagnostic tools and treatment strategies to avoid additional damage to the kidneys and providing adequate kidney support when needed.

2.8 SUMMARY OF THE CHAPTER

This systematic review demonstrated that ARDS development in COVID-19 patients leads to a higher incidence of AKI and increased mortality rate, particularly in elderly male patients with pre-existing comorbidities (e.g., hypertension, diabetes, obesity, and CKD). However, further studies are required that address some of the limitations in the existing literature. The long-term kidney outcomes and associated risk

factors among ICU admissions with COVID-19-related ARDS or non-COVID-19-related ARDS will be assessed in Chapter 3.

CHAPTER 3

3 INCIDENCE OF MAJOR ADVERSE KIDNEY EVENTS AFTER ICU ADMISSION IN COVID-19 AND NON-COVID-19 ARDS PATIENTS

3.1 INTRODUCTION

Acute kidney injury (AKI) is prevalent in patients with acute respiratory distress syndrome (ARDS) and is associated with worse outcomes (Liu and Matthay, 2008, Liu et al., 2011, Mehta et al., 2002). Major adverse kidney events (MAKEs) are increasingly known as a confirmed long-term indicator of the effect of AKI on patient-related outcomes, especially in critically ill patients (Billings and Shaw, 2014). Identifying patients with MAKEs in patients with ARDS and AKI could have clinical significance, as those with MAKEs have been observed to have worse outcomes. This chapter explores the incidence of MAKEs for up to 365 days (MAKE-365) and demographic and clinical parameters associated with MAKE-365 in COVID-19 or non-COVID-19 patients with ARDS. Part of this work has been presented in abstract form at the European Society of Intensive Care Medicine (ESICM) LIVES 2022 Congress and published in the Intensive Care Medicine Experimental Journal (see Appendix 7.5).

This work was conducted as a team effort, and the contributions of the authors are detailed below.

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Authors' contributions:

F.K.A. planned the study, designed the methodology, performed data analysis and visualisation, and wrote the manuscript. J.M.P., D.R.T. and D.P. assisted in the planning and design of the study and revised the manuscript. R.M. assisted in the data collection process and participated in the manuscript revision.

3.2 BACKGROUND

The pandemic of COVID-19 has caused significant challenges for the global healthcare systems and medical research. Two waves (the first and second waves) of coronavirus (COVID-19) hit the UK between March 2020 and May 2021. In England, Gray et al. (2021) revealed a decrease in the hospital mortality rates for hospitalised patients with COVID-19 across the early phase of the first wave, which was maintained across the second wave. Unlike in the first wave, when there was limited evidence concerning COVID-19, scientific understanding of the illness improved by the second wave. Accordingly, healthcare systems were involved in providing a better medical response.

The clinical course of COVID-19 can progress from a mild viral infection to hypoxia, ARDS, multiorgan failure, and mortality in vulnerable individuals (Huang et al., 2020). The initial pulmonary pathology exhibits diffuse alveolar damage and signs of direct viral cytopathy, demonstrating that virus-induced damage has a direct causal role in ARDS development rather than a generalised inflammatory response (Nadim et al., 2020). Acute kidney injury (AKI) among non-COVID-19 ARDS has been linked to the development of endothelial injury and the systemic release of pro-inflammatory mediators, such as IL-6, soluble Tumor Necrosis Factor (TNF) receptors, and plasminogen activator inhibitor-1, which are comparable to the processes of AKI development in COVID-19 patients (Legrand et al., 2021).

As described in the systematic review in Chapter 2 we have shown that AKI affected up to 59% of patients with COVID-19 and ARDS with 20% of those patients needing RRT and an associated mortality of COVID-19 patients with AKI was

significantly higher (Risk ratio= 4.46; 95% CI= 3.31-6; P<0.00001) than patients without AKI (Alenezi et al., 2021).

Major adverse kidney events (MAKEs) – a composite of need for RRT or reduction in estimated glomerular filtration rate (eGFR) of <75% of baseline or all-cause mortality – are increasingly recognised as a validated long-term assessment tool for the effects of AKI development on patient-related outcomes, especially in critically ill patients (Billings and Shaw, 2014). Previous studies have shown that patients with AKI or renal dysfunction at ICU admission have a high risk for progression to receive RRT, which is one of the components of the MAKEs outcome (Billings and Shaw, 2014). Flannery et al. (2021) found that early measures of kidney biomarkers in AKI patients (such as serum/urinary cystatin C and serum/urinary neutrophil gelatinase-associated lipocalin [NGAL]) were significantly higher in patients who experienced MAKEs.

There are limited studies assessing kidney outcomes in patients with long COVID. However, one recent study examined the kidney outcomes after the acute phase of illness, which revealed that 30-day survivors of COVID-19 had a greater risk of developing AKI (adjusted Hazard Ratio (aHR): 1.94; 95% CI: 1.86-2.04) and MAKEs outcome, including eGFR reduction ≥ 50% from baseline, end-stage kidney disease (ESKD), or any-cause mortality (HR: 1.66; 95% CI: 1.58-1.74) (Bowe et al., 2021). To date, long-term kidney outcomes among ICU admissions with confirmed COVID-19-related ARDS have not been investigated.

3.3 HYPOTHESIS

We hypothesised that the incidence of MAKE-365 would be higher among non-COVID-19 ARDS patients.

3.4 AIM

This study aimed to identify the incidence of MAKEs at 365 days (MAKE-365) from ICU admission in COVID-19 compared to non-COVID-19 ARDS patients.

3.5 METHODS

3.5.1 Study Design and Setting:

This was a retrospective cohort study of patients admitted to the ICU with or without COVID-19 and ARDS diagnosis to determine the incidence of MAKEs.

The study centre is one of the largest tertiary hospitals in the West Midlands, the Queen Elizabeth Hospital Birmingham (QEHB), part of University Hospitals Birmingham NHS Foundation Trust (UHB). This site has the UK's largest single critical care unit, with 1,213 inpatients and 100 ICU beds. During the COVID-19 pandemic (between March 2020 to April 2021), UHB has seen the highest number of COVID-19 cases in the country (13,677 cases) compared to other hospitals Trusts (Garvey et al., 2021).

Based on Health Research Authority guidance, ethical approval and consent were not required (https://www.hra.nhs.uk/covid-19-research/guidance-using-patient-data/).

3.5.2 Eligibility criteria:

3.5.2.1 Inclusion:

- Patients aged ≥18 years;
- Patients admitted to ICU and received IMV;
- Patients who met ARDS diagnostic criteria based on the Berlin Definition (Ranieri et al., 2012).

3.5.2.2 Exclusion:

- Any patients admitted into ICU who did not receive IMV.
- Any patient who did not meet the ARDS diagnostic criteria.

3.5.3 Participants:

The study included two ICU cohorts: adult patients admitted to ICU between 12 March 2020 and 29 April 2021 (during the 1st and 2nd waves of the COVID-19 pandemic), with COVID-19 confirmed by a polymerase chain reaction test and meeting the Berlin criteria for ARDS on ICU admission (COVID-19 group); and patients admitted to ICU between 8 April 2016 and 11 July 2019 and meeting the Berlin criteria for ARDS on ICU admission (non-COVID-19 group).

3.5.4 Study outcomes and definitions:

The study had the following outcomes:

3.5.4.1 Primary Outcomes:

The development of the MAKEs at 365 days (MAKE-365) after ICU admission in non-COVID-19 vs COVID-ARDS.

3.5.4.2 Secondary outcomes:

- Assessing each individual MAKE outcome at 30, 90, 180 and 365 days after ICU admission.
- The incidence of AKI, MAKE-30, MAKE-90, MAKE-180 and MAKE-365.
- The risk factors for AKI, MAKE-30, MAKE-90, MAKE-180 and MAKE-365.
- Assessing the complete renal recovery at hospital discharge.

MAKE outcome was defined as a composite of receiving new renal replacement therapy (RRT), or reduction in eGFR to <75% from the baseline, or all-cause mortality (Billings and Shaw, 2014). Each MAKE outcome was assessed individually at 30, 90, 180 and 365 days after ICU admission to determine the incidence of MAKEs during these time points.

AKI was diagnosed based on the KDIGO guidelines, which are defined AKI as "an increase in serum creatinine by ≥ 0.3 mg/dl (≥ 26.5 μmol/l) within 48 hours; or increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume < 0.5 ml/kg/h for 6 hours" (Kellum et al., 2012). The KDIGO criteria were also used to identify the stage of AKI, as described previously in Table 1.2 (Kellum et al., 2012).

Complete renal recovery was determined based on the KDIGO guidelines (eGFR at discharge ≥ 60 ml/min/1.73 m2), which have been approved by Xu et al. (2019), and which might be more appropriate for clinical use compared with other definitions of renal recovery.

3.5.5 Data collection:

3.5.5.1 Data sources:

Data were collected retrospectively using two electronic clinical data systems: the Prescribing Information and Communications System (PICS) and the Clinical portal. These systems allowed the extraction of patients' demographic information and routine clinical data, (such as haematology and biochemistry results), medications, and all observations. In addition, these systems allowed extraction of clinical

investigations, discharge letters, readmissions, and death certificates. All data within these systems were routinely collected.

3.5.5.2 Data Extraction:

In compliance with national and local guidance, all data were anonymised and recorded by the Local Clinical Care Team, with no links to any patient identification. Data extraction was conducted by independent researchers using a standardised data collection form. The pseudonymised data were imported to a Microsoft Excel spreadsheet. The data were wrangled using Microsoft Excel before being imported into R software (v.4.1.2; R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org) for statistical analysis.

Data collected from enrolled patients included demographics, comorbidities, initial assessment of routine laboratory blood tests and their observations after ICU admission. A summary of these data is displayed in Table 3.1.

Table 3.1. Data collected

Characteristics	Parameters
Demographics	Age Sex BMI Ethnicity Pre-existing comorbidities Date of ICU admission Date of ICU and hospital discharge
Routine laboratory blood tests	Creatinine WCC Neutrophils Lymphocyte Monocytes Eosinophils CRP Platelets Albumin Bilirubin
Observations	eGFR Need for RRT PaO_2 / FiO_2 ratio Received dexamethasone Incidence and stages of AKI Mortality

Abbreviations: BMI, Body mass index; ICU, intensive care unit; WCC, white cell count, CRP, C-reactive protein, eGFR, estimated glomerular filtration rate, RRT, renal replacement therapy; PaO_2 / FiO_2 ratio, the ratio of partial pressure arterial oxygen and the fraction of inspired oxygen.

The AKI diagnosis (and staging) during ICU stay were extracted retrospectively. Data related to renal function, including eGFR, serum creatinine, and receiving new RRT after ICU admission, were extracted retrospectively. The eGFR baseline value was extracted before ICU admission. In addition, the values of eGFR at 30, 90, 180, and 365 days after ICU admission were extracted retrospectively in chronological order to track the changes in renal function. Data on those receiving new RRT and mortality at 30, 90, 180, and 365 days from the ICU admission were extracted retrospectively through the electronic patient record.

If the eGFR baseline value was missing, the best pre-admission eGFR was extracted. If preadmission eGFR was also missing, the eGFR baseline value was estimated using the Modification of Diet in Renal Disease (MDRD) (Levey et al., 1999) or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (Levey et al., 2009). This method has been recommended by KDIGO guidelines (Kellum et al. (2012). The closest values to those time points were extracted when the eGFR values were missing at 30, 90, 180, and 365 days from ICU admission.

3.5.6 Follow-up and study period:

The period of data collection was from April 2016 to April 2022: a total of 73 months. The follow-up period for patients commenced from the date of their ICU admission until death or for a maximum of 365 days. The study period concluded upon reaching the 365-day mark from the last patient's admission to QEHB in April 2021, according to the PICS database. Consequently, the data collection officially ended by April 2022. The data collection for the non-COVID-19 cohort included those patients admitted to ICU between 8 April 2016 and 11 July 2019 and developed ARDS, for the COVID-19 cohort included those patients admitted to ICU between 12 March 2020 and 29 April 2021 and developed ARDS.

3.5.7 Data Management:

In compliance with the Data Protection Act 2018, all identifiable data were securely stored on the NHS Trust servers. Only anonymised data were securely stored in a separate database with password encryption on the University of Birmingham server as needed. Only authorised persons who complied with UHB policy on collecting, storing, processing and disclosure of personal information and who were involved in this study had access to the data.

3.5.8 Statistical analysis:

All statistical analyses were conducted using R statistical software (v.4.1.2; R Foundation for Statistical Computing, Vienna, Austria: https://www.r-project.org). Baseline characteristics of patients in non-COVID-19 vs COVID-ARDS groups were reported as frequencies with percentages for categorical variables. Data distribution was determined using the Shapiro-Wilk test. Since all continuous variables were not normally distributed, they were presented as medians with an Interquartile Range (IQR).

Categorical variables were compared using the chi-squared test or Fisher's exact test. Wilcoxon's rank-sum test (for independent samples) or Wilcoxon signed-rank test (for related samples) were used for non-parametric data analyses when comparing two groups. For comparisons between more than two groups, the Kruskal-Wallis test was used.

In the conducted analysis, all variables exhibited less than 5% missing data, which led to the classification of these values as missing completely at random. Consequently, case-wise deletion was employed to handle the missing data.

Univariate and multivariate analysis with logistic regression was conducted to determine the association between the outcomes and the investigated parameters, represented as an odds ratio (OR) with a 95% confidence interval (CI). Variables associated with the study outcomes in the univariable analysis were included in a backward stepwise multivariable model. Time-to-event data for each component of MAKE-365 in non-COVID-19 and COVID-19 groups were plotted using Kaplan-Meier curves, and observed differences were analysed using the Log-rank test. For all analyses, a P-value of < 0.05 was considered statistically significant.

3.6 RESULTS

In total, 768 ICU admissions within the study duration were screened for eligibility (Figure 3.1). Of these, 64 patients admitted to ICU and did not receive IMV were excluded, as well as three patients aged < 18 years and three patients who did not meet ARDS diagnostic criteria. The analysis included in the remaining 708 patients.

Among these patients, 458, who tested positive for COVID-19 and met the ARDS diagnostic criteria after ICU admission, were assigned to the COVID-19 group. A total of 250 patients who were admitted to the ICU before the COVID-19 pandemic and met the ARDS diagnostic criteria were assigned to the non-COVID-19 group.

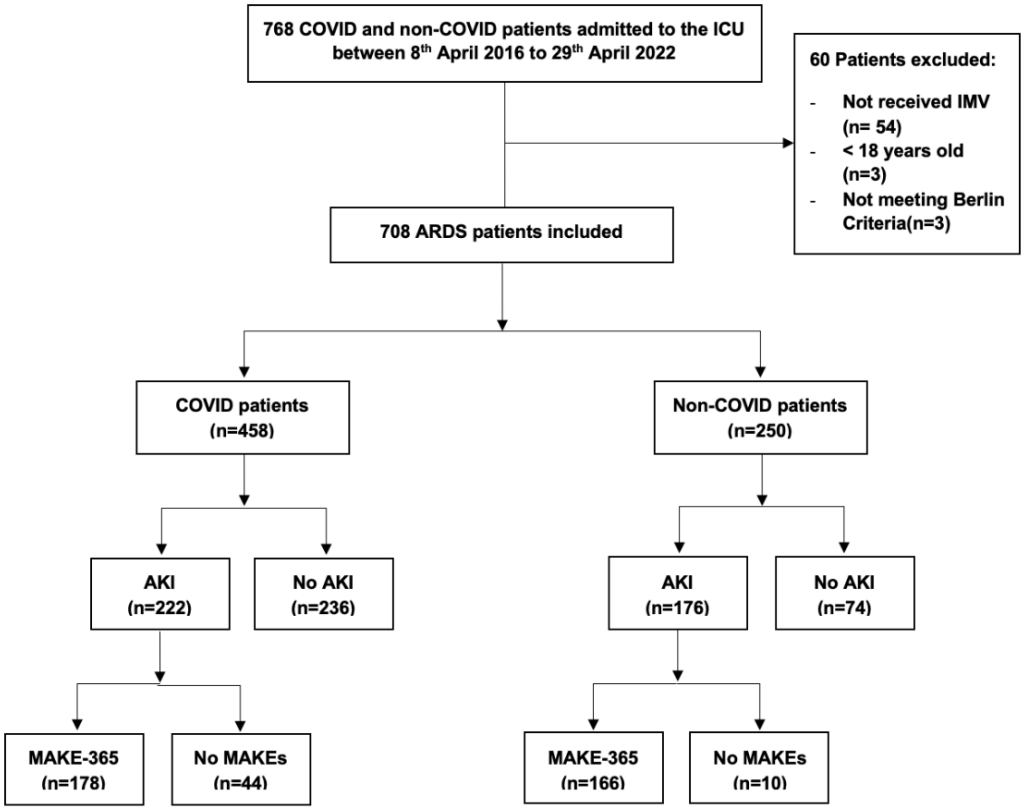


Figure 3.1. Modified CONSORT Diagram.

This diagram illustrates the process of participant screening and enrolment for the study.
Abbreviations: ARDS, acute respiratory distress syndrome; ICU, intensive care unit; IMV, invasive mechanical ventilation; AKI, acute kidney injury; MAKEs, major adverse kidney events.

3.6.1 Characteristics of ARDS patients in COVID-19 vs non-COVID-19 groups

The demographic and clinical characteristics of ARDS patients in the COVID-19 and non-COVID-19 groups are shown in Table 3.2.

Table 3.2. The demographic and clinical characteristics of COVID-19 vs non-COVID-19 groups

	Overall (N=708)	COVID-19 (N=458)	Non-COVID-19 (N=250)	P-value*
Demographics				
Age (years)	59.0 [49.0-68.0]	57.0 [49.0-66.0]	61.0 [49.3-71.0]	<0.001
Male (n, %)	459 (64.8%)	307 (67.0%)	152 (60.8%)	0.115
Ethnicity (n, %)				
White	374 (52.8%)	187 (40.8%)	187 (74.8%)	<0.001
Asian / Asian British	177 (25.0%)	139 (30.3%)	38 (15.2%)	
Black / African / Caribbean	49 (6.9%)	32 (7.0%)	17 (6.8%)	
Other	108 (15.3%)	100 (21.8%)	8 (3.2%)	
BMI (kg/m^2)	29.0 [25.0-33.1]	30.1 [27.0-35.5]	26.0 [22.0-31.0]	<0.001
BMI severity, (n, %)				
Underweight	50 (7.1%)	14 (3.1%)	36 (14.4%)	<0.001
Healthy weight	143 (20.2%)	59 (12.9%)	84 (33.6%)	
Overweight	200 (28.2%)	150 (32.8%)	50 (20.0%)	
Obese	245 (34.6%)	178 (38.9%)	67 (26.8%)	
Severely obese	69 (9.7%)	56 (12.2%)	13 (5.2%)	
Comorbidities (n, %)				
Hypertension	220 (31.1%)	154 (33.6%)	66 (26.4%)	0.057
Diabetes mellitus	202 (28.5%)	153 (33.4%)	49 (19.6%)	<0.001
Obesity	318 (44.9%)	238 (52.0%)	80 (32.0%)	<0.001
Ischemic heart disease	75 (10.6%)	39 (8.5%)	36 (14.4%)	0.021
Asthma	79 (11.2%)	61 (13.3%)	18 (7.2%)	0.019
COPD	30 (4.2%)	15 (3.3%)	15 (6.0%)	0.127
Cancer	68 (9.6%)	20 (4.4%)	48 (19.2%)	<0.001
CKD	70 (9.9%)	44 (9.6%)	26 (10.4%)	0.837
ARDS aetiology				
Direct Lung Injury				
- COVID-19	458 (64.7%)	458 (100%)	N/A	

Table 3.2. The demographic and clinical characteristics of COVID-19 vs non-COVID-19 groups

	Overall (N=708)	COVID-19 (N=458)	Non-COVID-19 (N=250)	P-value*
- Pneumonia (Bacterial, Viral, Fungal)	196 (27.6%)	N/A	196 (78.4%)	
- Acute Bronchitis	1 (0.1%)	N/A	1 (0.4%)	
- Exacerbation of Bronchiectasis	1 (0.1%)	N/A	1 (0.4%)	
- Influenza	2 (0.3%)	N/A	2 (0.8%)	
Indirect Lung Injury				
- Sepsis or Septic Shock	33 (4.7%)	N/A	33 (13.2%)	
- Non-cardiogenic Pulmonary Oedema	17 (2.4%)	N/A	17 (6.8%)	
Laboratory blood tests				
White cell count ($x10^9$/L)	10.4 [7.00-14.5]	9.55 [7.00-13.3]	12.5 [7.30-18.2]	<0.001
Neutrophils ($x10^9$/L)	8.60 [5.60-12.4]	8.10 [5.70-11.6]	9.60 [5.50-14.4]	0.025
Lymphocytes ($x10^9$/L)	0.76 [0.50-1.20]	0.77 [0.55-1.20]	0.70 [0.40-1.20]	0.005
Monocytes ($x10^9$/L)	0.50 [0.28-0.80]	0.455 [0.28-0.69]	0.60 [0.30-1.10]	<0.001
Eosinophils ($x10^9$/L)	0.00 [0.00-0.02]	0.00 [0.00-0.02]	0.00 [0.00-0.02]	0.077
CRP (mg/L)	128 [61.5-226]	117 [59.0-208]	160 [72.0-266]	<0.001
Platelets ($x10^9$/L)	245 [169-327]	261 [200-336]	195 [100-304]	<0.001
Creatinine (µmol/L)	77.0 [55.5-115]	72.0 [55.0-97.0]	93.0 [58.3-164]	<0.001
Albumin (g/L)	27.0 [23.0-31.0]	25.0 [22.0-29.0]	31.0 [27.0-36.0]	<0.001
Bilirubin (µmol/L)	10.0 [7.00-16.0]	10.0 [7.00-14.0]	10.0 [6.00-23.8]	0.385
ICU observations				
eGFR, ml/min per 1.73 m^2	90.0 [57.8-90.0]	90.0 [76.3-90.0]	69.5 [33.3-90.0]	<0.001
RRT (n, %)	257 (36.3%)	142 (31.0%)	115 (46.0%)	<0.001
PaO_2 / FiO_2 ratio, kPa	14.0 [11.0-19.0]	14.0 [11.0-18.0]	14.5 [11.0-23.0]	0.070
ARDS severity (n, %)				
Mild	80 (11.3%)	39 (8.5%)	41 (16.4%)	0.005
Moderate	307 (43.4%)	209 (45.6%)	98 (39.2%)	
Severe	321 (45.3%)	210 (45.9%)	111 (44.4%)	
ICU LOS days	12.0 [6.00-23.0]	13.0 [6.25-25.0]	10.0 [6.00-20.0]	0.024
Hospital LOS days	18.0 [10.0-36.0]	18.0 [10.0-33.8]	19.0 [9.00-39.8]	0.862
ICU admission to death days	12.0 [6.00-23.0]	13.0 [6.25-25.0]	10.0 [6.00-20.0]	0.12
Mortality (n, %)	266 (37.6%)	138 (30.1%)	128 (51.2%)	<0.001

Table 3.2. The demographic and clinical characteristics of COVID-19 vs non-COVID-19 groups

	Overall (N=708)	COVID-19 (N=458)	Non-COVID-19 (N=250)	P-value*
AKI incidence	398 (56.2%)	222 (48.5%)	176 (70.4%)	<0.001
AKI stages				
No AKI	310 (43.8%)	236 (51.5%)	74 (29.6%)	<0.001
Stage 1	130 (18.4%)	93 (20.3%)	37 (14.8%)	
Stage 2	76 (10.7%)	42 (9.2%)	34 (13.6%)	
Stage 3	192 (27.1%)	87 (19.0%)	105 (42.0%)	

Data is presented as median (IQR), unless otherwise stated.
* p-values from chi-squared test or Wilcoxon rank-sum test represent the differences between COVID-19 vs non-COVID-19 groups.
Abbreviations: BMI, body mass index; COPD, Chronic obstructive pulmonary disease; CKD, chronic kidney disease; CRP, C-reactive protein; ICU, intensive care unit; eGFR, estimated glomerular filtration rate; RRT, renal replacement therapy; PaO_2/FiO_2 ratio, the ratio of partial pressure arterial oxygen and the fraction of inspired oxygen; ARDS, acute respiratory distress syndrome; LOS, length of stay; AKI, acute kidney injury; MAKEs, major adverse kidney events.

The median age of the total cohort (n=708) was 59.0 years [IQR, 49.0–68.0]; 64.8% (n=459) were male and 52.8% (n= 374) were of White ethnicity. Compared to the COVID-19 group, the non-COVID-19 group were older, with a median age of 61.0 years [IQR, 49.3–71.0] vs 57.0 years [IQR, 49.0–66.0]; (P < 0.001, Wilcoxon rank-sum test). Both COVID-19 and non-COVID-19 groups showed a male predominance (307 (67.0%) vs 152 (60.8%), P = 0.115, chi-squared test). The COVID-19 group had a higher BMI compared with the non-COVID-19 group (30.1 kg/m^2 [IQR, 27.0–35.5kg/m^2] vs 26.0 kg/m^2 [IQR, 22.0–31.0], P < 0.001, Wilcoxon rank-sum test). The majority of patients in the COVID-19 and non-COVID-19 groups were of White ethnicity (187 (40.8%) vs 187 (74.8%), P < 0.001, chi-squared test) and had presented with different comorbidities, included obesity (238 (52.0%) vs 80 (32.0%), P < 0.001), hypertension (154 (33.6%) vs 66 (26.4%), P = 0.057), diabetes mellitus (153 (33.4%) vs 49 (19.6%), P < 0.001), ischemic heart disease (39 (8.5%) vs 36 (14.4%), P =

0.021), asthma (61 (13.3%) vs 18 (7.2%), P = 0.019), cancer (20 (4.4%) vs 48 (19.2%), P < 0.001), and CKD (44 (9.6%) vs 26 (10.4%), P = 0.837, chi-squared test).

Within the non-COVID-19 cohort, ARDS aetiology was further categorised based on the underlying cause of lung injury: 200 patients were identified with ARDS resulting from direct lung injury - such as 78.4% (n=196) pneumonia (bacterial, viral, fungal), Influenza 0.8% (n=2), acute bronchitis 0.4% (n=1), and exacerbation of bronchiectasis 0.4% (n=1). The remaining 50 patients were classified as having ARDS from an indirect lung injury, which included cases associated with systemic inflammatory responses such as sepsis or septic shock 13.2% (n=33) and non-cardiogenic pulmonary oedema 6.8% (n=17) (Table 3.2).

Compared with the COVID-19 group, the non-COVID-19 group had significantly higher baseline levels for white cell count (9.55 $x10^9$/L [IQR, 7.00–13.3 $x10^9$/L] vs 12.5 $x10^9$/L [IQR, 7.30–18.2 $x10^9$/L] P < 0.001), neutrophils (8.10 $x10^9$/L [IQR, 5.70–11.6 $x10^9$/L] vs 9.60 $x10^9$/L [IQR, 5.50–14.4 $x10^9$/L], P = 0.025), monocytes (0.455 $x10^9$/L [IQR, 0.28–0.69 $x10^9$/L] vs 0.600 $x10^9$/L [IQR, 0.30–1.10 $x10^9$/L], P < 0.001), C-reactive protein (117 mg/L [IQR, 59.0–208 mg/L] vs 160 mg/L [IQR, 72.0–266 mg/L], P < 0.001), and serum creatinine (72.0 µmol/L [IQR, 55.0–97.0 µmol/L] vs 93.0 µmol/L [IQR, 58.3–164 µmol/L], P < 0.001, Wilcoxon rank-sum test). Patients in the COVID-19 group had lower levels of platelets (261 $x10^9$/L [IQR, 200–336 $x10^9$/L] vs 195 $x10^9$/L [IQR, 100–304 $x10^9$/L], P < 0.001) and albumin (25.0 g/L [IQR, 22.0–29.0 g/L] vs 31.0 g/L [IQR, 27.0–36.0 g/L], P < 0.001, Wilcoxon rank-sum test). The median levels of eosinophils (0.00 $x10^9$/L [IQR, 0.00–0.02 $x10^9$/L] vs 0.00 $x10^9$/L [IQR, 0.00–0.02 $x10^9$/L], P = 0.077)

and bilirubin (10.0 µmol/L [IQR, 7.00–14.0 µmol/L] vs 10.0 µmol/L [IQR, 6.00–23.8 µmol/L], P = 0.385, Wilcoxon rank-sum test) were similar in both groups.

There was a difference in the median eGFR on ICU admission between the COVID-19 and non-COVID-19 groups (90.0 ml/min per 1.73 m^2 [IQR, 76.3–90.0] vs 69.5 ml/min per 1.73 m^2 [IRQ, 33.3–90.0], P < 0.001, Wilcoxon rank-sum test). The proportion of patients who received RRT was greater in the non-COVID-19 group (31.0% vs 46.0%, P < 0.001, chi-squared test). There was no difference in the PaO_2 / FiO_2 ratio among the groups (14.0 kPa [IQR, 11.0–18.0 kPa] vs 14.5 kPa [IQR, 11.0–23.0 kPa], P = 0.070, Wilcoxon rank-sum test). Overall, there were more patients with moderate (43.4%) and severe (45.3%) ARDS compared to mild ARDS (11.3%), according to the Berlin criteria (P = 0.004 and P = 0.016, respectively, chi-squared test). The ICU length of stay median was longer in the COVID-19 group (13.0 days [IQR, 6.25–25.0 days] vs 10.0 days [IQR, 6.00–20.0 days], P = 0.024, Wilcoxon rank-sum test). Overall mortality was higher in the non-COVID-19 group (138 (30.1%) vs 128 (51.2%), P < 0.001, chi-squared test).

3.6.2 Characteristics of AKI patients in both groups

The AKI incidence was higher in the non-COVID-19 group (222 (48.5%) vs 176 (70.4%), P < 0.001, chi-squared test). The demographic and clinical characteristics of AKI patients in the COVID-19 and non-COVID-19 groups are shown in Table 3.3.

Table 3.3. Demographic and clinical characteristics of AKI patients in the COVID-19 vs non-COVID-19 groups.

	Overall (N=398)	COVID-AKI (N=222)	Non-COVID AKI (N=176)	P-value*
Demographics				
Age median [IQR]	60.0 [51.0-69.0]	60.0 [52.3-68.0]	60.0 [49.8-71.0]	0.487
Male (n, %)	266 (66.8%)	160 (72.1%)	106 (60.2%)	0.017
Ethnicity (n, %)				
White	225 (56.5%)	99 (44.6%)	126 (71.6%)	<0.001
Asian / Asian British	93 (23.4%)	62 (27.9%)	31 (17.6%)	
Black / African / Caribbean	34 (8.5%)	21 (9.5%)	13 (7.4%)	
Other	46 (11.6%)	40 (18.0%)	6 (3.4%)	
BMI median [IQR], kg/m^2	29.0 [25.0-33.0]	30.1 [27.7-36.1]	26.0 [23.0-31.0]	<0.001
BMI severity (n, %)				
Underweight	32 (8.0%)	7 (3.2%)	25 (14.2%)	<0.001
Healthy weight	79 (19.8%)	23 (10.4%)	56 (31.8%)	
Overweight	111 (27.9%)	74 (33.3%)	37 (21.0%)	
Obese	135 (33.9%)	86 (38.7%)	49 (27.8%)	
Severely obese	40 (10.1%)	31 (14.0%)	9 (5.1%)	
Comorbidities (n, %)				
Hypertension	137 (34.4%)	91 (41.0%)	46 (26.1%)	0.003
Diabetes mellitus	121 (30.4%)	86 (38.7%)	35 (19.9%)	<0.001
Obesity	176 (44.2%)	118 (53.2%)	58 (33.0%)	<0.001
Ischemic heart disease	53 (13.3%)	26 (11.7%)	27 (15.3%)	0.363
Asthma	44 (11.1%)	29 (13.1%)	15 (8.5%)	0.203
COPD	15 (3.8%)	8 (3.6%)	7 (4.0%)	1
Cancer	45 (11.3%)	7 (3.2%)	38 (21.6%)	<0.001
CKD	58 (14.6%)	34 (15.3%)	24 (13.6%)	0.743
Laboratory blood tests, median [IQR]				
White cell count (x10^9/L)	11.5 [7.30-15.2]	10.1 [7.43-13.7]	12.6 [7.13-18.2]	0.022
Neutrophils (x10^9/L)	9.20 [5.90-12.8]	8.68 [6.09-12.2]	9.60 [5.70-14.8]	0.176
Lymphocytes (x10^9/L)	0.71 [0.49-1.10]	0.75 [0.54-1.10]	0.70 [0.30-1.13]	0.061
Monocytes, (x10^9/L)	0.52 [0.28-0.84]	0.49 [0.28-0.69]	0.60 [0.30-1.10]	0.014
Eosinophils (x10^9/L)	0.00 [0.00-0.03]	0.00 [0.00-0.04]	0.00 [0.00-0.02]	0.003
CRP (mg/L)	143 [75.0-247]	137 [75.5-226]	157 [74.3-274]	0.19
Platelets (10^9/L)	222 [147-313]	241 [185-309]	191 [88.0-314]	<0.001

Table 3.3. Demographic and clinical characteristics of AKI patients in the COVID-19 vs non-COVID-19 groups.

	Overall (N=398)	COVID-AKI (N=222)	Non-COVID AKI (N=176)	P-value*
Creatinine (µmol/L)	96.0 [64.0-165]	87.0 [63.0-151]	109 [68.8-192]	0.058
Albumin (g/L)	27.0 [23.0-31.0]	25.0 [22.0-28.0]	30.0 [25.0-34.0]	<0.001
Bilirubin (µmol/L)	11.0 [7.00-19.0]	11.0 [8.00-15.0]	11.0 [6.00-33.0]	0.265
ICU observations				
eGFR, ml/min per 1.73 m^2	72.0 [38.0-90.0]	84.5 [49.5-90.0]	56.0 [29.0-90.0]	<0.001
Need for RRT (n, %)	257 (64.6%)	142 (64.0%)	115 (65.3%)	0.857
PaO_2 / FiO_2 ratio, kPa	14.0 [11.0-19.0]	14.0 [11.0-18.0]	14.0 [11.0-20.0]	0.564
ARDS severity (n, %)				
Mild	38 (9.5%)	15 (6.8%)	23 (13.1%)	0.031
Moderate	175 (44.0%)	108 (48.6%)	67 (38.1%)	
Severe	185 (46.5%)	99 (44.6%)	86 (48.9%)	
ICU LOS, days	14.0 [8.00-26.0]	17.0 [9.00-27.8]	11.0 [7.00-21.3]	0.001
Hospital LOS, days	19.0 [9.00-40.0]	22.0 [11.3-40.8]	17.0 [7.00-39.0]	0.032
ICU admission to death, days	12.0 [6.00-23.0]	14.0 [8.00-23.0]	10.0 [5.00-23.5]	0.15
Mortality (n, %)	216 (54.3%)	100 (45.0%)	116 (65.9%)	<0.001

Data is presented as median (IQR), unless otherwise stated.
* p-values from the chi-squared test or Wilcoxon rank-sum test represent the differences between COVID-AKI vs non-COVID-AKI groups.
Abbreviations: BMI, body mass index; COPD, Chronic obstructive pulmonary disease; CKD, chronic kidney disease; CRP, C-reactive protein; ICU, intensive care unit; eGFR, estimated glomerular filtration rate; RRT, renal replacement therapy; PaO2 / FiO2 ratio, the ratio of partial pressure arterial oxygen and the fraction of inspired oxygen; ARDS, acute respiratory distress syndrome; LOS, length of stay; AKI, acute kidney injury.

The median age of AKI patients was similar in both groups (60.0 years [IQR, 52.3–68.0 years] vs 60.0 years [IQR, 49.8–71.0 years], P = 0.487; Wilcoxon rank-sum test). Most AKI patients in both groups were male (66.8%) and were of White ethnicity (56.5%). The median BMI was significantly higher in the COVID-19 group (30.1 kg/m^2 [IQR, 27.7–36.1 kg/m^2] vs 26.0 kg/m^2 [IQR, 23.0–31.0 kg/m^2], P < 0.001, Wilcoxon rank-sum test).

A larger proportion of AKI patients in the COVID-19 group were obese (118 (53.2%) vs 58 (33.0%), P = < 0.001) and had a history of hypertension (91 (41.0%) vs 46 (26.1%), P = 0.003), and diabetes (86 (38.7%) vs 35 (19.9%), P < 0.001, chi-squared test). A history of cancer was significantly higher among AKI patients in the non-COVID-19 group (3.2% vs 21.6%, P < 0.001, chi-squared test).

AKI patients in the non-COVID-19 group had higher levels of white cell count 10.1 $x10^9$/L [IQR, 7.43–13.7 $x10^9$/L] vs 12.6 $x10^9$/L [IQR, 7.13–18.2 $x10^9$/L], P = 0.022), monocytes 0.49 $x10^9$/L [IQR, 0.28–0.69 $x10^9$/L] vs 0.60 $x10^9$/L [IQR, 0.30–1.10 $x10^9$/L], P = 0.014), and eosinophils (0.00 $x10^9$/L [IQR, 0.00–0.04] vs 0.00 $x10^9$/L [IQR, 0.00–0.02 $x10^9$/L], P = 0.003), and a lower level of platelets (241 $x10^9$/L [IQR, 185–309 $x10^9$/L] vs 191 $x10^9$/L [88.0–314 $x10^9$/L], P < 0.001, Wilcoxon rank-sum test). AKI patients in COVID-19 ARDS had a lower level of albumin (25.0 g/L [IQR, 22.0–28.0 g/L] vs 30.0 g/L [IQR, 25.0–34.0 g/L], P < 0.001, Wilcoxon rank-sum test). There were no significant differences in the levels of neutrophils (8.68 $x10^9$/L [IQR, 6.09–12.2 $x10^9$/L] vs 9.60 $x10^9$/L [IQR, 5.70–14.8 $x10^9$/L], P = 0.176), lymphocytes (0.75 $x10^9$/L [IQR, 0.54–1.10 $x10^9$/L] vs 0.70 $x10^9$/L [IQR, 0.30–1.13 $x10^9$/L], P = 0.061, CRP (137 mg/L [IQR, 75.5–226 mg/L] vs 157 mg/L [IQR, 74.3–274 mg/L], P = 0.19), creatinine (87.0 µmol/L [IQR, 63.0–151 µmol/L] vs 109 µmol/L [IQR, 68.8–192 µmol/L], P = 0.058) or bilirubin (11.0 µmol/L [IQR, 8.00–15.0 µmol/L] vs 11.0 µmol/L [IQR, 6.00–33.0 µmol/L], P = 0.265, Wilcoxon rank-sum test) between AKI patients in the two groups.

AKI patients within the non-COVID-19 group had a lower median eGFR on ICU admission compared to the COVID-19 group (84.5 ml/min per 1.73 m^2 [IQR, 49.5–90.0] vs 56.0 ml/min per 1.73 m^2 [IQR, 29.0–90.0], P < 0.001). There was a difference

in the length of ICU and hospital stay between the COVID-19 and non-COVID-19 groups (17.0 days [IQR, 9.00–27.8 days] vs 11.0 days [IQR, 7.00–21.3 days], P = 0.001 and 22.0 days [IQR, 11.3–40.8 days] vs 17.0 days [IQR, 7.00–39.0 days], P = 0.032, respectively, Wilcoxon rank-sum test). Overall mortality was higher among AKI patients within the non-COVID-19 group (100 (45.0%) vs 116 (65.9%), P < 0.001, chi-squared test) (Table 3.3).

3.6.3 The incidence of MAKEs:

The incidence and cause of MAKEs outcome at 30, 90, 180 and 365 days after ICU admission are shown in Table 3.4. The incidence of MAKE-365 was higher in the non-COVID-19 group 178 (38.9%) vs 166 (66.4%), P < 0.001, chi-squared test). In terms of the individual cause for MAKE-365, the need for RRT was the highest cause of MAKEs in both COVID-19 and non-COVID-19 groups (142 (31.0%) vs 115 (46.0%)), followed by deaths (21 (4.6%) vs 31 (12.4%)) and a decline in eGFR (15 (3.3%) vs 22 (8.8%)).

Compared to the MAKE-365, the incidence of MAKE-30, MAKE-90, and MAKE-180 were also greater in the non-COVID-19 group (172 (37.6%) vs 149 (59.6%), P < 0.001; 175 (38.2%) vs 155 (62.0%), P < 0.001; 178 (38.9%) vs 162 (64.8%), P < 0.001, respectively, chi-squared test). In terms of the individual cause for MAKE-30, MAKE-90 and MAKE-180, the need for RRT was the highest cause of MAKE-30, MAKE-90 and MAKE-180, followed by deaths and a decline in eGFR in both COVID-19 and non-COVID-19 groups (Table 3.4).

Table 3.4. The incidence of MAKEs outcome and cause of MAKEs in COVID-19 vs non-COVID-19 groups

	Overall (N=708)	COVID (N=458)	Non-COVID (N=250)	P-value*
MAKEs outcome:				
MAKE-30	**321 (45.3%)**	**172 (37.6%)**	**149 (59.6%)**	<0.001
- RRT	253 (35.7%)	141 (30.8%)	112 (44.8%)	0.291
- eGFR < 75% of baseline	22 (3.1%)	11 (2.4%)	11 (4.4%)	
- Death	46 (6.5%)	20 (4.4%)	26 (10.4%)	
MAKE-90	**330 (46.6%)**	**175 (38.2%)**	**155 (62.0%)**	<0.001
- RRT	255 (36.0%)	142 (31.0%)	113 (45.2%)	0.13
- eGFR < 75% of baseline	26 (3.7%)	12 (2.6%)	14 (5.6%)	
- Death	51 (7.2%)	21 (4.6%)	30 (12.0%)	
Patients still requiring RRT	32 (4.5%)	20 (4.4%)	12 (4.8%)	0.939
MAKE-180	**340 (48.0%)**	**178 (38.9%)**	**162 (64.8%)**	<0.001
- RRT	256 (36.2%)	142 (31.0%)	114 (45.6%)	0.087
- eGFR < 75% of baseline	34 (4.8%)	15 (3.3%)	19 (7.6%)	
- Death	52 (7.3%)	21 (4.6%)	31 (12.4%)	
Patients still requiring RRT	5 (0.7%)	2 (0.4%)	3 (1.2%)	0.49
MAKE-365	**344 (48.6%)**	**178 (38.9%)**	**166 (66.4%)**	<0.001
- RRT	257 (36.3%)	142 (31.0%)	115 (46.0%)	0.055
- eGFR < 75% of baseline	37 (5.2%)	15 (3.3%)	22 (8.8%)	
- Death	52 (7.3%)	21 (4.6%)	31 (12.4%)	
Patients still requiring RRT	4 (0.6%)	2 (0.4%)	2 (0.8%)	0.927

Data presented as frequencies with percentages.
* p-values from chi-squared test represent the differences of incidence of MAKEs outcome and the first event that caused MAKEs of RRT, eGFR decline, and death by 30, 90, 180, and 365 days from ICU admission in COVID-19 vs non-COVID-19 groups.
Abbreviations: eGFR, estimated glomerular filtration rate, RRT, renal replacement therapy, MAKE, major adverse kidney events.

3.6.4 Individual MAKE outcome:

3.6.4.1 Need for RRT:

There was no difference among patients who continued to require RRT at 90, 180 and 365 days in both groups (20 (4.4%) vs 12 (4.8%), P = 0.939; 2 (0.4%) vs 3 (1.2%), P = 0.49; 2 (0.4%) vs 2 (0.8%), P = 0.927, respectively, chi-squared test) (Table 3.5). The need for RRT was higher in the non-COVID-19 group at 30 days after ICU admission (141 (30.8%) vs 112 (44.8%), P < 0.001, chi-squared test), as well patients' need for RRT at 90, 180 and 365 days (142 (31.0%) vs 113 (45.2%), P < 0.001; 142 (31.0%) vs 114 (45.6%), P < 0.001; 142 (31.0%) vs 115 (46.0%), P < 0.001, respectively, chi-squared test) (Table 3.5).

3.6.4.2 The decline in eGFR:

In terms of assessing the eGFR decline (< 75% of baseline) over 365 days from ICU admission, there was no significant difference among patients who had a decline in their eGFR at 30, 90 and 180 days in the COVID-19 and non-COVID-19 groups (92 (20.1%) vs 51 (20.4%), P = 0.999; 98 (21.4%) vs 61 (24.4%), P = 0.412; 103 (22.5%) vs 72 (28.8%), P = 0.077, respectively, chi-squared test). In the non-COVID-19 group, the eGFR decline was significantly higher at 365 days compared with COVID-19 group (104 (22.7%) vs 75 (30.0%), P = 0.041, chi-squared test) (Table 3.5).

Table 3.5. The incidence of individual MAKE outcome during one-year follow-up in COVID-19 vs non-COVID-19 groups

	Overall (N=708)	COVID (N=458)	Non-COVID (N=250)	P-value*
Need for RRT at:				
30 days	253 (35.7%)	141 (30.8%)	112 (44.8%)	<0.001
90 days	255 (36.0%)	142 (31.0%)	113 (45.2%)	<0.001
180 days	256 (36.2%)	142 (31.0%)	114 (45.6%)	<0.001
365 days	257 (36.3%)	142 (31.0%)	115 (46.0%)	<0.001
eGFR < 75% of baseline at:				
30 days	143 (20.2%)	92 (20.1%)	51 (20.4%)	0.999
90 days	159 (22.5%)	98 (21.4%)	61 (24.4%)	0.412
180 days	175 (24.7%)	103 (22.5%)	72 (28.8%)	0.077
365 days	179 (25.3%)	104 (22.7%)	75 (30.0%)	0.041
Death at:				
30 days	180 (25.4%)	89 (19.4%)	91 (36.4%)	<0.001
90 days	200 (28.2%)	98 (21.4%)	102 (40.8%)	<0.001
180 days	210 (29.7%)	100 (21.8%)	110 (44.0%)	<0.001
365 days	216 (30.5%)	100 (21.8%)	116 (46.4%)	<0.001

Data presented as frequencies with percentages.
* p-values from the chi-squared test.
Abbreviations: eGFR, estimated glomerular filtration rate, RRT, renal replacement therapy.

3.6.4.3 Mortality:

The mortality rate of patients with MAKEs at 30 days was higher in the non-COVID-19 group (89 (19.4%) vs 91 (36.4%), P < 0.001, chi-squared test). Only a few patients who had MAKEs died in the COVID-19 group compared with the non-COVID-19 group at 90, 180 and 365 days (98 (21.4%) vs 102 (40.8%), P < 0.001; 100 (21.8%) vs 110 (44.0%), P < 0.001; 100 (21.8%) vs 116 (46.4%), P < 0.001, chi-squared test) (Table 3.5).

3.6.5 Factors Associated with MAKEs:

In the COVID-19 group, factors associated with MAKE-30 (n= 172), MAKE-90 (n= 175), MAKE-180 (n= 178), and MAKE-365 (n= 178) development are shown in Tables 3.6-3.9. In the univariable analysis, male sex, older age, Black ethnicity, presence of hypertension, diabetes, ischemic heart disease, CKD, lower albumin level and higher bilirubin level were all associated with MAKE-30 (Table 3.6), MAKE-90 (Table 3.7), MAKE-180 (Table 3.8), and MAKE-365 (Table 3.9). In the multivariable analysis, older age, CKD, diabetes, and higher bilirubin level were all associated factors with MAKE-30, MAKE-90, MAKE-180, and MAKE-365. Most of the previous MAKEs risk factors were consistent over MAKE timeframes (i.e., 30, 90, 180, and 365 days) an increase in OR was noted in the presence of diabetes (OR: 2.00, 95% CI: 1.25–3.23, P= 0.004) and CKD (OR: 7.25, 95% CI: 3.37–16.88, P <0.001) among patients with MAKE-365.

Table 3.6. Binomial logistic regression analysis of factors associated with MAKE-30 in COVID-19 vs non-COVID-19 groups

Characteristic	COVID-ARDS						Non-COVID-19 ARDS					
	Univariate Analysis			Multivariate analysis			Univariate Analysis			Multivariate analysis		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Age	1.04	1.02–1.05	**<0.001***	1.03	1.01–1.05	**0.001**	0.99	0.98–1.01	0.48			
Male	1.59	1.05–2.42	**0.027***	1.47	0.93–2.35	0.105	0.89	0.53–1.50	0.67			
BMI	1	0.97–1.02	0.87				1.01	0.97–1.05	0.65			
Ethnicity			**0.01***						0.22			
White	—	—		—	—		—	—				
Asian / Asian British	0.8	0.50–1.25		0.73	0.43–1.21	0.224	1.69	0.82–3.67				
Black / African / Caribbean	2.13	1.00–4.67		2.21	0.96–5.20	0.064	2.54	0.86–9.27				
Other	0.57	0.33–0.95		0.56	0.31–0.99	**0.049**	1.3	0.31–6.49				
Hypertension	2.11	1.42–3.15	**<0.001***	1.31	0.81–2.10	0.263	1.15	0.65–2.07	0.63			
Diabetes mellitus	1.68	1.13–2.50	**0.011***	1.86	1.16–3.00	**0.011**	0.98	0.52–1.87	0.95			
Obesity	0.79	0.54–1.15	0.22				1.51	0.88–2.66	0.14			
Asthma	0.79	0.44–1.38	0.41				0.84	0.32–2.27	0.72			
Ischemic heart disease	2.07	1.07–4.05	**0.031***	1.04	0.49–2.21	0.919	1.08	0.53–2.26	0.84			
Cancer	0.89	0.33–2.22	0.81				1.84	0.95–3.73	0.073			
CKD	5.94	3.00–12.6	**<0.001***	6.34	3.00–14.34	**<0.001**	3.15	1.23–9.70	**0.015***	4.76	1.81–14.97	**0.003**
White cell count	1.01	0.99–1.03	0.43				0.97	0.94–1.00	**0.029***	0.97	0.94–1.00	0.087
Neutrophils	1.03	1.00–1.07	0.075				0.99	0.97–1.01	0.36			
Lymphocyte	1.03	0.98–1.21	0.27				0.91	0.72–1.14	0.41			
Monocytes	1	0.94–1.06	0.95				1.07	0.84–1.43	0.61			
Eosinophils	2.43	0.94–15.0	0.073				0.65	0.17–2.03	0.45			
Platelets	1	0.99–1.00	<0.001				1	1.00–1.00	0.051			
Albumin	0.95	0.91–0.99	**0.011***	0.98	0.93–1.02	0.315	0.92	0.89–0.96	**<0.001***	0.93	0.89–0.97	**0.002**
Bilirubin	1.02	1.01–1.05	**0.002***	1.04	1.01–1.07	**0.007**	1.03	1.01–1.05	**<0.001***	1.03	1.01–1.05	**0.002**
CRP	1	1.00–1.01	<0.001				1	1.00–1.00	0.95			

* Variables associated with MAKE-30 in the univariable analysis and included in a backward multivariable model.
Abbreviations: BMI, body mass index; CKD, chronic kidney disease; CRP, C-reactive protein.

Table 3.7. Binomial logistic regression analysis of factors associated with MAKE-90 in COVID-19 vs non-COVID-19 groups

Characteristic	COVID-19 group						Non-COVID-19 group					
	Univariate Analysis			Multivariate analysis			Univariate Analysis			Multivariate analysis		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Age	1.03	1.02–1.05	**<0.001***	1.03	1.01–1.05	**0.001**	0.99	0.98–1.01	0.47			
Male	1.65	1.10–2.52	**0.016***	1.58	1.00–2.53	0.055	0.85	0.50–1.44	0.55			
BMI	1	0.97–1.03	0.96				1	0.97–1.04	0.82			
Ethnicity			**0.011***						0.17			
White	—	—					—	—				
Asian / Asian British	0.76	0.48–1.19		0.67	0.40–1.12	0.13	2	0.95–4.56				
Black / African / Caribbean	2.04	0.96–4.47		2.2	0.95–5.18	0.066	2.33	0.79–8.50				
Other	0.57	0.34–0.95		0.56	0.32–0.99	0.05	1.19	0.28–5.95				
Hypertension	2.02	1.36–3.00	**<0.001***	1.22	0.76–1.95	0.417	1.2	0.67–2.18	0.54			
Diabetes mellitus	1.74	1.17–2.59	**0.006***	2.01	1.25–3.24	**0.004**	1.07	0.56–2.07	0.84			
Obesity	0.83	0.57–1.21	0.34				1.31	0.75–2.30	0.34			
Asthma	0.83	0.46–1.44	0.51				0.96	0.36–2.70	0.94			
Ischemic heart disease	2.01	1.04–3.92	**0.039***	0.99	0.46–2.11	0.976	1.47	0.70–3.25	0.31			
Cancer	0.87	0.32–2.16	0.76				1.63	0.84–3.31	0.15			
CKD	6.58	3.27–14.4	**<0.001***	7.26	3.38–16.88	**<0.001**	3.76	1.38–13.2	**0.008***	5.52	1.98–19.69	**0.003**
White cell count	1.01	0.99–1.03	0.48				0.97	0.94–1.00	**0.046***	0.98	0.95–1.01	0.124
Neutrophils	1.03	1.00–1.07	0.09				0.99	0.97–1.01	0.29			
Lymphocyte	1.03	0.98–1.20	0.29				0.92	0.73–1.17	0.5			
Monocytes	1	0.94–1.06	0.97				1.06	0.83–1.42	0.67			
Eosinophils	2.59	0.95–16.5	0.067				0.6	0.16–1.89	0.38			
Platelets	1	0.99–1.00	<0.001				1	1.00–1.00	0.087			
Albumin	0.95	0.91–0.99	**0.011***	0.98	0.93–1.02	0.29	0.92	0.88–0.95	**<0.001***	0.92	0.88–0.96	**<0.001**
Bilirubin	1.02	1.01–1.05	**0.003***	1.03	1.01–1.06	**0.011**	1.03	1.01–1.05	**<0.001***	1.03	1.01–1.05	**0.006**
CRP	1	1.00–1.01	<0.001				1	1.00–1.00	0.83			

* Variables associated with MAKE-90 in the univariable analysis and included in a backward multivariable model.
Abbreviations: BMI, body mass index; CKD, chronic kidney disease; CRP, C-reactive protein.

Table 3.8. Binomial logistic regression analysis of factors associated with MAKE-180 in COVID-19 vs non-COVID-19 groups

Characteristic	COVID-19 group						Non-COVID-19 group					
	Univariate Analysis			Multivariate analysis			Univariate Analysis			Multivariate analysis		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Age	1.04	1.02–1.06	**<0.001***	1.04	1.02–1.06	**<0.001**	1	0.98–1.02	>0.99			
Male	1.65	1.10–2.50	**0.016***	1.57	0.99–2.51	0.0555	0.96	0.56–1.64	0.89			
BMI	1	0.97–1.02	0.87				1	0.97–1.04	0.82			
Ethnicity			**0.026***						0.38			
White	—	—		—	—		—	—				
Asian / Asian British	0.79	0.50–1.23		0.71	0.42–1.19	0.202	1.71	0.81–3.90				
Black / African / Caribbean	2.04	0.96–4.47		2.24	0.97–5.28	0.061	1.99	0.67–7.28				
Other	0.63	0.37–1.04		0.64	0.36–1.11	0.117	1.02	0.24–5.09				
Hypertension	1.93	1.30–2.87	**0.001***	1.13	0.70–1.81	0.611	1.23	0.68–2.26	0.5			
Diabetes mellitus	1.74	1.17–2.58	**0.006***	2.00	1.25–3.23	**0.004**	1.03	0.54–2.01	0.93			
Obesity	0.82	0.56–1.19	0.29				1.41	0.80–2.52	0.23			
Asthma	0.87	0.49–1.51	0.63				1.09	0.41–3.24	0.86			
Ischemic heart disease	1.95	1.01–3.80	0.048	**0.95**	0.44–2.02	0.889	1.28	0.61–2.83	0.52			
Cancer	0.84	0.31–2.10	0.72				1.59	0.81–3.29	0.18			
CKD	6.37	3.17–14.0	**<0.001***	7.25	3.37–16.88	**<0.001**	4.69	1.57–20.2	**0.004***	6.89	2.25–30.08	**0.003**
White cell count	1.01	0.99–1.03	0.54				0.97	0.94–1.00	**0.042***	0.97	0.94–1.01	0.116
Neutrophils	1.03	0.99–1.07	0.12				0.99	0.96–1.00	0.21			
Lymphocyte	1.03	0.98–1.18	0.31				0.9	0.71–1.14	0.39			
Monocytes	1	0.94–1.05	>0.99				1.03	0.81–1.38	0.81			
Eosinophils	2.39	0.93–14.8	0.078				0.51	0.13–1.60	0.25			
Platelets	1	0.99–1.00	<0.001				1	1.00–1.00	0.078			
Albumin	0.95	0.92–0.99	**0.013***	0.98	0.94–1.02	0.345	0.91	0.88–0.95	**<0.001***	0.92	0.88–0.96	**<0.001**
Bilirubin	1.02	1.01–1.05	**0.003***	1.04	1.01–1.06	**0.009**	1.03	1.01–1.05	**<0.001***	1.03	1.01–1.05	**0.005**
CRP	1	1.00–1.00	0.001				1	1.00–1.00	0.53			

* Variables associated with MAKE-180 in the univariable analysis and included in a backward multivariable model.
Abbreviations: BMI, body mass index; CKD, chronic kidney disease; CRP, C-reactive protein.

Table 3.9. Binomial logistic regression analysis of factors associated with MAKE-365 in COVID-19 vs non-COVID-19 groups

Characteristic	COVID-19 group						Non-COVID-19 group					
	Univariate Analysis			Multivariate analysis			Univariate Analysis			Multivariate analysis		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Age	1.04	1.02–1.06	**<0.001**	1.04	1.02–1.06	**<0.001**	1	0.98–1.01	0.8			
Male	1.65	1.10–2.50	**0.016**	1.57	0.99–2.51	0.055	1.08	0.63–1.85	0.77			
BMI	1	0.97–1.02	0.87				1.01	0.97–1.05	0.57			
Ethnicity			**0.026**						0.2			
White	—	—		—	—		—	—				
Asian / Asian British	0.79	0.50–1.23		0.71	0.42–1.19	0.202	2.19	0.99–5.37				
Black / African / Caribbean	2.04	0.96–4.47		2.24	0.97–5.28	0.061	1.9	0.64–6.95				
Other	0.63	0.37–1.04		0.64	0.36–1.11	0.117	0.97	0.23–4.87				
Hypertension	1.93	1.30–2.87	**0.001**	1.13	0.70–1.81	0.603	1.12	0.62–2.06	0.72			
Diabetes mellitus	1.74	1.17–2.58	**0.006**	2.00	1.25–3.23	**0.004**	1.18	0.61–2.38	0.62			
Obesity	0.82	0.56–1.19	0.29				1.39	0.79–2.50	0.26			
Asthma	0.87	0.49–1.51	0.63				1.34	0.49–4.31	0.58			
Ischemic heart disease	1.95	1.01–3.80	**0.048**	**0.95**	0.44–2.02	0.889	1.37	0.65–3.13	0.42			
Cancer	0.84	0.31–2.10	0.72				1.9	0.94–4.12	0.074			
CKD	6.37	3.17–14.0	**<0.001**	7.25	3.37–16.88	**<0.001**	6.93	1.99–43.8	**0.001**	10.81	3.02–69.25	**0.002**
White cell count	1.01	0.99–1.03	0.54				0.97	0.94–1.00	**0.042**	0.98	0.94–1.01	0.132
Neutrophils	1.03	0.99–1.07	0.12				0.99	0.96–1.00	0.21			
Lymphocyte	1.03	0.98–1.18	0.31				0.9	0.71–1.14	0.37			
Monocytes	1	0.94–1.05	>0.99				1.01	0.80–1.36	0.91			
Eosinophils	2.39	0.93–14.8	0.078				0.46	0.11–1.46	0.19			
Platelets	1	0.99–1.00	**<0.001**				1	1.00–1.00	**0.035**			
Albumin	0.95	0.92–0.99	**0.013**	0.98	0.94–1.02	0.345	0.91	0.87–0.95	**<0.001**	0.92	0.88–0.96	**<0.001**
Bilirubin	1.02	1.01–1.05	**0.003**	1.04	1.01–1.06	**0.009**	1.04	1.02–1.06	**<0.001**	1.04	1.02–1.07	**0.002**
CRP	1	1.00–1.00	0.001				1	1.00, 1.00	0.66			

* Variables associated with MAKE-365 in the univariable analysis and included in a backward multivariable model.
Abbreviations: BMI, body mass index; CKD, chronic kidney disease; CRP, C-reactive protein.

In non-COVID-19 group, factors associated with MAKE-30 (n= 149), MAKE-90 (n= 155), MAKE-180 (n= 162), and MAKE-365 (n= 166) development are shown in Tables 3.7-3.10. In the univariable analysis, the presence of CKD, lower white cell counts, lower albumin level, and higher bilirubin level were all associated with MAKE-30 (Table 3.7), MAKE-90 (Table 3.8), MAKE-180 (Table 3.9), and MAKE-365 (Table 3.10). In the multivariable analysis, CKD, lower albumin levels, and higher bilirubin levels were all associated factors with MAKE-30, MAKE-90, MAKE-180 and MAKE-365 development. Most of the previous MAKEs risk factors were consistent over MAKE timeframes (i.e., 30, 90, 180, and 365 days) an increase in OR was only noted in presence of CKD (OR: 10.81, 95% CI: 3.02–69.25, P= 0.002) among patients with MAKE-365.

3.6.6 Time-to-Event of individual MAKE outcome:

Kaplan-Meier curves for time-to-event data for each MAKE component at 365 days from ICU admission among patients with MAKE-365 in the COVID-19 and non-COVID-19 groups are displayed in Figure 3.2. Kaplan–Meier method revealed that there was no difference in the initiating RRT among patients with MAKE-365 in the COVID-19 and non-COVID-19 groups, and the initiating RRT was commonly observed within the first 30 days following ICU admission (P= 0.53, log-rank test). Patients with MAKE-365 in the non-COVID-19 group had a higher risk of eGFR decline (<75% from baseline) during the 365 days compared with the COVID-19 group (P< 0.0056, log-rank test). Patients with MAKE-365 in the non-COVID-19 group had reduced 1-year survival compared with the COVID-19 group (P< 0.0052, log-rank test).

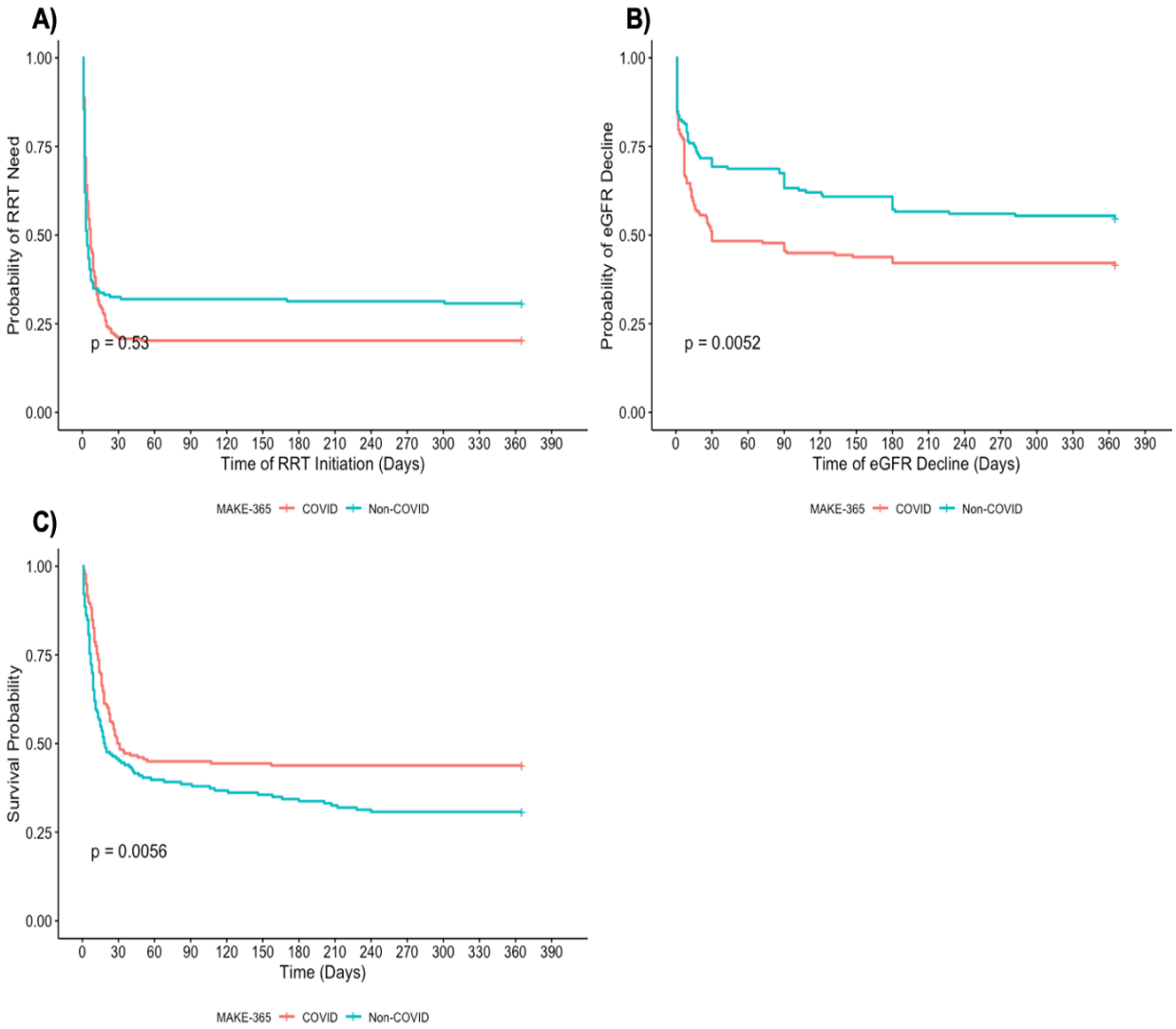


Figure 3.2. Kaplan-Meier Curves for Time to Event of Individual MAKE Outcome

Legend: These Kaplan-Meier curves illustrate no difference in the initiation of RRT (**A**) for patients with MAKE-365 across both groups. However, the non-COVID-19 group demonstrated a higher risk of eGFR decline (**B**) and decreased 1-year survival (**C**) compared to the COVID-19 group.
Abbreviations: eGFR, estimated glomerular filtration rate, RRT, renal replacement therapy.

3.6.7 The eGFR and mortality after initiating RRT:

The relationship between initiation of RRT within 30 days and the eGFR and mortality in both groups are displayed in Tables 3.10 to 3.11. In the COVID-19 group, 141 patients received RRT within 30 days of ICU admission, and 317 patients did not. The median of eGFR at 365 days from ICU admission was significantly lower in those who had RRT within 30 days (90.0 ml/min per 1.73 m^2 [IQR, 80.5-90.0] vs 54.0 ml/min per 1.73 m^2 [IQR, 27.5-73.5], P <0.001, Wilcoxon rank-sum test) (Table 3.10). The mortality rate at 365 days was significantly higher in patients who had RRT within 30 days from ICU admission (65 (20.5%) vs 73 (51.8%), P < 0.001, chi-squared test) (Table 3.10).

Table 3.10. Comparisons between patients who received RRT and those who did not within 30 days in the COVID-19 group

Variables *	Overall (N=458)	No RRT (N=317)	RRT (N=141)	P-value
eGFR, ml/min per 1.73 m^2	84.0 [60.0-90.0]	90.0 [80.5-90.0]	54.0 [27.5-73.5]	<0.001
Mortality, (n, %)	138 (30.1%)	65 (20.5%)	73 (51.8%)	<0.001

Data is presented as median (IQR), unless otherwise stated.
* Data collected by 365 days from ICU admission.
Abbreviations: eGFR, estimated glomerular filtration rate, RRT, renal replacement therapy, CI, confidence interval.

In the non-COVID-19 group, 112 patients had received RRT within 30 days from ICU admission, and 138 patients had not. The median of eGFR at 365 days from ICU admission was significantly lower in those who had RRT within 30 days (79.0 ml/min per 1.73 m^2 [IQR, 58.0-90.0] vs 36.0 ml/min per 1.73 m^2 [IQR, 26.0-51.0], P <0.001, Wilcoxon rank-sum test). The mortality rate at 365 days was significantly higher in patients who received RRT within 30 days from ICU admission (54 (39.1%) vs 74 (66.1%), P < 0.001, chi-squared test) (Table 3.11).

Table 3.11. Comparisons between patients who received RRT and those who did not within 30 days in the non-COVID-19 group

Variables*	Overall (N=250)	No RRT (N=138)	RRT (N=112)	P-value
eGFR, ml/min per 1.73 m^2	63.0 [38.5-87.5]	79.0 [58.0-90.0]	36.0 [26.0-51.0]	<0.001
Mortality, (n, %)	128 (51.2%)	54 (39.1%)	74 (66.1%)	<0.001

Data is presented as median (IQR), unless otherwise stated.
* Data collected by 365 days from ICU admission.
Abbreviations: eGFR, estimated glomerular filtration rate, RRT, renal replacement therapy, CI, confidence interval.

In the COVID-19 group, patients who received RRT within 30 days and completed one-year follow-up had a significant decrease in the median eGFR by 365 days compared with their eGFR on ICU admission (77.0 ml/min per 1.73 m^2 [IQR, 39.5-90.0] vs 54.0 ml/min per 1.73 m^2 [IQR, 27.5-73.5], P= 0.00048, Wilcoxon signed-rank test), while there was no significant difference in median eGFR in non-COVID-19 patients (30.0 ml/min per 1.73 m^2 [IQR, 18.0-47.0] vs 36.0 ml/min per 1.73 m^2 [IQR, 26.0-51.0], P= 0.35, Wilcoxon signed-rank test), as displayed in Figure 3.3.

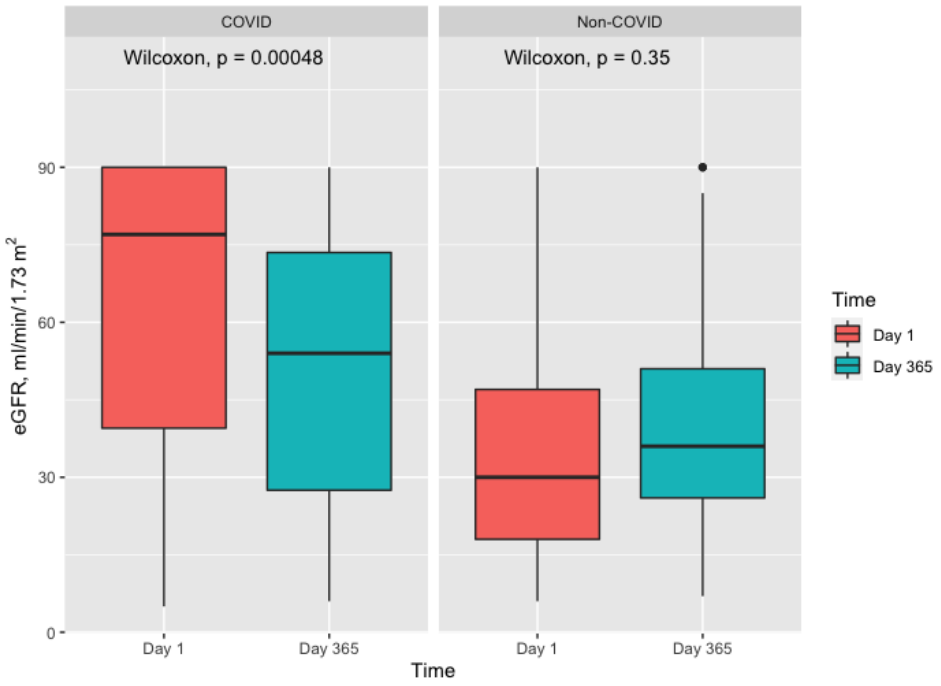


Figure 3.3 Comparison of Median eGFR on Day 1 and Day 365 Following ICU Admission in Patients who Received RRT within 30 days.

Legend: This figure illustrates a significant difference in the median eGFR by 365 days compared with their eGFR on ICU admission while there was no significant difference in median eGFR in non-COVID-19 patients.
Abbreviations: eGFR, estimated glomerular filtration rate, RRT, renal replacement therapy.

3.6.8 Factors Associated with Acute Kidney Injury:

In the COVID-19 group (n=222), the univariable analysis shown that older age (OR: 1.03, 95% CI: 1.02–1.05; P < 0.001), male sex (OR: 1.56, 95% CI: 1.06–2.32; P = 0.026), Black ethnicity (OR: 1.7, 95% CI: 0.79–3.84; P = 0.029), presence of hypertension (OR: 1.91, 95% CI: 1.29–2.84; P = 0.001), diabetes (OR: 1.6, 95% CI: 1.08–2.36; P = 0.019), ischemic heart disease (OR: 2.28, 95% CI: 1.16–4.68; P = 0.017), CKD (OR: 4.09, 95% CI: 2.04–8.93; P < 0.001), higher neutrophils (OR: 1.04, 95% CI: 1.00–1.08, P = 0.037) and higher bilirubin level (OR: 1.03, 95% CI: 1.01–1.06; P = 0.002) were all associated with AKI (Table 3.12). In the multivariable analysis, older age (OR: 1.03, 95% CI: 1.01–1.05; P = 0.001), diabetes (OR: 1.69, 95% CI: 1.07–2.68,

P = 0.024), CKD (OR: 4.34, 95% CI: 2.05–9.93; P < 0.001), and higher bilirubin level (OR:1.03, 95% CI: 1.01–1.07; P = 0.014) were only associated factors with AKI (Table 3.12).

In the non-COVID-19 group (n=176), the univariable analysis revealed that the presence of CKD (OR: 5.68, 95% CI: 1.63–36.0; P = 0.004), lower albumin level (OR: 0.91, 95% CI: 0.87–0.95; P < 0.001) and higher bilirubin level (OR: 1.03, 95% CI: 1.01–1.06; P < 0.001) were all associated with AKI (Table 3.12). In the multivariable analysis, CKD (OR: 8.27, 95% CI: 2.31–52.96, P = 0.005)), lower albumin level (OR: 0.92, 95% CI: 0.88–0.96; P = 0.001) and higher bilirubin level (OR: 1.03, 95% CI: 1.01–1.06, P = 0.005) were only associated factors with AKI (Table 3.12).

Table 3.12. Binomial logistic regression analysis of factors associated with AKI in the COVID-19 vs non-COVID-19 group

Characteristic	COVID-19 group						Non-COVID-19 group					
	Univariate Analysis			Multivariate analysis			Univariate Analysis			Multivariate analysis		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Age	1.03	1.02–1.05	**<0.001***	1.03	1.01–1.05	**0.001**	0.99	0.98–1.01	0.44			
Male	1.56	1.06–2.32	**0.026***	1.41	0.92–2.19	0.116	0.92	0.52–1.60	0.77			
BMI	1.02	0.99–1.04	0.23				1.01	0.97–1.05	0.79			
Ethnicity			**0.029***						0.30			
White	—	—		—	—		—	—				
Asian / Asian British	0.72	0.46–1.11		0.67	0.41–1.09	0.112	2.14	0.94–5.55				
Black / African / Caribbean	1.7	0.79–3.84		1.68	0.74–4.01	0.224	1.57	0.53–5.77				
Other	0.59	0.36–0.97		0.57	0.33–0.97	**0.04**	1.45	0.32–10.1				
Hypertension	1.91	1.29–2.84	**0.001***	1.25	0.79–1.98	0.335	0.96	0.52–1.79	0.88			
Diabetes mellitus	1.6	1.08–2.36	**0.019***	1.69	1.07–2.68	**0.024**	1.06	0.54–2.18	0.86			
Obesity	1.1	0.76–1.58	0.62				1.16	0.65–2.12	0.62			
Asthma	0.96	0.56–1.64	0.88				2.2	0.70–9.73	0.19			
Ischemic heart disease	2.28	1.16–4.68	**0.017***	1.26	0.59–2.76	0.557	1.31	0.60–3.09	0.51			
Cancer	0.56	0.21–1.39	0.21				1.76	0.85–3.94	0.13			
CKD	4.09	2.04–8.93	**<0.001***	4.34	2.05–9.93	**<0.001**	5.68	1.63–36.0	**0.004***	8.27	2.31–52.96	**0.005**
White cell count	1.01	0.99–1.03	0.5				0.99	0.96–1.02	0.34			
Neutrophils	1.04	1.00–1.08	**0.037***	1.03	0.99–1.07	0.128	0.99	0.97–1.00	0.21			
Lymphocyte	1.02	0.97–1.20	0.38				0.96	0.76–1.24	0.74			
Monocytes	0.99	0.93–1.05	0.79				1.01	0.79–1.37	0.94			
Eosinophils	1.69	0.86–9.38	0.18				0.43	0.10–1.36	0.15			
Platelets	1	1.00–1.00	0.003				1	1.00–1.00	0.19			
Albumin	0.97	0.93–1.01	0.11				0.91	0.87–0.95	**<0.001***	0.92	0.88–0.96	**0.001**
Bilirubin	1.03	1.01–1.06	**0.002***	1.03	1.01–1.07	**0.014**	1.03	1.01–1.06	**<0.001***	1.03	1.01–1.06	**0.005**
CRP	1	1.00–1.01	<0.001				1	1.00–1.00	0.89			

* Variables associated with AKI in the univariable analysis and included in a backward multivariable model.
Abbreviations: BMI, body mass index; CKD, chronic kidney disease; CRP, C-reactive protein

3.6.9 Renal recovery:

There were no differences between groups among AKI patients who had complete renal recovery at hospital discharge within 30, 90, and 180 days from ICU admission (Table 3.13).

Table 3.13. Renal recovery of AKI patients at hospital discharge in both group

	Overall (N=398)	COVID-AKI (N=222)	Non-COVID AKI (N=176)	P-value*
Discharge 30 days				
Incomplete renal recovery	26 (6.5%)	17 (7.7%)	9 (5.1%)	1
Complete renal recovery	71 (17.8%)	47 (21.2%)	24 (13.6%)	
Discharge 90 days				
Incomplete renal recovery	61 (15.3%)	34 (15.3%)	27 (15.3%)	0.195
Complete renal recovery	129 (32.4%)	86 (38.7%)	43 (24.4%)	
Discharge 180 days				
Incomplete renal recovery	62 (15.6%)	35 (15.8%)	27 (15.3%)	0.208
Complete renal recovery	136 (34.2%)	91 (41.0%)	45 (25.6%)	

Data is presented as median (IQR), unless otherwise stated.
* p-values from the chi-squared test represent the differences between COVID-AKI vs non-COVID-AKI groups.
Abbreviations: AKI, acute kidney injury.

In the COVID-19 group, 47 (73%) of the 64 AKI patients had achieved complete renal recovery within 30 days, of whom only 7 had received RRT. These figures were similar to those for the non-COVID-19 group, in which 24 (73%) of 33 AKI patients had achieved complete renal recovery within 30 days, of whom 11 had received RRT. Among patients who had been discharged at 90 days, 86 (72%) of the 120 AKI patients in the COVID-19 group had achieved complete renal recovery, of whom 37 had received RRT, compared to the non-COVID-19 group, in which 43 (61%) of the 70 AKI patients had achieved complete renal recovery, of whom 20 had received RRT. After 180 days of follow-up, 91 (72%) of the 126 AKI patients in the COVID-19 group had

achieved complete renal recovery, of whom 42 had received RRT, while 45 (62%) of the 72 AKI patients in the non-COVID-19 group had achieved complete renal recovery, of whom 22 had received RRT.

3.6.10 Incidence of AKI and MAKE-365 across ARDS severities:

In the COVID-19 group (N=458), there was no statistically significant differences in the incidence of AKI and MAKE-365 across ARDS severities (P= 0.276 and P= 0.17, respectively), as detailed in Table 3.14. Specifically, the incidence of AKI was observed in 38.5% of patients with mild ARDS, 51.7% with moderate ARDS, and 47.1% with severe ARDS. Similarly, MAKE-365 occurrences were noted in 25.6% of mild ARDS cases, 41.6% of moderate, and 38.6% of severe cases. Despite the lack of statistical significance, there was a noted trend with higher incidences of AKI and MAKE-365 in the moderate to severe ARDS categories compared to mild ARDS.

Table 3.14. Incidence of AKI and MAKE-365 across ARDS severity in COVID-19 group

	Overall (N=458)	Mild (N=39)	Moderate (N=209)	Severe (N=210)	P-value*
AKI Incidence	222 (48.5%)	15 (38.5%)	108 (51.7%)	99 (47.1%)	0.276
MAKE-365	178 (38.9%)	10 (25.6%)	87 (41.6%)	81 (38.6%)	0.17

Data presented as frequencies with percentages.
* p-values from Kruskal-Wallis test represent the differences in the incidence of AKI and MAKE-365 across ARDS severity in COVID-19 group.
Abbreviations: AKI, acute kidney injury, MAKE, major adverse kidney events.

Contrastingly, in the non-COVID-19 group, there were significant differences in the incidence of AKI (P= 0.032) and MAKE-365 (P= 0.027) across ARDS severity cohorts, as shown in Table 3.15. AKI incidence was reported in 56.1% of patients with mild ARDS, 68.4% with moderate ARDS, and 77.5% with severe ARDS. Similarly, the

incidence of MAKE-365 was 53.7% in mild ARDS cases, 62.2% in moderate, and 74.8% in severe cases. These data indicate that in the non-COVID-19 ARDS population, there is a stronger association between ARDS severity and the incidences of AKI and MAKE-365.

Table 3.15. Incidence of AKI and MAKE-365 across ARDS Severity in non-COVID-19 group

	Overall (N=250)	Mild (N=41)	Moderate (N=98)	Severe (N=111)	P-value
AKI Incidence	176 (70.4%)	23 (56.1%)	67 (68.4%)	86 (77.5%)	0.032
MAKE-365	166 (66.4%)	22 (53.7%)	61 (62.2%)	83 (74.8%)	0.027

Data presented as frequencies with percentages.
* p-values from Kruskal-Wallis test represent the differences in the incidence of AKI and MAKE-365 across ARDS severity in non-COVID-19 group.
Abbreviations: AKI, acute kidney injury, MAKE, major adverse kidney events.

3.6.11 Incidence of MAKE among ARDS patients with mainly respiratory infection:

The incidence MAKEs outcome at 30, 90, 180 and 365 days after ICU admission among ARDS patients with mainly respiratory infection are shown in Table 3.16. This analysis included 658 patients, of which 458 were in the COVID-19 group and 200 in the non-COVID-19 group. The incidence of MAKE-365 was higher in the non-COVID-19 group (178 (38.9%) vs 122 (61.0%), P < 0.001, chi-squared test).

Table 3.16 Incidence of MAKE among ARDS patients with mainly respiratory infection

	Overall (N=658)	COVID (N=458)	Non-COVID (N=200)	P-value
MAKE-30	280 (42.6%)	172 (37.6%)	108 (54.0%)	<0.001
MAKE-90	288 (43.8%)	175 (38.2%)	113 (56.5%)	<0.001
MAKE-180	297 (45.1%)	178 (38.9%)	119 (59.5%)	<0.001
MAKE-365	300 (45.6%)	178 (38.9%)	122 (61.0%)	<0.001

Data presented as frequencies with percentages.
* p-values from chi-squared test represent the differences of incidence of MAKEs outcome among ARDS patients with mainly respiratory infection in COVID-19 vs non-COVID-19 groups.
Abbreviations: MAKE, major adverse kidney events.

3.7 DISCUSSION

The work presented in this chapter examined the hypothesis that the incidence of MAKE-365 would be higher in non-COVID-19 patients with ARDS, compared to COVID-19 ARDS patients. In agreement with the original hypothesis, the incidence of MAKE-365 was higher in the non-COVID-19 group. Overall, the RRT initiation was the most frequently observed cause of MAKE365 in both groups, followed by mortality and decline in eGFR. This study also explored the risk factors of MAKE-365 and found that CKD and high bilirubin were the strongest independent risk factors for MAKE-365 in both groups, in addition to older age and diabetes in the COVID-19 group, and lower albumin levels in the non-COVID-19 group.

The current study found that the incidence of MAKEs in both groups progressively increased over MAKE timeframes (i.e., 30, 90, 180, and 365 days) and a higher incidence of MAKE-365 was mostly observed in the non-COVID-19 group. This aligns with a study published by Vinclair et al. (2020), who examined a group of patients who received veno-arterial extracorporeal membrane oxygenation (VA-ECMO) during their ICU stay and found that the incidence of MAKE-30, MAKE-90 and MAKE-360 was 59.9%, 60.5%, and 85.1%, respectively.

It has been well-known that AKI contributes to higher rates of morbidity and mortality rates, especially in patients with ARDS (McNicholas et al., 2019). The present study showed that AKI was greater among the non-COVID group, as previously reported (Panitchote et al., 2019b). Consequently, the mortality was higher in the non-COVID group, which is consistent with McNicholas et al. (2019). Several mechanisms have been proposed that could lead to the onset of AKI, includ imbalances in

haemodynamic, metabolic and neurohormonal status (Hepokoski et al., 2017, Husain-Syed et al., 2016). Over the years, a growing body of literature has linked ARDS and IMV as independent risk factors for the onset of AKI, in addition to previously recognised risk factors such as older age, diabetes, and cardiac dysfunction (Vashisht and Duggal, 2020). The management used with ARDS patients, such as low oxygen saturation and hypercapnia targets, leads to increases in diuresis and renal resistive indices (Darmon et al., 2009a). These conditions contribute to a reduction in the eGFR and subsequently AKI.

In the present study, individuals in the non-COVID-19 group were older and exhibited a higher prevalence of pre-existing comorbidities, including ischemic heart disease and cancer. The serum creatinine levels were elevated, and eGFR was decreased in the non-COVID-19 group, indicating potential kidney dysfunction among these patients. Furthermore, the elevated counts of circulating leukocytes and neutrophils in the non-COVID-19 group align with findings from a prior study comparing characteristics and outcomes of ARDS patients with and without COVID-19 (Mahida et al., 2020). These differences may highlight the severity of the illness and its potential contribution to long-term kidney dysfunction and MAKE-365 in the non-COVID-19 group.

Although most MAKEs risk factors have been consistent over MAKE timeframes (i.e., 30, 90, 180, and 365 days) an increase in OR was noted in CKD and diabetes in the COVID-19 group and only CKD in the non-COVID-19 group. In contrast to the current study, McKown et al. (2017) found no association between CKD and the risk of developing MAKE-30 (OR: 1.2, 95% CI: 0.95–1.51, P = 0.13). Although the

researchers investigated only ICU patients, this difference is probably because fewer subjects were mechanically ventilated (28%) and fewer comorbidities were reported. This study also revealed that the risk of MAKE-30 was increased in patients who were mechanically ventilated (OR: 1.59, 95% CI: 1.34–1.89, P < 0.001). As previously discussed, IMV could increase the risk of AKI and contribute to an increased risk of MAKE-30, especially in critically ill patients with pre-existing comorbidities. Previous studies have indicated the association between elevated bilirubin levels upon ICU admission and an increased risk of ARDS development and mortality (Zhai et al., 2009). This may explain the graded increase in mortality among ARDS patients with AKI and the subsequent increase in the incidence of MAKE-365 in the non-COVID-19 group.

There was limited published data investigating the risk factors for MAKE-365 in COVID-19-related ARDS. The present study found that older age, diabetes, CKD, and elevated bilirubin level were strongly associated with a higher risk of MAKE-365 in the COVID-19 group. Bowe et al. (2021) examined the incidence of MAKE-30 between 89,216 COVID-19 survivors and 1,637,467 uninfected controls and found that the risk of MAKE-30 was higher in COVID-19 patients (aHR, 1.66; 95% CI: 1.58–1.74). The authors also revealed that ICU patients had a significant 7-fold higher risk for MAKE-30 compared with controls. Thus, the higher incidence of MAKE-30 in the COVID-19 group in the current study might be because only ventilated ICU patients were included, and the incidence of MAKEs was reported directly after ICU admission. In the United States, Gupta et al. (2020) examined 3,099 critically ill COVID-19 patients with ARDS admitted to ICU and found that 42.4% of those patients developed MAKE-90. A recent published study demonstrated that COVID-19 patients with high direct bilirubin levels

had higher risks of shock and respiratory failure during hospitalisation (Chen et al., 2022). These consequences might be related to liver dysfunction in the production of coagulation factors, albumin, and acute reactants, leading to multi-system manifestations of COVID-19, such as ARDS and multiple organ failure (Nardo et al., 2021).

The current study found that the initiation of RRT was a major cause of MAKE-365 in both groups. Interestingly, the initiation of RRT was highly observed within 30 days after ICU admission compared to other timeframes (i.e., 90, 180, and 365 days). The initiation of RRT was higher in the non-COVID-19 group, consistent with the current literature (Klein et al., 2018, Darmon et al., 2014a). This difference might be attributed to the different pathophysiological presentations upon ICU admission between these patient groups. While patients with COVID-19 ARDS tend to present with single-organ (primarily pulmonary) failure, non-COVID-19 ARDS patients often exhibit multi-organ failure, leading to a high risk of renal impairment and requiring more frequent RRT initiation (Mahida et al., 2020).

Fluid overload is known to contribute to worsening respiratory function in ARDS patients with AKI (Klein et al., 2019). The well-recognised indications for initiating RRT in ARDS patients include prevention of fluid overload, AKI, and diuretic resistance, and electrolyte imbalance refractory to medical management (Lameire and Vanmassenhove, 2018, Chang et al., 2021). In addition, early initiation of RRT may potentially have beneficial effects in disease processes such ARDS and improve outcomes (Han et al., 2015).

In keeping with current findings, Lumlertgul et al. (2021) found that 32% of COVID-19 patients received RRT during their early ICU stay. There is insufficient evidence to support the early initiation of RRT in patients who have both COVID-19 and AKI (Adapa et al., 2020). A previous study revealed several primary indications for initiating RRT in COVID-19 patients with ARDS, including high urea, oliguria, hyperkalaemia, acidosis, pulmonary oedema, rhabdomyolysis, fluid and electrolyte imbalances (Lumlertgul et al., 2021). A common rationale while treating ARDS patients with AKI is that early initiation of RRT prevents fluid overload and uraemia, thus promoting a faster recovery (Klein et al., 2019). However, in contrast with the previous study, we found that patients who had RRT within 30 days were at a higher risk of mortality by 365 days in both groups. It's important to note that these patients also had lower baseline eGFRs. Therefore, it appears that it is the severity of the AKI, rather than the RRT itself, that increases the mortality risk. The recent STARRT-AKI study provides additional support for this view, showing that accelerated RRT could worsen longer-term renal outcomes particularly in patients with CKD (Bagshaw et al., 2022).

Mortality was greater in the non-COVID-19 group compared to the COVID-19 group, particularly in patients who developed AKI. These findings are in keeping with literature that found that AKI is associated with higher mortality in patients with ARDS (Darmon et al., 2014a, Shebl et al., 2020). The present study found that mortality was significantly increased among patients with MAKE-365 in the non-COVID-19 group. The mortality of patients with MAKE-365 was mainly observed within 30 days from ICU admission in both groups, which also increased progressively after 365 days in the non-COVID-19 group.

In assessing the impact of ARDS severity on AKI and MAKE-365 outcomes within the COVID-19 group, we observed that the variations in the incidence of AKI and MAKE-365 did not reach statistical significance. This contrasted with the non-COVID-19 group, where ARDS severity significantly impacted these renal outcomes. The differential findings between the groups suggest that the factors contributing to renal complications in ARDS patients may extend beyond the severity of ARDS itself, particularly in the COVID-19 group. Notably, most of the current population had moderate to severe ARDS; consequently, ARDS severity could also contribute to increased mortality in both groups.

The presence of comorbidities such as hypertension, diabetes, and obesity, which are prevalent among COVID-19 patients, likely play a role in obscuring the effects of ARDS severity on renal outcomes. A larger proportion of the COVID-19 group were older and had pre-existing comorbidities such as hypertension, diabetes, and obesity, which are well-known to be risk factors for worsening outcomes and increased risk of mortality in patients with COVID-19 and ARDS (Gibson et al., 2020, Zangrillo et al., 2020b). Bellani et al. (2016b) conducted a study on the mortality rate among ICU patients with ARDS. They discovered a hospital mortality rate of 40.3% in cases of moderate ARDS, which increased to 46.1% for those with severe ARDS.

Our current study examined the incidence of MAKE-365 among patients with ARDS due to mainly respiratory infection in both groups, and we observed that the incidence of MAKE-365 was significantly higher in non-COVID-19 groups. Several factors could contribute to the increased vulnerability of non-COVID-19 ARDS patients to renal complications. As previously discussed, the pathophysiological mechanisms

of ARDS due to non-COVID-19 respiratory infections may lead to multi-organ failure, leading to a high risk of renal impairment and requiring more frequent RRT initiation (Mahida et al., 2020). Moreover, Su et al. (2021) indicated that the presence of kidney disease is associated with a higher risk of death in patients with non-COVID-19 respiratory infections, particularly in those with pneumonia. This could indicate the reason for the increased incidence of MAKE-365 in the non-COVID-19 group in addition to the differences in the management of these patients or by a higher burden of pre-existing comorbidities.

Although RRT initiation was higher at 30 days in the non-COVID-19 group, mortality progressively increased from day 30 to day 365. Gaudry et al. (2018) studied the impact of an early RRT initiation strategy on 60-day mortality in ARDS patients and found that early RRT initiation was not associated with any improvement in 60-day mortality. The current study found that patients who developed AKI and those who required RRT within 30 days from their ICU admission had higher mortality rates. This is consistent with findings from a study of 3,099 COVID-19 patients with ARDS, which showed that those patients with AKI who were treated using RRT were associated with hospital mortality >60% (Gupta et al., 2020). Sullivan et al. (2021) also suggested that the mortality risk increased in hospitalised COVID-19 patients who were receiving RRT (adjusted odds ratio (aOR) 3.06: 95% CI: 2.75–3.39) and who developed AKI (aOR 1.91: 95% CI: 1.82–2.01). Nardo et al. (2021) pointed out that liver dysfunction is a common complication in critically ill patients with COVID-19 and is associated with increased mortality in those patients. This may explain the high mortality among patients in the COVID-19 group.

The present study showed no significant differences in the eGFR decline between COVID-19 and non-COVID-19 groups within 180 days of follow-up from ICU admission. However, the eGFR decline was significantly observed in the non-COVID-19 group within 365 days after ICU admission. A potential explanation for this could be that the non-COVID-19 ARDS patients had lower baseline eGFRs, indicating that these patients might have already had renal impairment.

The eGFR decline could be caused by various factors in critically ill patients with ARDS, including IMV, fluid overload, hypoxemia, hypercarbia, and acidosis. For example, IMV decreases preload in those patients, which can cause a decrease in cardiac output and neurohormonal activation, both of which can affect renal blood flow and consequently decline the eGFR (Cortesi, 2020). When diuretics are inadequate to manage fluid overload, initiating RRT should be considered to offset or prevent its adverse outcomes in ARDS patients (Cortesi, 2020). However, comparing the median of eGFR on day 1 and day 364 among patients who had RRT within 30 days from ICU admission, we found no differences in the non-COVID-19 group, compared to the COVID-19 group whose eGFR had significantly decreased by 365 days. Furthermore, in the COVID-19 patients, initiating RRT within 30 days was strongly associated with the eGFR decline and mortality at 365 days.

The risk factors for developing AKI were comparable to those associated with MAKE-365 in the non-COVID-19 group, which are consistent with well-known risk factors in the literature (Hsu and Hsu, 2016, Shebl et al., 2020, Wiedermann, 2019). The findings reported by both Kongsayreepong and Nitikaroon (2013) and Shum et al. (2016) were mostly consistent with the present study, as the authors demonstrated

that lower albumin level was an independent risk predictor for the development of AKI. Shebl et al. (2020) investigated 81 ARDS patients and revealed that platelet counts were significantly lower and bilirubin levels were significantly higher in patients who developed AKI ($P = 0.014$, $P < 0.001$, respectively).

Although the incidence of AKI was higher in the non-COVID-19 group, the risk of AKI development still increased in patients in the COVID-19 group, which is consistent with the previous reports (Chan et al., 2021, Alenezi et al., 2021, Lumlertgul et al., 2021). COVID-19 patients frequently develop AKI after the onset of ARDS, suggesting lung–kidney crosstalk as the dominant mechanism of kidney injury (Zhou et al., 2020a, Hirsch et al., 2020). A few COVID-19 studies that investigated the risk factors of AKI and in which more than 90% of their populations had ARDS found that older age, diabetes, and CKD increase the risk of AKI (Ch et al., 2020, Arentz et al., 2020, Zheng et al., 2020).

Recently, Sullivan et al. (2022) conducted the largest prospective cohort study to date that investigated AKI related to COVID-19 in 41,294 hospitalised patients. Of those, only 31% developed AKI, and the risk of AKI was higher in patients aged 50-79 years compared with patients aged < 50 years. Male sex, Black ethnicity, diabetes, CKD, and hypertension were also associated with a higher risk of AKI. Although the population of the previous study was not consistent with the current study, the results still showed that older age, CKD, and diabetes were positively associated with increased risk of AKI in COVID-19 patients.

The present study assessed the renal recovery of AKI patients at hospital discharge and found that there were no significant differences among those who had

complete renal recovery in the two groups at 30, 90, and 180 days. Interestingly, the number of patients who had completed renal recovery and received RRT in the COVID-19 group increased from 14% at 30 days up to 43% at 90 days and 46% at 180 days. A recently published article by Sullivan et al. (2021) suggested that the use of dexamethasone was positively associated with RRT, and there was no association between dexamethasone and AKI. This may explain the increase in using RRT with the COVID-19 group, as most of the patients in this group were given dexamethasone during their hospitalisation.

This study has several strengths. The inclusion of a large sample of ICU patients allowed investigation of performance characteristics throughout a wide spectrum of underlying illnesses, including patients with ARDS, COVID-19, AKI, and comorbidities such as hypertension, diabetes, obesity, and CKD. Also, an adequate follow-up period allowed us to observe the development of MAKE. The use of clinical variables that are obtained as part of routine care strengthens the clinical value of our results. However, there were some limitations to this study. First, it reported the experience of a single centre, which might limit the external validity of the findings. Second, there was a lack of pre-hospital baseline eGFR measurements, particularly in COVID-19 patients. Therefore, in accordance with current guidelines, the eGFR baseline value was estimated using the MDRD or CKD-EPI formula (Kellum et al., 2012). This was important to evaluate the eGFR decline during the follow-up period. Third, this study lacked information on ventilator settings and receipt of VA-ECMO during ICU stay: these losses may have had a huge impact on the findings, such as promoting the development of AKI and consequently increased mortality rates (Vinclair et al., 2020, Darmon et al., 2014a). Additionally, a competing risk analysis was not performed,

which is acknowledged as a limitation due to the potential for attrition bias of mortality versus the need for RRT.

3.8 CONCLUSION

In conclusion, this study shows that MAKE-365 is common in both groups but greater in those with non-COVID ARDS. Both groups' strongest independent risk factors for MAKE-365 were CKD and a raised bilirubin. Other independent risk factors for MAKE-365 were older age and diabetes in the COVID-19 group, and lower albumin levels in the non-COVID-19 group. The initiation of RRT was mostly observed within 30 days and it was the major cause for MAKE-365 in the two groups. Both initiation of RRT and mortality were significantly higher in the non-COVID-19 group during follow-up timeframes (i.e., 30, 90, 180, and 365 days), however, the eGFR decline was significantly higher in the non-COVID-19 group by 365 days of follow-up. Multiple advanced critical care interventions and treatment strategies help to decrease adverse outcomes associated with COVID-19 who developed ARDS. However, further investigations of major adverse kidney events associated with ARDS patients are still recommended. MAKE-365 is a significant long-term measure of the influence of AKI on patient-related outcomes, and interventions should be targeted at reducing it, especially in elderly patients with ARDS and comorbidities. Recognition of factors associated with MAKE-365 might help guide future practice and management strategies in critical care. Creating a risk score system to predict MAKE-365 in ICU patients with ARDS is recommended to prevent or reduce the adverse outcomes associated with ARDS.

3.9 SUMMARY OF THE CHAPTER

This retrospective cohort study demonstrated the incidence of MAKE-365 is common in both groups but higher in those with non-COVID ARDS. CKD and high bilirubin were found to be predictors of MAKE-365 in both groups. Other predictors of MAKE-365 were older age and diabetes in the COVID-19 group and lower albumin levels in the non-COVID-19 group. As MAKE-365 was demonstrated to be prevalent in non-COVID-19 ARDS patients, in Chapter 4, the capacity of kidney biomarkers to predict MAKE-365 were evaluated in non-COVID-19 patients, with or without ARDS.

CHAPTER 4

4 KIDNEY BIOMARKERS AND MAJOR ADVERSE KIDNEY EVENTS IN CRITICALLY ILL PATIENTS WITH SEPSIS IN THE PRESENCE OR ABSENCE OF ACUTE RESPIRATORY DISTRESS SYNDROME

4.1 INTRODUCTION

The retrospective cohort study discussed in Chapter 3 highlighted that the incidence of MAKE-365 was more common in non-COVID-19 ARDS patients than in those with COVID-19. Age, CKD, and raised bilirubin levels were identified as clinical indicators for MAKE-365 in ARDS patients, irrespective of their COVID-19 status. Yet, there is an unexplored area regarding using these clinical predictors in combination with early kidney biomarker measurements to predict MAKE-365 in ARDS patients. Therefore, this retrospective cohort study was conducted to assess the association between kidney biomarkers and MAKE-365 in sepsis patients and test the utility of combining the biomarker data with a clinical prediction model for MAKE-365. An abstract of this study was presented at the Intensive Care Society State of the Art Congress 2023 and published in the Journal of the Intensive Care Society.

This work was conducted collaboratively, and the individual contributions of the authors are detailed below.

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Authors' contributions:

F.K.A. planned the study, designed the methodology, performed data analysis and visualisation, and wrote the manuscript. D.P., D.R.T., and J.M.P. assisted in the planning and design of the study and contributed to manuscript revision. R.M. assisted in the sample collection and participated in the manuscript revision.

4.2 BACKGROUND

Sepsis, a serious clinical syndrome, is characterised by an imbalanced host response to infection resulting in organ dysfunction. This definition is according to the Third International Consensus (Sepsis-3), highlighting the role of both innate and adaptive immune responses in the progression of the condition (Singer et al., 2016).

Acute respiratory distress syndrome (ARDS) often occurs in settings of severe sepsis and might also be due to pneumonia (viral and bacterial), aspiration of gastric contents or severe trauma with shock (Matthay et al., 2019, Kumar, 2007). Approximately one-third of sepsis patients develop ARDS (Shi et al., 2022). ARDS development might lead to multi-organ dysfunction, including renal dysfunction (Park and Faubel, 2021). Many sepsis patients, especially those in intensive care units (ICU), are prone to acute kidney injury (AKI), AKI affects between 40% to 50% of sepsis patients in critical care, with 15% to 20% requiring renal replacement therapy (RRT), includes both haemodialysis (HD) and Continues Veno-Venous Haemofiltration (CVVH) (Hoste et al., 2015, Uchino et al., 2005). It is worth noting that the incidence of AKI can increase up to 60% among ICU patients with ARDS (van den Akker et al., 2013, Darmon et al., 2014a).

Transient AKI may progress to chronic kidney disease (CKD) and impact health-related quality of life (Chawla et al., 2014) and may result in worse long-term survival, particularly in sepsis patients who do not recover from AKI by hospital discharge (Fiorentino et al., 2018). Additionally, new RRT initiation during hospitalisation increases the risk of CKD and death after hospital discharge (De Corte et al., 2016, Kirwan et al., 2015). Therefore, a more comprehensive measure that

reflects the long-term outcomes related to AKI, such as the progression of CKD and survival, is required. The National Institute of Diabetes and Digestive and Kidney Diseases workgroup recommends a composite measure known as major adverse kidney events (MAKEs) as a patient-centred outcome for phase 3 trials. This measure, which includes new initiation for RRT, a decrease in eGFR to less than 75% of baseline, or all-cause mortality, is seen as a robust indicator of AKI progression and its short-term and long-term impacts on patient outcomes (Palevsky et al., 2012).

The alterations in serum creatinine levels and urine output are still the standard measures to identify the onset and severity of AKI worldwide. However, a critical limitation of these standard measures is that significant renal damage may have already occurred by the time these changes can be detected. This points to the urgent need for more proactive approaches to AKI detection. Over the past decade, studies on new biomarkers for AKI prediction have expanded. These studies were primarily focused on finding a biomarker that may identify AKI earlier than serum creatinine, allowing for earlier diagnosis and better management (Kashani et al., 2013, Parikh et al., 2011). In 2014, a combination of two urinary biomarkers (including tissue inhibitor of metalloprotease-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP-7) was approved by the US Food and Drug Administration as promising clinical early predictors for the AKI development (Griffin et al., 2020a, Vijayan et al., 2016a). Over 15 different biomarkers have been studied, and only a few of these biomarkers have now been approved for clinical use, including neutrophil gelatinase-associated lipocalin (NGAL), TIMP-2 and IGFBP-7 (Vijayan et al., 2016a, Kashani et al., 2013, Albert et al., 2020). The Sapphire study findings revealed that urinary [TIMP-2]*[IGFBP-7] was superior to other identified biomarkers for early prediction of AKI

development, such as plasma cystatin C and urinary NGAL ($p < 0.002$) (Kashani et al., 2013).

To the best of our knowledge, most of the previous biomarker studies have primarily focused on predicting short-term outcomes such as AKI or MAKEs at 30 days (MAKE-30) in critically ill patients. However, current literature assessing the prediction of MAKE at 365 days (MAKE-365), particularly in ICU patients with sepsis, is limited. Therefore, the association between early kidney biomarker measurements (including plasma cystatin C, urinary NGAL, urinary [TIMP-2] *[IGFBP-7], and urinary C-C motif chemokine ligand 14 (CCL-14)) and MAKE-365 in sepsis patients with or without ARDS remains largely unexplored. Thus, our study aims to address this gap in the literature by assessing the association of kidney biomarkers with MAKE-365 in patients with sepsis and testing the utility of combining the biomarker data with a clinical prediction model for MAKE-365. Our findings may help in identifying patients at risk of developing MAKE-365 using available novel biomarkers, which may help in enhancing long-term outcomes and intervention strategies in critically ill patients with sepsis.

4.3 HYPOTHESIS

We hypothesise those novel kidney biomarkers (including plasma cystatin C, urinary NGAL, urinary [TIMP-2]*[IGFBP-7], and urinary CCL-14) can effectively predict MAKE-365 risk in critically ill sepsis patients with or without ARDS.

4.4 AIMS

- To investigate the MAKE-365 in critically ill patients with sepsis in the presence or absence of ARDS.
- To determine the association between novel kidney biomarkers and MAKE-365.
- To evaluate the predictive ability of kidney biomarkers for MAKE-365.

4.5 METHODS

4.5.1 Study Design and Setting:

This retrospective cohort study focused on patients admitted to the intensive care units (ICUs) in a tertiary hospital in the West Midlands of the UK. The study was conducted single centre.

4.5.2 Ethical Approvals:

This study utilised biological samples collected initially under a previous study entitled: “A research study to investigate whether transgenic mesenchymal stem cells expressing hydroxysteroid dehydrogenase type-1 can attenuate inflammation in Acute Respiratory Distress Syndrome” (AM-ARDS). Ethical approval for collecting these samples had been obtained from the Wales Research and Ethics Committee 1 (REC 16/WA/0169), and Health Research Authority (HRA) approval for the study was subsequently given. University Hospitals Birmingham and Heart of England NHS Trusts approved the AM-ARDS study (NIHR Portfolio, registration number 32296).

Given the time limitations of this current PhD project, we decided to use these previously collected samples to investigate new research questions relevant to our study. It's important to note that utilising these samples for the present study's objectives does not violate the terms of the original ethical approval. Furthermore, all patient data were de-identified and used per the Data Protection Act 2018 guidelines.

4.5.3 Participants:

This study included all adult patients admitted to the ICUs at the Queen Elizabeth Hospital Birmingham from 2016 to 2019, who were diagnosed with sepsis on admission to ICU based on the Sepsis-3 criteria (Singer et al., 2016). Only data from the first ICU admission were included in the analysis if patients had several ICU admissions.

4.5.4 Eligibility criteria:

4.5.4.1 Inclusion criteria:

- Adult patients (aged ≥ 18 years);
- Patients admitted to ICU who received invasive mechanical ventilation (IMV);
- Patients diagnosed with sepsis upon ICU admission based on the Sepsis-3 criteria (Singer et al., 2016);
- Patients who had at least two serum creatinine measurements within the first seven days of enrolment;
- Patients with available blood or urine samples were taken within 48 hours of their sepsis diagnosis upon ICU admission.

4.5.4.2 Exclusion criteria:

- Patients admitted to the ICU who did not receive IMV;
- Any patient who did not meet the Sepsis-3 criteria;
- Patients missing blood or urine samples within 48 hours of their sepsis diagnosis;
- Paediatric patients (aged <18 years);
- Patients who had undergone a kidney transplant;

- Patients diagnosed with end-stage kidney disease prior to, or at the time of, hospital admission, or those with a baseline eGFR <15 mL/min/1.73 m^2;
- Patients who died within the first seven days of enrolment without developing AKI.

4.5.5 Study Outcomes:

The study had the following outcomes:

4.5.5.1 Primary Outcomes:

- The development of MAKE-365 in sepsis patients with or without ARDS.
- The association between biomarker measurements (including plasma cystatin C, urinary NGAL, urinary [TIMP-2]*[IGFBP-7], and urinary CCL-14) and MAKE outcome up to 365 days.

4.5.5.2 Secondary outcomes:

- The association of kidney biomarkers with a simple clinical prediction model in patients with MAKE-365.

4.5.6 Definitions:

Sepsis was diagnosed following the Sepsis-3 criteria (Singer et al., 2016), and ARDS was defined based on the Berlin Definition (Ranieri et al., 2012). The MAKE outcome was defined as a composite of receiving any modality of RRT or reduction in eGFR to less than 75% from the baseline or all-cause mortality (Billings and Shaw, 2014). AKI was diagnosed based on the KDIGO guidelines, which are defined AKI as "an increase in serum creatinine by ≥ 0.3 mg/dl (≥ 26.5 μmol/l) within 48 hours; or

increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume < 0.5 ml/kg/h for 6 hours" (Kellum et al., 2012). The KDIGO criteria were also used to identify the stage of AKI, as described previously in Table 1.2 (Kellum et al., 2012).

4.5.7 Data Collection:

Patient demographics, outcome characteristics, and routinely collected clinical data were obtained retrospectively through using two electronic clinical data systems that make up the electronic patient record as described previously.

All data were anonymised and recorded by the Local Clinical Care Team, with no links to patient identification according to the national and local guidance. Independent researchers carried out data extraction using a standardised data collection form. The pseudonymised data were imported into a Microsoft Excel spreadsheet. Then, the data were wrangled using Microsoft Excel before being imported into R software (v.4.1.2; R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org) for statistical analysis. Data collected from enrolled patients included demographics, comorbidities, initial assessment of routine laboratory blood tests, and observations since they were diagnosed with sepsis at admission to the ICU. A summary of these data is displayed in Table 4.1.

Table 4.1. Data collected through PICS

Characteristics	Parameters
Demographics	Age Sex BMI Ethnicity Pre-existing comorbidities Date of sepsis diagnosed on ICU admission. Date of ICU and hospital discharge
Routine laboratory blood tests	Creatinine Urea WCC Neutrophils Lymphocyte Monocytes Eosinophils CRP Platelets Albumin Bilirubin
Observations	eGFR Need for RRT PaO_2 / FiO_2 ratio Incidence and stages of AKI Duration of mechanical ventilation APACHE II score SOFA score Mortality

Abbreviations: BMI, Body mass index; ICU, intensive care unit; WCC, white cell count, CRP, C-reactive protein, eGFR, estimated glomerular filtration rate, RRT, renal replacement therapy; PaO_2 / FiO_2 ratio, the ratio of partial pressure arterial oxygen and the fraction of inspired oxygen; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment.

Most of the data related to renal function, including serum creatinine, estimated glomerular filtration rate (eGFR), and receiving new RRT, were extracted retrospectively from patients who developed sepsis with or without ARDS during their ICU stay. The serum creatinine and eGFR baseline values were extracted before ICU admission. Also, the eGFR values and initiating new RRT at 30, 90, 180, and 365 days after patients diagnosed with sepsis at admission to the ICU were extracted

retrospectively in chronological order to track the changes in renal function. In addition, mortality data at 30, 90, 180, and 365 days were extracted retrospectively.

If the eGFR baseline value was missing, the best pre-admission eGFR was extracted. If preadmission eGFR was also missing, the eGFR baseline value was estimated using the Modification of Diet in Renal Disease (MDRD) (Levey et al., 1999) or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (Levey et al., 2009). This method has been recommended by the KDIGO group (Kellum et al. (2012). The closest values to those time points were extracted when the eGFR values were missing at 30, 90, 180, and 365 days from ICU admission.

4.5.8 Follow-up and study period:

The period of collected data for this study was from 2016 to 2019. Patients were followed up since they developed sepsis with or without ARDS at admission to the ICU until death or for a maximum of 365 days. The study period concluded upon reaching the 365-day. Subsequently, the data collection officially ended by January 2020.

4.5.9 Data Management:

In compliance with the Data Protection Act 2018, all identifiable data were securely stored on the NHS Trust servers. Only anonymised data were securely stored in a separate database with password encryption on the University of Birmingham server as needed. Only authorised persons who complied with UHB policy on collecting, storing, processing, and disclosing personal information and who were involved in this study had access to the data.

4.5.10 Patient Sample Processing:

4.5.10.1 Sample Collection:

Blood and urine samples were collected from all patients within 48 hours after patients were diagnosed with sepsis at admission to the ICU. Then, the first step involved centrifuging all those samples at 560g for 10 minutes at 4°C (Eppendorf AG 5810R centrifuge, Germany). Following this, the supernatant urine and plasma were portioned into 1ml cryovials and stored at a temperature of -80°C until the time of biomarker measurement.

4.5.10.2 Sample Storage:

Acellular samples were labelled with the participant's study ID code. They were stored in alarmed -80 centigrade freezers at the University of Birmingham Respiratory Research Laboratories. All freezers had continuous temperature monitoring as per ICH GCP guidelines.

4.5.11 Biomarker assays:

The Enzyme-Linked Immunosorbent Assays (ELISAs) were used to measure the concentration of plasma cystatin C, urinary NGAL and urinary CCL-14 and the NephroCheck® test was used to measure the concentrations of urinary [TIMP2]*[IGFBP7].

4.5.11.1 Plasma cystatin C

Plasma cystatin C concentrations were determined using Human Cystatin C Quantikine ELISA Kits (R&D Systems, US). This kit includes a 96-well polystyrene microplate pre-coated with a monoclonal antibody specific for human Cystatin C, a

standard solution, wash buffer, substrate solution, and reagent diluent. The assay protocol was executed in accordance with the manufacturer's instructions. Before starting assays, all frozen plasma samples were thawed at room temperature (18-25°). All samples, working standards, and reagents were prepared following the manufacturer's protocol. The plasma samples were diluted 30-fold in Reagent Diluent before adding per well in duplicate according to assay protocol. After completing all steps of the assay procedure, a microplate reader (Synergy HT, Biotek) was used to determine the absorbance values of each well. The concentrations of plasma cystatin C were extrapolated from the appropriate standard curve (Figure 4.1). The standard curve was generated using a four-parameter logistic curve fit on Prism software (GraphPad, US), and the cystatin C concentrations were reported in ng/ml.

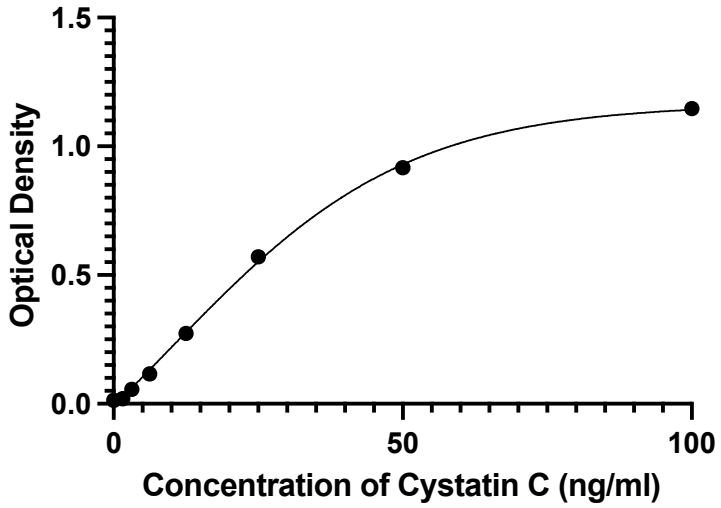


Figure 4.1. Representative standard curve for human cystatin C ELISA.

4.5.11.2 Urinary NGAL

Urinary NGAL concentrations were determined using Human Lipocalin-2/NGAL Quantikine ELISA Kits (R&D Systems, US). This kit contained 96 well-polystyrene microplate pre-coated with a monoclonal antibody specific for human Lipocalin-2,

Standard, Wash Buffer, Substrate Solution, and Reagent Diluent. As per the manufacturer's instructions, this assay was performed. Before starting assays, all frozen urine samples were thawed at room temperature (18-25°). All samples, working standards, and reagents were prepared following the manufacturer's protocol.

There was no specific dilution suggested for the urine sample by the manufacturer. Therefore, the urine samples were initially diluted 50-fold in Reagent Diluent before adding per well in duplicate according to assay protocol. After completing all steps of the assay procedure, a microplate reader (Synergy HT, Biotek) was used to determine the absorbance values of each well. However, some of the samples could not be detected with 50-fold dilution. Thus, the assay procedure was repeated with 100-fold and 200-fold dilution to get the concentrations of the most samples. The concentrations of urinary NGAL were extrapolated from the appropriate standard curve (Figure 4.2). The standard curve was generated using a four-parameter logistic curve fit on Prism software (GraphPad, US), and the urinary NGAL concentrations were reported in ng/ml.

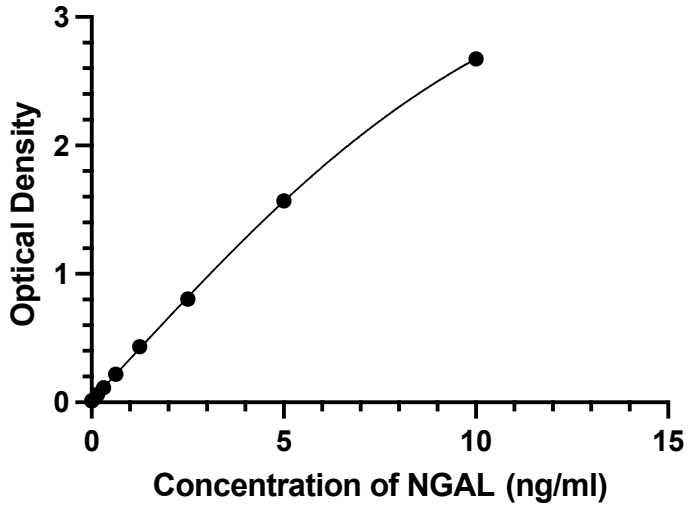


Figure 4.2. Representative standard curve for human NGAL ELISA.

4.5.11.3 Urinary CCL-14

The Human HCC-1 / CCL14a ELISA Kits (Sigma-Aldrich, UK) were utilised to determine the concentration of urinary CCL-14. The ELISA kit instructions were strictly followed. This ELISA kit contained 96 wells microplate coated with anti-Human HCC-1, Standard, Wash Buffer, Biotinylated Human HCC-1 Detection Antibody, HRP-Streptavidin, HRP Substrate, and Assay/Sample Diluent Buffer. Before starting assays, all frozen urine samples were thawed at room temperature (18-25°). This kit wasn't validated for urine samples. Therefore, an optimisation experiment was performed using four samples and four dilutions (10-fold, 100-fold, 250-fold, and 500-fold dilution) to ensure reliable results. Based on the optimisation findings, the samples were diluted 10-fold in the Diluent Buffer before distributing them into wells in duplicate. After completing all steps of the assay procedure, a microplate reader (Synergy HT, Biotek) was used to determine the absorbance values of each well. The concentrations of urinary CCL-14 were extrapolated from the appropriate standard curve (Figure 4.3). A standard curve was created using a four-parameter logistic curve fit on Prism software (GraphPad, US). The concentrations of urinary CCL-14 were reported in units of ng/ml.

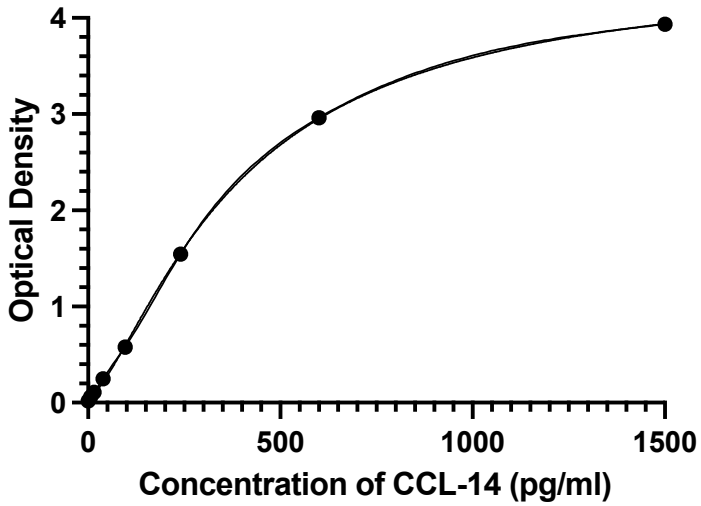


Figure 4.3. Representative standard curve for human CCL-14 ELISA.

4.5.11.4 Urinary [TIMP2][IGFBP7]*

The urinary [TIMP2]*[IGFBP7] concentrations were measured using the NephroCheck® test kit and Astute140 Meter (Astute Medical, San Diego, CA, US). As per the manufacturer's instructions, this assay was performed. Before starting assays, all frozen urine samples were thawed at room temperature (18-25°). The NephroCheck® Test Kit contains all the reagents required to detect TIMP-2 and IGFBP-7 biomarkers in human urine samples. The NephroCheck® test process involves the application of a mixed thawed urine sample with a labelled fluorescent conjugate onto the NephroCheck® Test cartridge. The cartridge is then inserted into the Astute140® Meter. The Astute140 Meter performs several functions: it incubates the test, reads the fluorescent signals from both the TIMP-2 and IGFBP-7 immunoassays, calculates the results, and displays these on the device (Figure 4.4). These fluorescent signals are translated into a single numerical outcome named the AKIRisk® Score. This Score represents the concentrations of urinary [TIMP2]*[IGFBP7] and was reported in units of $(ng/ml)^2/1000$.

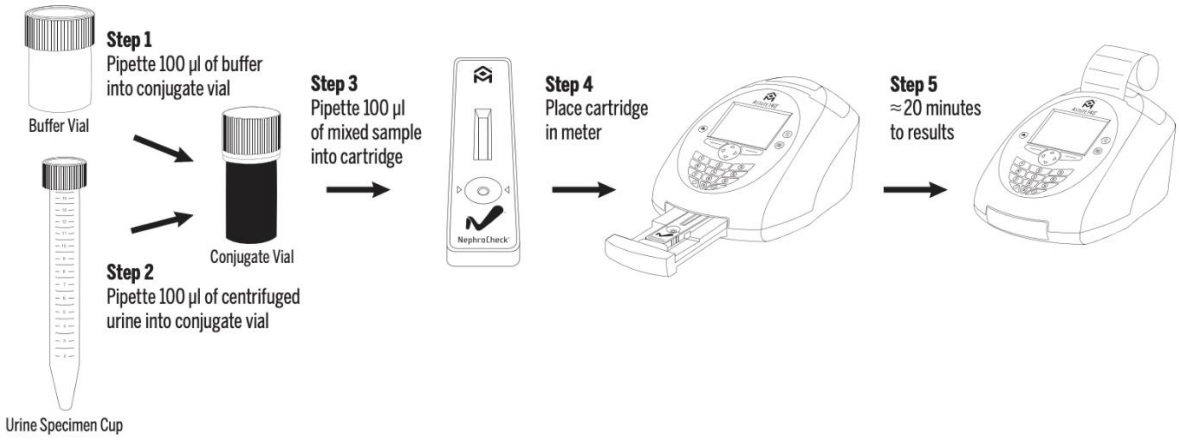


Figure 4.4. Nephrocheck® Test Preparation Process

4.5.12 Statistical analysis:

All statistical analyses were conducted by R statistical software (v.4.1.2; R Foundation for Statistical Computing, Vienna, Austria: https://www.r-project.org). Baseline characteristics were reported as frequencies with percentages for categorical variables. Continuous variables were tested for normality using Shapiro-Wilk's test, with means and standard deviations reported for normally distributed variables and medians with interquartile ranges (IQR) for variables not following a normal distribution. All continuous variables were analysed using parametric/non-parametric tests (Student's t-test, Wilcoxon's rank-sum test and Kruskal-Wallis test). For categorical variables, comparisons were made using either the chi-squared test or Fisher's exact test, as appropriate.

An alpha level of 0.05 was considered statistically significant for all analyses. The Receiver Operating Characteristic (ROC) analysis was conducted to explore the ability of kidney biomarkers to predict MAKE-365 in patients diagnosed with sepsis upon ICU admission. The quality of this prediction was evaluated via the area under the ROC curve (AUC). Furthermore, the AUC analysis was utilised to derive cut-off

values and estimate specificity and sensitivity. The optimal cut-off points were determined based on the highest Youden index.

A logistic regression model for the incidence of MAKE-365 was used to compute a simple clinical prediction model with two variables, including age and bilirubin levels, based on the findings presented in the previous chapter (Chapter 3)). Bilirubin concentrations were obtained within 48 hours after patients were diagnosed with sepsis at admission to the ICU. This corresponds to the time point of biomarker measurements (median time from sepsis diagnosis to a sample collection of 2 days).

4.6 RESULTS

A total of 37 ICU admissions with sepsis within the study period were screened for eligibility (Figure 4.5). Five patients with missing samples from the first two days of sepsis diagnosis at the time of ICU admission were excluded, along with one patient who was not diagnosed with AKI and died before the 7th day of enrollment. Consequently, 31 patients were included in the analyses, including 16 with ARDS and 15 without ARDS.

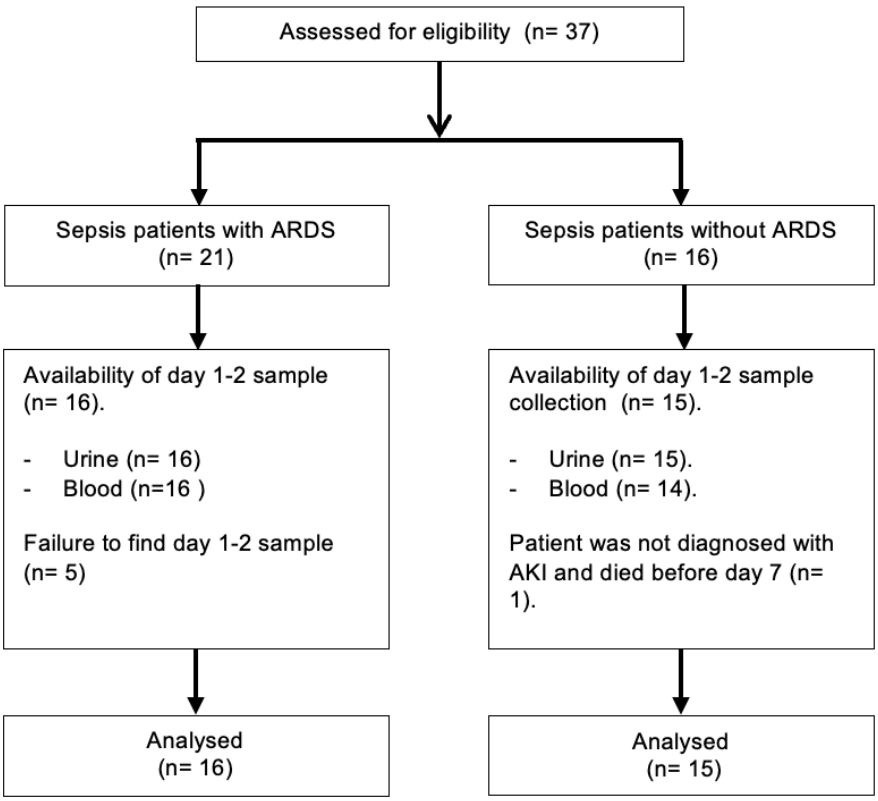


Figure 4.5. Modified CONSORT Diagram for the study.

Legend: This diagram illustrates the process of participant screening and enrolment for the study.
Abbreviations: ARDS, acute respiratory distress syndrome; AKI, acute kidney injury.

4.6.1 Characteristics of sepsis patients with and without ARDS:

The demographic and clinical characteristics of the studied cohorts are shown in Table 4.2. The median age of the total cohort (n=31) was 59.0 years [IQR: 47.0-67.5]; 61.3% (n=19) were male, and all cohort members (100%) were of White ethnicity.

In examining the characteristics of sepsis patients with and without ARDS, there was no difference in age (median: 60.0 years [IQR: 53.5-70.0] vs 52.0 years [IQR: 44.5-65.0]; P=0.514, Wilcoxon rank-sum test). Also, there were no differences in body mass index (BMI) (median: 27.5 kg/m^2 [IQR: 24.9-29.9 kg/m^2] vs 26.0 kg/m^2 [IQR: 24.4–29.3], P=0.782, Wilcoxon rank-sum test) or pre-existing comorbidities among sepsis patients with or without ARDS. Most routine laboratory blood tests taken within 48 hours after sepsis diagnosis at ICU admission showed no differences between patients with or without ARDS, except for C-reactive protein (CRP) levels, which were higher in sepsis patients without ARDS (median: 127mg/L [IQR: 98.3-250 mg/L] vs 258 mg/L [IQR: 202–318 mg/L], P=0.019, Wilcoxon rank-sum test). Sepsis patients with ARDS had longer durations on mechanical ventilation compared to patients without ARDS (median: 13 [IQR: 6.75-23.5 days] vs 6 days [IQR: 3-16.5 days], P=0.04, Wilcoxon rank-sum test).

No differences were noted in AKI development among the groups. However, most of the patients with sepsis and ARDS (n=12 (75%)) and without ARDS (n=8 (53.3%)) developed AKI, with a few patients with ARDS requiring RRT (n=5 (41.7%)).

Table 4.2. The demographic and clinical characteristics of sepsis patients with and without ARDS.

	Overall (N=31)	With ARDS (N=16)	Without ARDS (N=15)	P-value*
Demographics:				
Age (years)	59.0 [47.0-67.5]	60.0 [53.5-70.0]	52.0 [44.5-65.0]	0.514
Male	19 (61.3%)	10 (62.5%)	9 (60.0%)	1
BMI, (kg/m^2)	26.6 [24.4-29.7]	27.5 [24.9-29.9]	26.0 [24.4-29.3]	0.782
Comorbidities (n, %):				
Hypertension	3 (9.7%)	1 (6.3%)	2 (13.3%)	0.953
Diabetes mellitus	1 (3.2%)	0 (0%)	1 (6.7%)	0.974
Obesity	7 (22.6%)	4 (25.0%)	3 (20.0%)	1
Ischemic heart disease	3 (9.7%)	2 (12.5%)	1 (6.7%)	1
COPD	2 (6.5%)	1 (6.3%)	1 (6.7%)	1
Cancer	6 (19.4%)	4 (25.0%)	2 (13.3%)	0.714
Lab parameters:				
WCC (x10^9/L)	12.7 [9.15-19.2]	11.3 [8.7-18.6]	15.0 [10.3-20.8]	0.363
Neutrophils (x10^9/L)	9.9 [7.4-17.4]	8.7 [7.48-14.7]	12.1 [8.00-19.0]	0.304
Eosinophils (x10^9/L)	0.10 [0-0.25]	0.05 [0-0.23]	0.10 [0-0.25]	0.819
Lymphocyte (x10^9/L)	0.90 [0.55-1.40]	1.0 [0.58-1.4]	0.90 [0.60-1.35]	0.706
Monocytes (x10^9/L)	0.80 [0.55-1.15]	0.85 [0.68-1.6]	0.70 [0.45-0.95]	0.165
Platelets (x10^9/L)	182 [93.0-226]	146 [70.5-225]	199 [152-226]	0.465
CRP (mg/L)	214 [127-301]	127 [98.3-250]	258 [202-318]	**0.019**
Albumin (g/L)	28 [25-29.5]	26 [24.5-29]	29 [26-31]	0.19
Bilirubin (µmol/L)	11 [7.00-22.5]	12.5 [7-38.3]	11 [7.5-18]	0.692
Urea (mmol/L)	7.75 [6-10.3]	8.65 [5.33-9.9]	7.10 [6.48-11.7]	1
Creatinine values (µmol/L):				
Baseline	62.0 [51.0-65.0]	61.5 [51.0-66.5]	63.0 [48.5-65.0]	0.812
Day 1	88.0 [62.0-118]	81.0 [61.8-115]	98.0 [71.8-134]	0.589
Day 7	63.0 [48.3-93.0]	57.0 [44.0-93.5]	72.0 [57.3-93.0]	0.817
Day 30	66.0 [48.0-82.0]	62.0 [50.5-100]	70.5 [51.3-76.5]	0.948
Day 90	66.0 [55.0-81.5]	67.5 [62.0-83.8]	59.0 [52.0-74.5]	0.562
Day 180	78.0 [69.0-86.0]	73.0 [63.3-80.5]	84.0 [77.0-97.5]	0.377
Day 365	85.5 [75.8-114]	85.5 [77.5-102]	91.5 [75.8-121]	0.885
eGFR values (ml/min per 1.73 m^2):				
Baseline	90.0 [88.0-90.0]	90.0 [89.0-90.0]	90.0 [85.5-90.0]	0.939
Day 1	76.0 [47.0-90.0]	81.0 [45.8-90.0]	68.0 [48.0-90.0]	0.903

Table 4.2. The demographic and clinical characteristics of sepsis patients with and without ARDS.

	Overall (N=31)	With ARDS (N=16)	Without ARDS (N=15)	P-value*
Day 7	90.0 [72.0-90.0]	84.5 [58.3-90.0]	90.0 [84.0-90.0]	0.201
Day 30	90.0 [67.5-90.0]	90.0 [56.8-90.0]	90.0 [80.5-90.0]	0.533
Day 90	90.0 [67.0-90.0]	90.0 [49.0-90.0]	90.0 [86.3-90.0]	0.465
Day 180	84.0 [64.0-87.5]	87.5 [77.5-90.0]	73.0 [59.0-78.5]	0.212
Day 365	67.0 [47.8-80.8]	67.0 [53.0-81.0]	63.5 [46.3-80.8]	0.772
Clinical outcomes:				
Need for RRT	5 (16.1%)	5 (31.3%)	0 (0%)	0.061
Incidence of AKI	20 (64.5%)	12 (75.0%)	8 (53.3%)	0.376
AKI stages				
1	11 (35.5%)	8 (50.0%)	3 (20.0%)	0.096
2	7 (22.6%)	2 (12.5%)	5 (33.3%)	
3	2 (6.5%)	2 (12.5%)	0 (0%)	
No AKI	11 (35.5%)	4 (25.0%)	7 (46.7%)	
PaO_2 / FiO_2 ratio (kPa)	23 [18.5-26.5]	23.5 [19-25]	23 [18-32]	0.476
ICU LOS (days)	10 [7.5-21.5]	16.5 [8-27.3]	9 [6-16.5]	0.063
Duration of MV (days)	8 [4-17.5]	13 [6.75-23.5]	6 [3-16.5]	**0.04**
Hospital LOS (days)	25 [10.5-47.0]	30.5 [18.0-47.0]	23.0 [9.5-39.5]	0.429
SOFA score	11 [9-13]	11 [9.75-15]	10 [9-11]	0.202
APACHE score	17 [12.5-21.5]	17.5 [13-21.5]	17 [11.5-21]	0.538
Mortality	11 (35.5%)	6 (37.5%)	5 (33.3%)	1

Data is presented as median (IQR), unless otherwise stated.
* p-values from the chi-squared test or Wilcoxon rank-sum test represent the differences between ARDS vs without ARDS cohorts.
Abbreviations: ARDS, acute respiratory distress syndrome; BMI, body mass index; COPD, Chronic obstructive pulmonary disease; CRP, C-reactive protein; AKI, acute kidney injury; ICU, intensive care unit; eGFR, estimated glomerular filtration rate; RRT, renal replacement therapy; PaO_2 / FiO_2 ratio, the ratio of partial pressure arterial oxygen and the fraction of inspired oxygen; LOS, length of stay; MV, mechanical ventilation; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment.

4.6.2 Incidence of MAKEs in sepsis patients with or without MAKE-365:

Among those who developed AKI in both groups, there was no difference in the incidence of MAKE-365 (n=9 (75.0%) vs n=4 (50.0%), P=0.503, chi-squared test) (Table 4.3).

Table 4.3. The incidence of MAKEs outcome among the AKI patients in both cohorts.

	All AKI (N=20)	With ARDS (N=12)	Without ARDS (N=8)	P-value*
MAKE-30	8 (40.0%)	6 (50.0%)	2 (25.0%)	0.514
Cause of MAKE-30				0.206
Need for RRT	5 (25.0%)	5 (41.7%)	0 (0%)	
eGFR < 75% of baseline	3 (15.0%)	1 (8.3%)	2 (25.0%)	
MAKE-180	10 (50.0%)	8 (66.7%)	2 (25.0%)	0.171
Cause of MAKE-180				0.153
Need for RRT	5 (25.0%)	5 (41.7%)	0 (0%)	
eGFR < 75% of baseline	4 (20.0%)	2 (16.7%)	2 (25.0%)	
Death	1 (5.0%)	1 (8.3%)	0 (0%)	
MAKE-365	13 (65.0%)	9 (75.0%)	4 (50.0%)	0.503
Cause of MAKE-365				0.164
Need for RRT	5 (25.0%)	5 (41.7%)	0 (0%)	
eGFR < 75% of baseline	6 (30.0%)	3 (25.0%)	3 (37.5%)	
Death	2 (10.0%)	1 (8.3%)	1 (12.5%)	

Data presented as frequencies with percentages.
* p-values from the chi-squared test represent the differences in the incidence of MAKE outcome and the individual cause of MAKE-365 among patients with and without ARDS
Abbreviations: AKI, acute kidney injury; MAKE, major adverse kidney events; eGFR, estimated glomerular filtration rate, RRT, renal replacement therapy.

Of nine patients with ARDS who experienced MAKE-365, five (56%) were categorised by initiation for RRT, three (33%) patients by a reduction in eGFR of less than 75% from baseline, and one (11%) by death. Of four patients without ARDS who experienced MAKE-365, three (75%) patients were categorised by a reduction in eGFR of less than 75% from baseline and only one (25%) by death.

Due to the small sample size of patients with sepsis and AKI in the presence or absence of ARDS, we decided to assess the association between novel kidney biomarkers and MAKE-365 in all critically ill sepsis patients with AKI. Of 31 patients enrolled in the study, 20 (64.5%) developed AKI, of which 13 (65%) experienced MAKE-365. Of the 13 patients with MAKE-365, six (46%) patients were categorised by a reduction in eGFR of less than 75% from baseline, five (38%) patients by new initiation of RRT, and two (15%) by decease.

4.6.3 Characteristics of sepsis patients with or without MAKE-365:

Demographic and clinical characteristics of patients with or without MAKE-365 are shown in Table 4.4. There were no differences in age, sex, BMI, and pre-existing comorbidities between patients with or without MAKE-365. Similarly, routine laboratory blood tests obtained within 48 hours after sepsis diagnosis at the ICU admission and clinical outcomes showed no differences between patients with or without MAKE-365. However, patients who experienced MAKE-365 and survived 365 days had lower eGFR at 365 days (median: 78.0 [IQR: 78.0-83.5] vs 46.5 ml/min per 1.73 m^2 [IQR: 42.5-50.8], P=0.049, Wilcoxon rank-sum test).

Table 4.4. Characteristics of sepsis patients with and without MAKE-365.

	Overall (N= 20)	No MAKE (N= 7)	MAKE-365 (N= 13)	P-value*
Demographics:				
Age (years)	56.0 [47.5-70.5]	65.0 [48.5-73.5]	55.0 [46.0-70.0]	0.606
Male	12 (60.0%)	5 (71.4%)	7 (53.8%)	0.774
BMI, (kg/m^2)	27.9 [25.7-29.9]	28.1 [26.2-29.2]	27.7 [25.7-31.6]	0.937
Comorbidities (n, %):				
Hypertension	2 (10.0%)	1 (14.3%)	1 (7.7%)	1
Obesity	5 (25.0%)	1 (14.3%)	4 (30.8%)	0.787
Ischemic heart disease	3 (15.0%)	1 (14.3%)	2 (15.4%)	1
COPD	2 (10.0%)	2 (28.6%)	0 (0%)	0.211
Cancer	2 (10.0%)	1 (14.3%)	1 (7.7%)	1
Lab parameters:				
WCC (x10^9/L)	13.8 [9.88-23.0]	18.3 [11.8-25.0]	12.7 [8.70-16.3]	0.154
Neutrophils (x10^9/L)	10.4 [7.75-21.1]	13.6 [9.35-23.3]	8.80 [7.60-13.9]	0.267
Eosinophils (x10^9/L)	0.10 [0-0.350]	0 [0-0.30]	0.20 [0-0.30]	0.51
Lymphocyte (x10^9/L)	1.05 [0.75-1.43]	1.20 [0.65-1.70]	1.00 [0.90-1.40]	0.842
Monocytes (x10^9/L)	0.90 [0.58-1.30]	0.90 [0.65-1.15]	0.90 [0.60-1.30]	0.842
Platelets (x10^9/L)	172 [70.5-223]	179 [87.5-226]	164 [73.0-190]	0.692
CRP (mg/L)	236 [103-312]	258 [196-303]	190 [103-305]	0.634
Albumin (g/L)	29.0 [25.8-31.3]	29.0 [27.5-30.5]	28.0 [25.0-31.0]	0.524
Bilirubin (µmol/L)	11.0 [7.00-32.0]	11.0 [8.50-18.0]	11.0 [7.00-48.0]	1
Urea (mmol/L)	9.10 [6.45-10.8]	8.20 [6.70-10.5]	9.45 [6.00-11.3]	0.933
Creatinine values (µmol/L):				
Baseline	62.5 [57.0-68.3]	65.0 [62.0-76.5]	62.0 [51.0-64.0]	0.104
Day 1	111 [78.8-147]	119 [97.5-142]	106 [67.0-156]	0.579
Day 7	92.0 [57.0-93.5]	92.0 [74.5-93.0]	76.0 [49.8-103]	0.767
Day 30	70.0 [60.5-83.5]	66.0 [61.5-70.5]	76.5 [57.0-115]	0.374
Day 90	66.0 [62.0-89.0]	65.0 [59.0-83.0]	73.0 [66.0-92.8]	0.41
Day 180	86.0 [82.5-93.8]	84.0 [84.0-84.0]	88.0 [83.0-99.5]	1
Day 365	87.0 [82.0-125]	80.0 [71.5-82.0]	125 [99.0-154]	0.052
eGFR values (ml/min per 1.73 m^2):				
Baseline	90.0 [89.0-90.0]	90.0 [74.5-90.0]	90.0 [90.0-90.0]	0.677
Day 1	57.5 [30.5-83.3]	49.0 [35.5-75.0]	67.0 [31.0-83.0]	0.662
Day 7	79.0 [59.0-90.0]	75.0 [64.0-84.5]	90.0 [59.0-90.0]	0.454
Day 30	90.0 [58.5-90.0]	90.0 [82.0-90.0]	90.0 [51.0-90.0]	0.227

Table 4.4. Characteristics of sepsis patients with and without MAKE-365.

	Overall (N= 20)	No MAKE (N= 7)	MAKE-365 (N= 13)	P-value*
Day 90	90.0 [67.0-90.0]	90.0 [85.0-90.0]	86.0 [59.5-90.0]	0.69
Day 180	69.5 [52.5-84.3]	84.0 [84.0-84.0]	55.0 [50.0-70.0]	1
Day 365	56.0 [46.5-78.0]	78.0 [78.0-83.5]	46.5 [42.5-50.8]	**0.049**
Clinical outcomes:				
PaO_2 / FiO_2 ratio (kPa)	23.0 [18.8-27.3]	23.0 [18.0-32.5]	23.0 [19.0-25.0]	0.721
ICU LOS (days)	14.5 [7.50-21.3]	14.0 [6.50-22.5]	15.0 [8.00-20.0]	0.968
Duration of MV (days)	10.0 [6.00-19.0]	10.0 [5.50-19.5]	10.0 [6.00-18.0]	1
Hospital LOS (days)	31.0 [18.0-48.0]	47.0 [29.5-51.5]	25.0 [18.0-44.0]	0.284
SOFA score	11.0 [9.75-15.0]	10.0 [9.50-12.5]	11.0 [10.0-15.0]	0.377
APACHE score	19.5 [16.0-23.3]	21.0 [17.0-22.5]	18.0 [13.0-24.0]	0.811

Data is presented as median (IQR), unless otherwise stated.
* p-values from the chi-squared test or Wilcoxon rank-sum test represent the differences between sepsis patients with vs without MAKE-365.
Abbreviations: BMI, body mass index; COPD, Chronic obstructive pulmonary disease; WCC, white cell count; CRP, C-reactive protein; ICU, intensive care unit; eGFR, estimated glomerular filtration rate; RRT, renal replacement therapy; PaO_2 / FiO2 ratio, the ratio of partial pressure arterial oxygen and the fraction of inspired oxygen; LOS, length of stay; MV, mechanical ventilation; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment.

4.6.4 Kidney Biomarkers in sepsis patients with or without MAKEs:

All kidney biomarkers were assessed within the first two days of diagnosing sepsis upon ICU admission in patients that experienced MAKE-30, MAKE-180, or MAKE-365. There were no differences in all kidney biomarkers among patients with or without MAKE-30 (Table 4.5). Similarly, there were no differences in all kidney biomarkers among patients with or without MAKE-180 (Table 4.6). Among all examined kidney biomarkers, urinary [TIMP-2]*[IGFBP-7] was the only biomarker that was higher in patients that experienced MAKE-365 (median: 0.50 [IQR: 0.28-0.69] vs 1.52 $(ng/ml)^2/1000$ [IQR: 0.65-2.40], P= 0.03, Wilcoxon rank-sum test) (Table 4.7; Figure 4.6).

Table 4.5. Kidney biomarkers in patients with and without MAKE-30.

	Overall (N=20)	No MAKE (N=12)	MAKE-30 (N=8)	P-value
Plasma Cystatin C	1320 [1020-1960]	1320 [1080-1680]	1360 [856-2020]	0.869
Urinary NGAL	76.2 [12.8-391]	60.2 [13.3-414]	157 [13.8-347]	0.901
Urinary CCL-14	1.85 [1.02-3.59]	1.64 [1.02-3.46]	2.42 [1.17-3.71]	0.847
Urinary [TIMP-2]*[IGFBP-7]	0.77 [0.45-2.00]	0.69 [0.28-1.54]	1.73 [0.63-2.49]	0.083

Data is presented as median (IQR).
* p-values from Wilcoxon rank-sum test represent the differences between patients with vs without MAKE-30.
Abbreviations: MAKE, major adverse kidney events; NGAL, neutrophil gelatinase-associated lipocalin; CCL-14, C-C motif chemokine ligand 14; TIMP-2, tissue inhibitor of metalloprotease-2; IGFBP-7, insulin-like growth factor-binding protein 7.

Table 4.6. Kidney biomarkers in patients with and without MAKE-180.

	Overall (N=20)	No MAKE (N=10)	MAKE-180 (N=10)	P-value
Plasma Cystatin C	1320 [1020-1960]	1330 [1180-1920]	1140 [888-1890]	0.414
Urinary NGAL	76.2 [12.8-391]	29.3 [9.53-101]	289 [31.1-408]	0.391
Urinary CCL-14	1.85 [1.02-3.59]	1.64 [0.758-3.76]	2.42 [1.38-3.31]	0.85
Urinary [TIMP-2]*[IGFBP-7]	0.77 [0.453-2.00]	0.57 [0.27-1.38]	1.29 [0.69-2.43]	0.054

Data is presented as median (IQR).
* p-values from Wilcoxon rank-sum test represent the differences between patients with vs without MAKE-180.

Table 4.7. Kidney biomarkers in patients with and without MAKE-365.

	Overall (N=20)	No MAKE (N=7)	MAKE-365 (N=13)	P-value
Plasma Cystatin C	1320 [1020-1960]	1380 [1320-1800]	1160 [978-2000]	0.405
Urinary NGAL	76.2 [12.8-391]	44.8 [20.1-322]	101 [8.56-372]	0.895
Urinary CCL-14	1.85 [1.02-3.59]	2.21 [1.64-4.69]	1.50 [0.627-3.19]	0.267
Urinary [TIMP-2]*[IGFBP-7]	0.77 [0.45-2.00]	0.50 [0.28-0.69]	1.52 [0.65-2.40]	0.03

Data is presented as median (IQR).
* p-values from Wilcoxon rank-sum test represent the differences between patients with vs without MAKE-365.

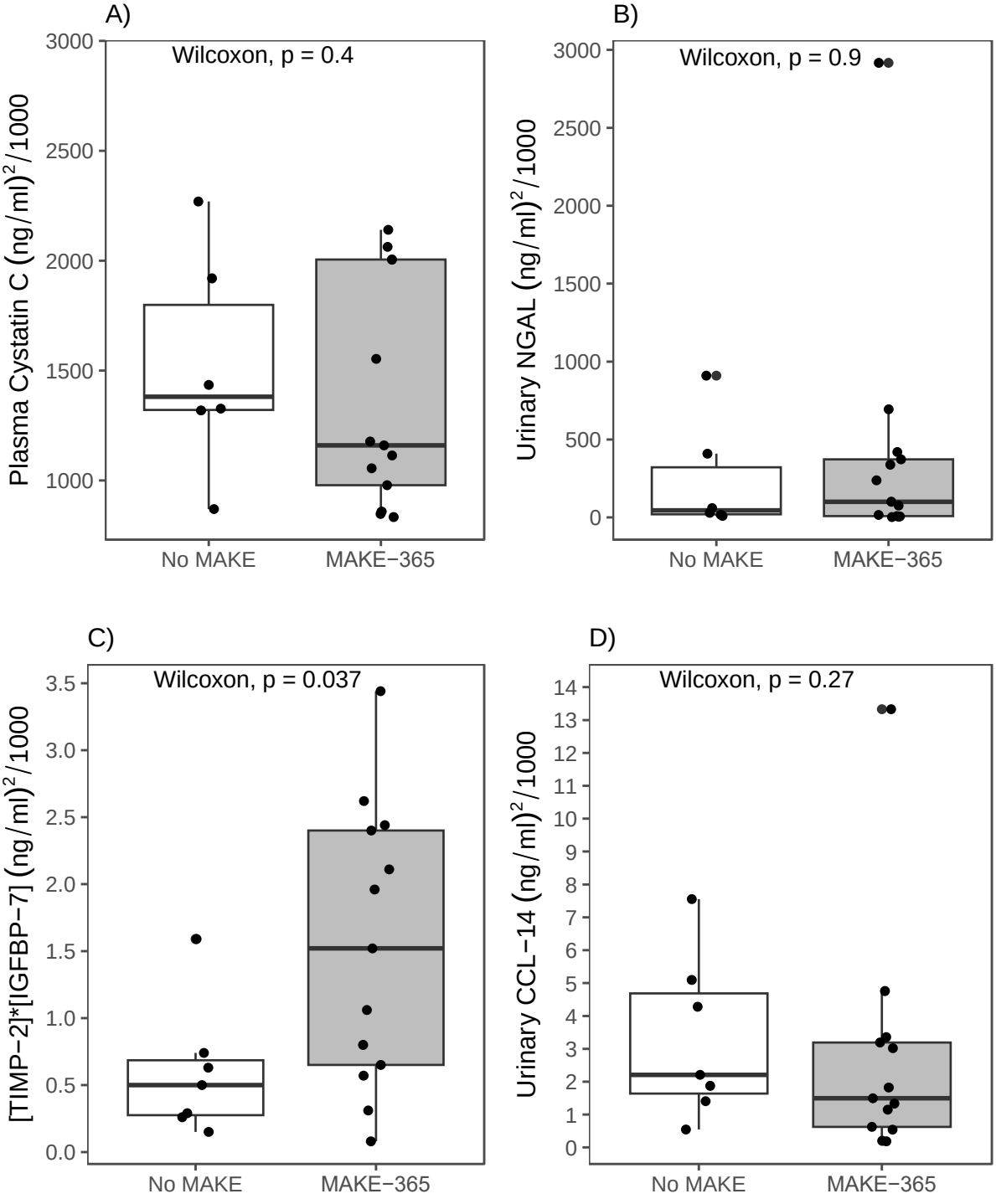


Figure 4.6. Boxplots of kidney biomarkers in patients with vs without MAKE-365.

Data is presented as median (IQR).
Legend: These boxplots showed that the median of urinary [TIMP-2]*[IGFBP-7] (C) was the only biomarkers indicating difference between patients with and without MAKE-365 compared to plasma cystatin C (A), urinary NGAL (B), and urinary CCL-14 (D).
Abbreviations: MAKE, major adverse kidney events; NGAL, neutrophil gelatinase-associated lipocalin; CCL-14, C-C motif chemokine ligand 14; TIMP-2, tissue inhibitor of metalloprotease-2; IGFBP-7, insulin-like growth factor-binding protein 7.

4.6.5 Biomarker Performance:

The logistic regression analysis revealed that none of the demographics, pre-existing comorbidities, laboratory parameters or clinical outcomes were associated with MAKE-365. Among four kidney biomarkers, the urinary [TIMP-2]*[IGFBP-7], commonly known as NephroCheck®, was the only independent risk predictor associated with MAKE-365 development (odds ratio (OR): 4.70; 95% confidence interval (CI): 1.22 -44.9).

The simple clinical model for MAKE-365 produced an AUC of 0.59, with both age (OR: 0.98; 95% CI, 0.92 -1.05) and bilirubin levels (OR: 1.03; 95% CI: 0.99 -1.11). Of the 4 kidney biomarkers examined, urinary [TIMP-2]*[IGFBP7] was the best performing in terms of predicting MAKE-365 with an AUC of 0.79 (95% CI: 0.58 -0.79), which was higher than the AUC values for plasma cystatin C (AUC: 0.63; 95% CI: 0.35 -0.63), urinary NGAL (AUC: 0.47; 95% CI: 0.18 -0.47), and urinary CCL-14 (AUC: 0.66; 95% CI: 0.4 -0.66) (Figure 4.7).

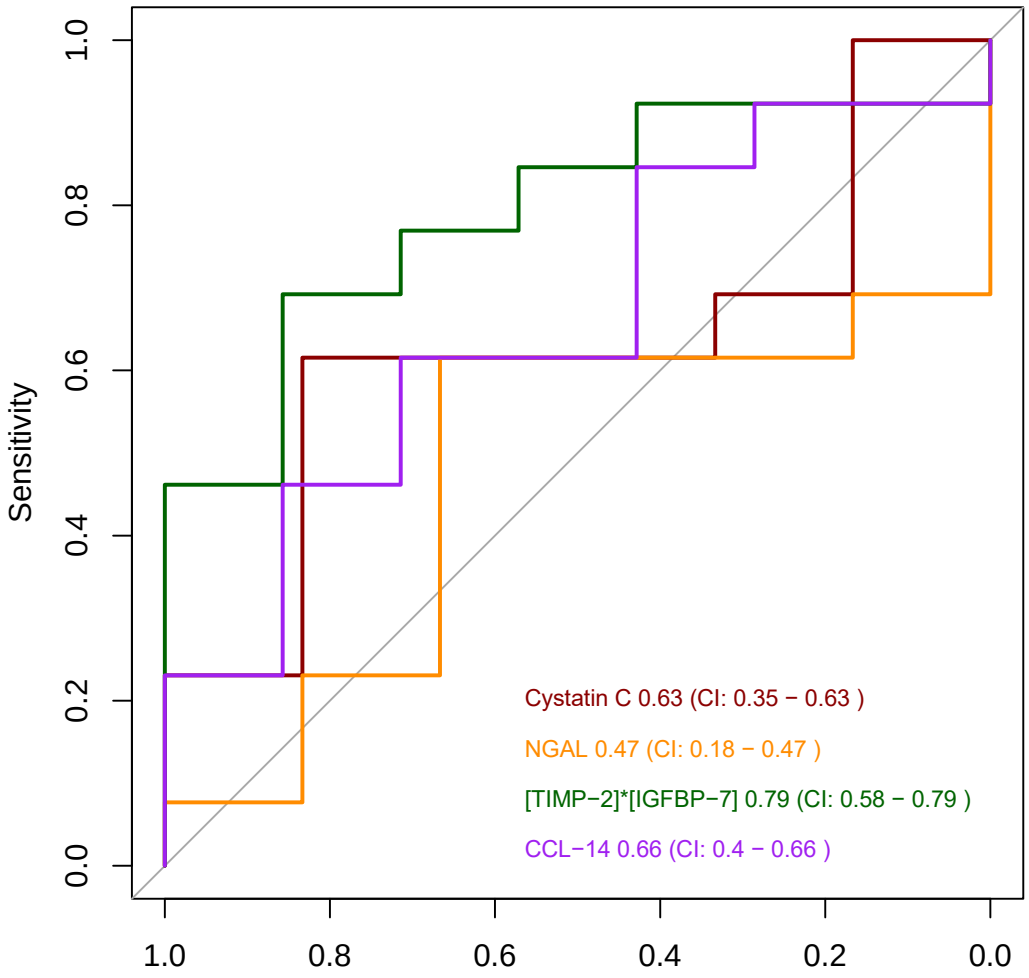


Figure 4.7. The area under the ROC curve results for the different kidney biomarkers alone to predict MAKE-365 in sepsis patients.

Legend: The ROC curve is used to assess the predictive ability of each biomarker for MAKE-365 in patients with sepsis. The AUC of each biomarker's ROC curve is calculated, with a higher AUC indicating better predictive performance. Among the tested biomarkers, urinary [TIMP-2]*[IGFBP-7] demonstrated the best performance in predicting MAKE-365, compared to plasma cystatin C, urinary NGAL, and urinary CCL-14.
Abbreviations: AUC, area under the curve; MAKE, major adverse kidney events; TIMP-2, tissue inhibitor of metalloprotease-2; IGFBP-7, insulin-like growth factor-binding protein 7; NGAL, neutrophil gelatinase-associated lipocalin; CCL-14, C-C motif chemokine ligand 14.

In our comparative analysis, the performance of the simple clinical model was evaluated against models that included additional kidney biomarkers. The discriminative ability of these models were assessed through the AUC value. While independently adding plasma cystatin C (AUC=0.64, P=0.64), urinary NGAL (AUC=0.64, P=0.797), and urinary CCL-14 (AUC=0.46, P=0.739) to the simple clinical

model did not result in any improvement in the prediction of MAKE-365, the incorporation of urinary [TIMP-2]*[IGFBP-7] into the clinical model did yield significant enhancement (AUC=0.82, P=0.037) (Figure 4.8).

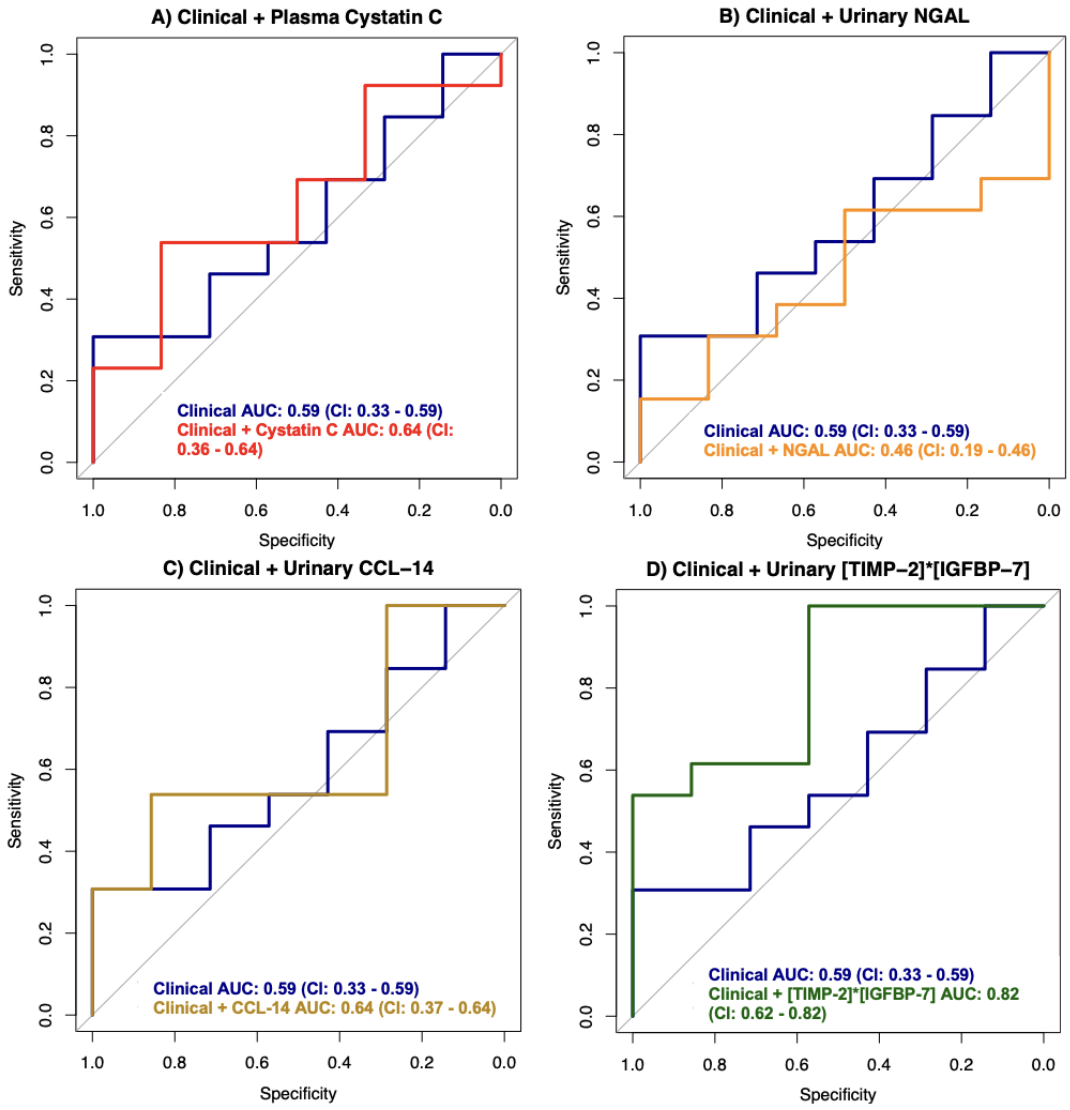


Figure 4.8 The area under the ROC curve results for the combination of plasma Cystatin C (A), urinary NGAL (B), urinary CCL-14 (C), or urinary [TIMP-2]*[IGFBP-7] (D) with the Clinical model for the prediction of MAKE-365 in sepsis patients.

Legend: This figure illustrates the comparative performance of the simple clinical model when enhanced with different biomarkers. The discriminative ability of each enhanced model is evaluated using the AUC. Notably, the addition of urinary [TIMP-2]*[IGFBP-7] to the clinical model significantly improves its predictive performance (P=0.037), compared to the addition of plasma cystatin C (P=0.64), urinary NGAL (P=0.797), and urinary CCL-14 (P=0.739).
Abbreviations: AUC, area under the curve; TIMP-2, tissue inhibitor of metalloprotease-2; IGFBP-7, insulin-like growth factor-binding protein 7; NGAL, neutrophil gelatinase-associated lipocalin; CCL-14, C-C motif chemokine ligand 14.

4.6.6 Optimal cut-off values of Kidney biomarkers:

There is no published cut-off for urinary [TIMP-2]*[IGFBP7] to predict MAKE-365 in critically ill patients with sepsis. Therefore, the accuracy of the optimal cut-offs for urinary [TIMP-2]*[IGFBP7] to predict positive MAKE-365 was assessed using the Youden method. The optimal cut-offs and their performance are shown in Table 4.8.

Table 4.8. The accuracy of the optimal cut-offs for kidney biomarkers to predict MAKE-365 in critically ill patients.

Biomarkers	AUC (95% CI)	Optimal Cut-off	Sensitivity	Specificity	PPV	NPV
Plasma Cystatin C	0.372 (0.094, 0.649)	2005	31%	83%	80%	36%
Urinary NGAL	0.474 (0.185, 0.764)	76	62%	67%	80%	44%
Urinary [TIMP-2]*[IGFBP-7]	0.791 (0.585, 0.998)	0.80	69%	86%	90%	60%
Urinary CCL-14	0.341 (0.083, 0.598)	13	7%	100%	100%	37%

Abbreviations: AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value; TIMP-2, tissue inhibitor of metalloprotease-2; IGFBP-7, insulin-like growth factor-binding protein 7; NGAL, neutrophil gelatinase-associated lipocalin; CCL-14, C-C motif chemokine ligand 14.

The optimal cut-off value for plasma cystatin C in predicting MAKE-365 in sepsis patients was 2005 ng/ml; its sensitivity and specificity were 31% and 83%, respectively (AUC= 0.372). The sensitivity and specificity were 62% and 67% for urinary NGAL's cut-off value of 76 ng/ml (AUC= 0.474). The optimal cut-off value of urinary CCL-14 was 13 ng/ml, with low sensitivity (7%) and high specificity (100%) (AUC= 0.341) (Table 4.8). Compared to previous biomarkers, the cut-off value of 0.80 for urinary [TIMP-2]*[IGFBP7] had the best AUC with 0.791, and its sensitivity and specificity were 69% and 86%, respectively (Figure 4.9).

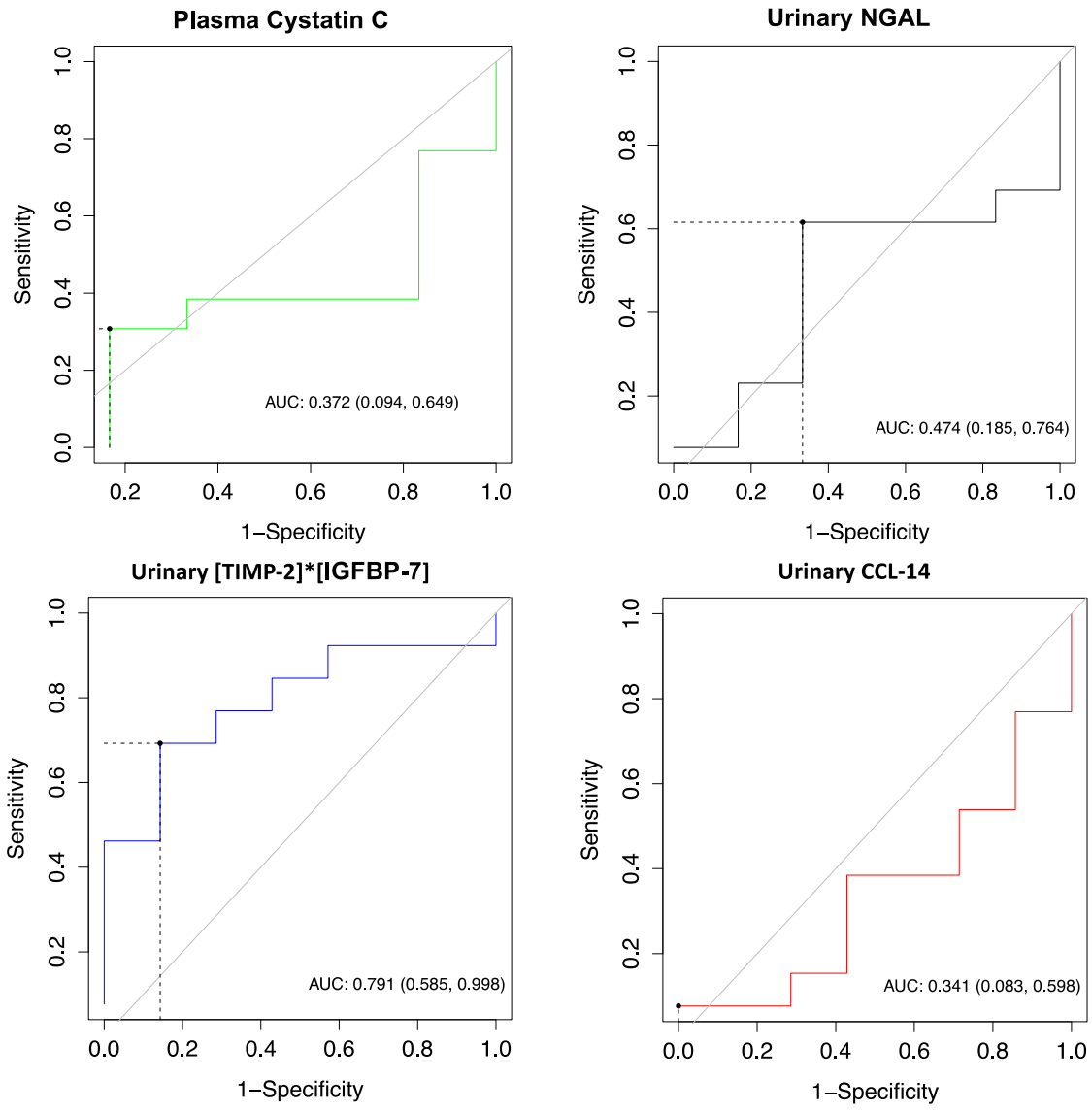


Figure 4.9 The area under the ROC curve for optimal cut-off values of kidney biomarkers to predict MAKE-365 in patients with sepsis.

Legend: This figure illustrates the ROC curve analysis for different kidney biomarkers at their optimal cut-off values in predicting MAKE-365 in patients with sepsis. Among these biomarkers, the cut-off value of 0.80 for urinary [TIMP-2]*[IGFBP7] had the best AUC with 0.791.
Abbreviations: AUC, area under the curve; TIMP-2, tissue inhibitor of metalloprotease-2; IGFBP-7, insulin-like growth factor-binding protein 7; NGAL, neutrophil gelatinase-associated lipocalin; CCL-14, C-C motif chemokine ligand 14.

4.6.7 Time-to-event of MAKE outcome:

Kaplan-Meier curves of time to the event of MAKEs at 365 days in AKI patients with or without ARDS are displayed in Figure 4.10. The Kaplan–Meier method revealed no difference in MAKE incidence at 365 days in the presence or absence of ARDS (P= 0.16, log-rank test). Interestingly, compared to patients with AKI and without ARDS, most patients with AKI and ARDS had experienced MAKE at 30 days (n=6 (50%) vs n=2 (25%)).

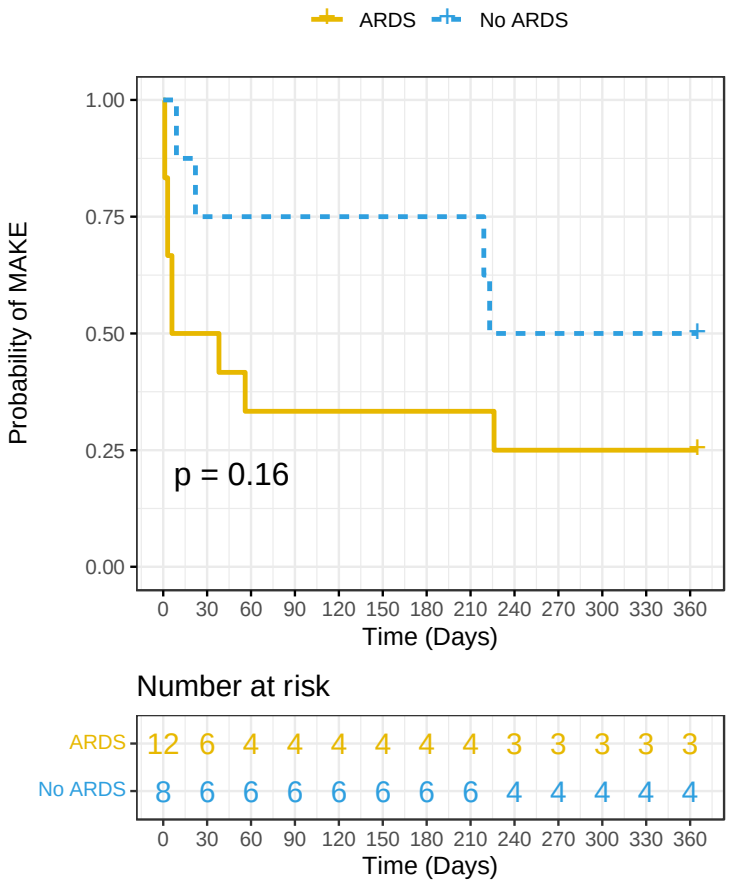


Figure 4.10. Kaplan-Meier curves of the Time to Event of MAKEs at 365 days in sepsis patients with AKI and ARDS or without ARDS.

Legend: This figure illustrates no difference in the incidence of MAKEs at 365 days between sepsis patients with AKI and ARDS or without ARDS (P = 0.16, log-rank test). However, within the first 30 days, a higher proportion of sepsis patients with both AKI and ARDS experienced MAKEs compared to those with AKI alone.
Abbreviations: MAKE, major adverse kidney events; ARDS, acute respiratory distress syndrome.

4.7 DISCUSSION

In this retrospective observational study of 31 critically ill patients diagnosed with sepsis, with or without ARDS, we aimed to investigate the incidence of MAKE-365 and its associations with various biomarkers. Our study revealed several key findings.

Firstly, we observed a common incidence of MAKE-365 in sepsis patients with and without ARDS, with 75% and 50% of patients experiencing MAKE-365, respectively. The main cause of MAKE-365 in patients with ARDS was initiating RRT within 7 days of AKI development, while a reduction in eGFR of less than 75% from the baseline was the common cause in sepsis patients without ARDS. Given the consistent results observed in both COVID-19 and non-COVID-19 ARDS cohorts, these findings align with our expectations. Due to the small sample size of patients who experienced MAKE-365 in both groups, we decided to examine the incidence of MAKE-365 and its associations with kidney biomarkers in sepsis patients, irrespective of ARDS status. Secondly, among the four kidney biomarkers assessed, only urinary [TIMP-2]*[IGFBP-7] demonstrated a significant elevation in patients who experienced MAKE-365. Furthermore, urinary [TIMP-2]*[IGFBP-7] emerged as an independent risk predictor associated with MAKE-365 in sepsis patients with AKI. Lastly, we explored the potential improvement in the predictive power for MAKE-365 occurrence by adding plasma cystatin C, urinary NGAL, urinary [TIMP-2]*[IGFBP-7], and urinary CCL-14 independently to a simple clinical model (including age and bilirubin levels based on the findings presented in the previous chapter (Chapter 3)). Our findings indicated that

incorporating urinary [TIMP-2]*[IGFBP-7] significantly enhanced the predictive power of the clinical model for MAKE-365 occurrence.

Our study discovered a high incidence of MAKE-365 in sepsis patients with AKI, regardless of their ARDS status. This highlights the importance of consistent monitoring and intervention strategies to reduce long-term kidney complications in this population. Notably, research specifically investigating MAKE-365 in sepsis patients is lacking, whereas most studies have focused on MAKE outcomes up to 30 days (MAKE-30). For instance, Mele et al. (2022) investigated MAKE-30 in a cohort of 1834 ICU-admitted sepsis patients and reported that 28% of these patients developed MAKE-30. However, this incidence is still lower than our observed rate for MAKE-30 (40%) or MAKE-365 (65%). A possible explanation for this difference may be that only 44% of the patients who developed MAKE-30 had AKI in their study, while our research targeted sepsis patients with AKI, who are known to be at a higher risk for long-term adverse outcomes (Gameiro et al., 2020).

Despite a comprehensive evaluation of potential risk factors MAKE-365 in the current study, none of those factors, including demographics, pre-existing comorbidities, and lab parameters, were associated with MAKE-365. This could be due to our cohort's relatively small sample size and fewer pre-existing comorbidities, potentially limiting identifying specific risk factors. Therefore, there is a need for larger and more diverse studies to explore further the potential risk factors for MAKE-365 in sepsis patients with AKI. Interestingly, Mele et al. (2022) in their research found a complex range of factors - older age, increased cumulative fluid balance, chronic liver disease, baseline creatinine, lower platelet count, immune deficiency, and IMV - to be

associated with a higher risk of MAKE-30. These findings emphasise the multifaceted nature of risk factors that may contribute to adverse kidney outcomes.

Our findings demonstrated that sepsis patients experiencing MAKE-365 had significantly elevated levels of urinary [TIMP-2]*[IGFBP-7], suggesting its potential role as a biomarker for predicting long-term adverse kidney outcomes. To our knowledge, no previous research has specifically evaluated the urinary [TIMP-2]*[IGFBP-7] biomarker in the context of MAKE-365 in sepsis patients. However, the findings of the current study do not support the findings of Flannery et al. (2021), who revealed that the levels of serum cystatin C and serum NGAL were significantly higher in patients who developed MAKE-365 (median: 1551 ng/ml [IQR: 801 -2804] vs 713 ng/ml [IQR: 560 -989]; P< 0.001 and 426 [188-927] vs 192 [133-279]; P= 0.001, respectively). Although a broad cohort population were recruited (including medical, surgical, and cardiac ICUs), Flannery et al. (2021) did not indicate the presence of sepsis in their study participants, which might limit the generalizability of their findings to the sepsis cohort.

CCL-14 has been recently identified as a potential biomarker for persistent KDIGO stage 3 AKI (Hoste et al., 2020). It is a chemokine that is released by tubular epithelial cells in response to cellular damage (Hoste et al., 2020, Detheux et al., 2000). The recruitment and subsequent activation of renal monocytes play a critical role in renal tissue damage pathophysiology, specifically through their influence on inflammatory and fibrotic responses (Meng et al., 2015). Earlier studies have highlighted that CCL14 functions as a crucial inflammatory marker, mediating the risk associated with the progression to ESRD in diabetic patients (Niewczas et al., 2019).

A recent small prospective observational study examined 48 sepsis patients and found that 23 of those patients developed persistent sepsis-associated AKI, and the urinary CCL-14 levels were not significantly different between transient and persistent sepsis-associated AKI (Jiang et al., 2023).

Other studies have explored the association between urinary [TIMP-2]*[IGFBP-7] with AKI development or the need for RRT in sepsis patients. Nusshag et al. (2019) found that urinary [TIMP-2]*[IGFBP-7] significantly increased in AKI patients with a need for RRT compared to those who did not require RRT. Similarly, a study of 999 critically ill patients with sepsis reported that higher levels of urinary [TIMP-2]*[IGFBP-7] were associated with lower survival and increased mortality at 30 days in patients with AKI (Molinari et al., 2022). In the Sapphire study, which included 728 patients with a subset diagnosed with sepsis, elevated levels of urinary [TIMP-2]*[IGFBP-7] above 0.3 ng/mL^2/1000 were associated with a significantly increased risk of MAKE-30, and the risk was even higher in patients with levels above 2 ng/mL^2/1000 (Kashani et al., 2013). Despite no statistically significant differences were found in the levels of urinary [TIMP-2]*[IGFBP-7] between patients with and without MAKE-30 in the current study, there was a trend toward higher levels in patients with MAKE-30 (median: 0.69 [IQR: 0.28-1.54] vs 1.73 (ng/ml)^2/1000 [IQR: 0.63-2.49]; P= 0.083). This absence of statistical significance could potentially be attributed to the limited sample size of the present study, which limits the statistical power to detect differences.

A secondary analysis of the Sapphire study revealed that higher urinary [TIMP-2]*[IGFBP-7] levels were linked to detrimental long-term outcomes, including the need for RRT or mortality at 180 days (Koyner et al., 2015). It is important to note that in this

secondary analysis study, not all patients who required RRT or died had AKI (69%), while only a smaller proportion had sepsis upon ICU admission (21%).

Sepsis patients with AKI development have been associated with a higher risk for mortality and additional adverse events, including cardiovascular events and CKD (Zarbock et al., 2023). Investigating kidney biomarkers in those patients is challenging due to the systemic inflammatory response syndrome (SIRS) inherent in sepsis and the complexity of interactions between sepsis and kidney function. Sepsis-induced AKI exhibits a unique pathophysiology compared to other diseases and may also display distinctive patterns of biomarkers in plasma and urine (Wang et al., 2018b). For instance, urinary and serum NGAL rapidly increases in response to renal tubular injury and conditions such as non-infectious SIRS, bacterial infections, and chronic and systemic diseases without bacterial infection (Schmidt-Ott et al., 2007). Thus, inflammation is considered a confounder, which complicates the routine use of NGAL as a biomarker for AKI in critically ill septic patients (Mårtensson et al., 2010, Mårtensson et al., 2013, Otto et al., 2015). However, these challenges may not apply to urinary [TIMP-2]*[IGFBP-7], as this measure is specifically indicative of renal tubular damage (Kashani et al., 2013). Therefore, its test performance for predicting AKI in septic patients is not significantly confounded by non-renal organ dysfunction (Honore et al., 2016). Accordingly, clinicians can depend on urinary [TIMP-2]*[IGFBP-7] for predicting AKI even in the presence of non-renal organ failures. This represents a noteworthy progression when contrasted with alternative biomarkers currently accessible globally (Bagshaw et al., 2007, Honore et al., 2007, Honore et al., 2012, Wong et al., 2015).

Cystatin C is produced by all nucleated cells in the human body and is found in various biological fluids (Abrahamson et al., 1990, Abrahasom et al., 1986). Its main function is inhibiting cysteine proteases, making it a crucial extracellular regulator of these enzymes (Workeneh and Mitch, 2013). Although Mussap et al. (2002) suggested that serum cystatin C is a more accurate GFR estimator than serum creatinine in diabetic patients, Knight et al. (2004b) identified non-renal factors influencing serum cystatin C levels. These factors include systemic inflammation, which could compromise its specificity as a kidney function marker. Similarly, NGAL is expressed in various human tissues and released extensively during inflammation (Mishra et al., 2003), particularly during SIRS and sepsis, which can affect NGAL concentrations and its diagnostic accuracy for AKI (Md Ralib et al., 2017, Schrezenmeier et al., 2017).

Several studies have highlighted the impact of SIRS on cystatin C and NGAL in sepsis patients (Knight et al., 2004b, Md Ralib et al., 2017, Schrezenmeier et al., 2017). NGAL has been studied as a potential biomarker for AKI in sepsis patients. However, its reliability is compromised by its strong correlation with systemic inflammation, reducing its specificity to AKI (Mårtensson et al., 2010). This explains the modest performance of these biomarkers in predicting AKI, despite some promising results in certain studies. These findings suggest that both cystatin C and urinary NGAL levels may be influenced by systemic inflammation, thus challenging their use as standalone biomarkers for predicting long-term kidney dysfunction in sepsis patients.

Although a small study found promising results with plasma and urinary NGAL as potential biomarkers for AKI in sepsis patients (with AUC of 0.83 and 0.89, respectively) most research has suggested modest performance of these biomarkers

in those patients. Leem et al. (2017) evaluated the value of serum cystatin C levels in ICU patients with sepsis and found higher levels in patients who developed AKI than those without AKI. The potential interpretation of our findings suggests that both cystatin C and urinary NGAL may be influenced by systemic inflammation in sepsis patients, which might be challenging to utilise these biomarkers alone for predicting long-term kidney dysfunction.

To the best of our knowledge, this study represents the first investigation specifically targeting the predictive capacity of kidney biomarkers for MAKE-365 in critically ill patients with sepsis. While previous research has primarily focused on different patient populations or endpoints, such as AKI or MAKE-30, our study addresses this gap in the literature by assessing the potential of kidney biomarkers to predict MAKE-365 in sepsis patients.

We utilised several kidney biomarkers, including plasma cystatin C, urinary NGAL, urinary [TIMP-2]*[IGFBP-7], and urinary CCL-14, to develop a prediction model for MAKE-365 identification. We found that none of these biomarkers demonstrated robust performance in predicting MAKE-365. However, urinary [TIMP-2]*[IGFBP-7] emerged as the most promising in terms of predictive ability for MAKE-365. Then, we assessed the combination of each biomarker prediction model with a simple clinical model. We also found that combining urinary [TIMP-2]*[IGFBP-7] with the clinical prediction model significantly improved accuracy in predicting MAKE-365 in sepsis patients. These results seem to be consistent with findings from the Sapphire study, which showed that urinary [TIMP-2]*[IGFBP-7] was significantly superior to urinary NGAL and plasma cystatin C in predicting AKI (KDIGO stage 2 to 3) and performed

very well in sepsis patients (AUC 0.82) (Kashani et al., 2013). In addition, secondary analysis from the prospective observational Finnish Acute Kidney Injury (FINNAKI) study showed that the performance of urinary NGAL alone was insufficient in predicting RRT and mortality at 90 days in septic patients (Törnblom et al., 2020). A recent retrospective cohort study of 406 sepsis patients with diabetes has demonstrated that cystatin C was a strong independent predictor for MAKE-30 in those patients (OR= 1.960; 95% CI:0.360-2.826) (Xin et al., 2022b).

The potential use of the novel biomarker CCL-14 as a predictive tool for MAKE-365 in sepsis patients remains unexplored. However, an earlier stated study by Jiang et al. (2023) evaluated the predictive capability of urinary CCL-14 at 24 hours to predict persistent sepsis-associated AKI and also showed poor predictive performance with an AUC of 0.60, which is contrary to previous studies that suggested that urinary CCL-14 was mainly used to predict persistent KDIGO stage 3 AKI (Hoste et al., 2020, Bagshaw et al., 2021, Koyner et al., 2022).

Flannery et al. (2021) found that the predictive accuracy for MAKEs at hospital discharge significantly improved when serum cystatin C (AUC=0.941) and serum NGAL (AUC=0.873) were individually added to a basic clinical model (P=0.001 and P=0.02, respectively). This outcome contrasts with the results of our study, which could be influenced by several factors, including the reporting time for MAKE development, the unidentified presence of sepsis patients, and the use of different variables in the basic clinical model, such as the Charlson Comorbidity Index (CCI) and APACHE II.

The current study's findings could potentially guide the development of more accurate predictive models for identifying sepsis patients at high risk of experiencing

MAKE-365. This could enable earlier interventions, tailored treatment, and improved patient outcomes. Furthermore, the kidney biomarkers studied could provide insights into the underlying pathophysiology of kidney injury, thereby opening new possibilities for therapeutic research.

Each kidney biomarker offers insights into different aspects of kidney function and injury: Cystatin C can help identify glomerular dysfunction; NGAL can indicate tubular damage and systemic inflammation, especially in sepsis; CCL-14 may highlight underlying inflammatory processes or fibrosis; and [TIMP-2]*[IGFBP-7] could alert us to early cell stress responses.

This enhanced understanding of the complex nature of kidney injury in sepsis can open new avenues for therapeutic research. We could develop targeted therapies by recognising the specific mechanistic drivers of kidney injury, such as glomerular dysfunction, tubular injury, systemic inflammation, or fibrosis. These therapies might protect specific kidney structures, modulate systemic responses, or promote recovery. Collectively, such strategies could lead to improved outcomes for patients with sepsis-induced AKI and reduce long-term MAKEs development.

However, these promising results need further validation. The utility of these biomarker combinations must be confirmed in external larger prospective cohorts, ensuring that these findings are generalisable and not simply specific to the patient population used in this study. By doing so, we could better understand the exact role of these biomarkers in predicting longer-term MAKEs, which are associated with worse patient outcomes and increased mortality. Consequently, this refines the current predictive models for improved patient care.

This chapter has several important strengths. This is the first evaluation of the association between novel kidney biomarkers and MAKE-365 in critically ill sepsis patients with and without ARDS. Additionally, we evaluated the predictive capacity of these biomarkers for MAKE-365. Based on the latest published literature, this is the first investigation of the novel biomarker CCL-14 for MAKEs. Moreover, the strength of our investigation is reinforced by our reliance on well-recognised and clinically accepted criteria for the diagnosis of AKI and the identification of primary outcomes (MAKE-365) (Kellum et al., 2012, Billings and Shaw, 2014).

However, this chapter has some limitations. Firstly, the limited sample size of the study may affect the generalizability of the results. Additionally, only critically ill sepsis patients from a single centre were included in this study, which limited the generalizability of current results. Furthermore, being a four-year retrospective study, substantial advancements in the management decision-making process during this period might have impacted the development of Major Adverse Kidney Events (MAKE). A significant methodological challenge was the high rate of missing data for eGFR values at day 365, with approximately 74% of these values unavailable. This considerable proportion of missing data presents substantial challenges, potentially introducing considerable bias, especially when the missingness is associated with critical outcomes such as patient mortality or loss to follow-up. The implications of this missing data are particularly relevant when considering longitudinal analyses and interpretations of long-term renal outcomes. This underscores the critical need for enhanced data collection and retention methods in future studies, particularly those adopting a prospective design, to enable more comprehensive analyses of long-term outcomes.

The predictive accuracy of the novel biomarkers was not evaluated within validation cohorts in this study. Additionally, kidney biomarkers were assessed at only a single time point. Therefore, further multi-centre prospective studies with adequate sample size are necessary to validate the results and establish an optimal time point for assessing these biomarkers. Moreover, predicting the development of longer-term MAKE outcomes at ICU discharge is essential for appropriate follow-up and assessment of modifiable risk factors to prevent progression. This could significantly improve patient management and outcomes. Finally, it should also be noted that the assay results for urinary biomarkers were not standardized, for instance, through adjustment with a urinary biomarker to urinary creatinine ratio, potentially affecting the interpretation of biomarker levels.

4.8 CONCLUSION

Our study demonstrated that urinary [TIMP-2]*[IGFBP-7] showed promise as a biomarker for predicting long-term outcomes in sepsis patients with AKI (MAKE-365). However, further research is needed to validate and expand on these findings. The contrasting results concerning plasma cystatin C and urinary NGAL highlight the complex nature of these biomarkers in the context of sepsis, highlighting the need for a comprehensive understanding of their role in predicting long-term kidney dysfunction. Although the results are promising, validation using a larger sample size will be more beneficial.

4.9 SUMMARY OF THE CHAPTER

This chapter highlights the significance of assessing urinary [TIMP-2]*[IGFBP-7] in critically ill sepsis patients with or without ARDS to limit or prevent the risk of developing MAKE-365. Combining urinary [TIMP-2]*[IGFBP-7] with the clinical variables could enhance the prediction accuracy of long-term outcomes related to sepsis patients with AKI such as MAKE-365. This has two key clinical implications, firstly, identifying patients at risk of MAKE-365 in routine practice will enable clinicians to monitor signs of deterioration and investigate interventions to prevent adverse events. Secondly, these results could help guide future practice and enhance the management strategies of critically ill sepsis patients with AKI.

CHAPTER 5

5 GENERAL DISCUSSION

The presented thesis aimed to evaluate the incidence of short- and long-term kidney dysfunction outcomes, identify associated risk factors and biomarkers and explore the potential predictive utility of these factors for MAKE development for up to 365 days in patients with sepsis and ARDS.

The first results chapter consisted of a systematic review to assess the knowledge related to AKI development and associated risk factors in COVID-19 patients, both with and without ARDS. We also evaluated the need for RRT and mortality rates. Data published from the first wave of COVID-19 supported our hypothesis, indicating that COVID-19 patients with ARDS were more likely to develop AKI than those without ARDS.

Subsequently, in chapter three, we conducted a retrospective cohort study primarily on ARDS patients to assess the occurrence of MAKEs up to 365 days (MAKE-365) post-ICU admission in non-COVID-19 ARDS versus COVID-19 ARDS cohorts. This chapter focused on 708 ARDS patients, comprising COVID-19 (n= 458) and non-COVID-19 (n= 250). MAKE-365 development was more common in the non-COVID-19 cohort, with CKD and high bilirubin levels emerging as the most significant independent risk factors in both cohorts. Other independent risk factors included older age and diabetes in the COVID-19 cohort and lower albumin levels in the non-COVID-19 cohort.

Given the high incidence of long-term kidney dysfunction (such as MAKE-365) in non-COVID-19 ARDS patients, we conducted a retrospective cohort study in chapter four, assessing MAKE-365 development and evaluating the predictive capability of kidney biomarkers for MAKE-365 in septic patients, with or without ARDS. This study revealed a higher prevalence of MAKE-365 in septic patients with AKI, irrespective of their ARDS status. Among the biomarkers evaluated, urinary [TIMP-2]*[IGFBP-7] showed the most promising predictive capability for MAKE-365. Additionally, combining urinary [TIMP-2]*[IGFBP-7] with the clinical prediction model significantly improved the accuracy of predicting MAKE-365 in septic patients.

In summary, the primary findings of this thesis include:

- AKI and the need for RRT are more prevalent in COVID-19 patients with ARDS than those without ARDS.
- Patients with AKI exhibit a higher risk of mortality.
- The incidence of AKI, MAKE-30, MAKE-90, MAKE-180, and MAKE-365 are more common in non-COVID-19 ARDS patients than in COVID-19 ARDS patients.
- CKD and high bilirubin levels are commonly associated with MAKE-365 in all ARDS patients, along with older age and diabetes mellitus in the COVID-19 group and lower albumin levels in the non-COVID-19 group.
- Urinary [TIMP-2]*[IGFBP-7] is a promising biomarker for predicting MAKE-365 in septic patients, irrespective of their ARDS status, particularly when combined with the clinical prediction model.

5.1 AKI IN COVID-19 PATIENTS (WITH OR WITHOUT ARDS)

AKI is a frequent complication in patients with ARDS, leading to adverse outcomes, such as prolonged hospital stays and increased mortality rates (Liu and Matthay, 2008, Liu et al., 2011, Mehta et al., 2002). The emergence of the COVID-19 pandemic has posed significant challenges to healthcare systems, as the disease is often associated with severe or life-threatening complications (Baj et al., 2020). ARDS has been recognised as the most common complication in critically ill patients severely affected by COVID-19 (Yang et al., 2020). AKI is the second most common complication associated with COVID-19, particularly in critically ill patients. The occurrence of AKI ranges from 20% to 80% among ICU patients and is mainly associated with increased mortality (Gabarre et al., 2020, Pei et al., 2020). Emerging literature highlights the detrimental interaction between lung and kidney dysfunctions (Li et al., 2009, Husain-Syed et al., 2016, Cortesi, 2020).

As explored in this thesis, evidence suggests that before the emergence of COVID-19, the incidence of AKI in ARDS was around 35-50%, coupled with a high mortality rate which nearly doubled in the ICU (Cooke et al., 2008, Darmon et al., 2014b). It was initially inferred that the incidence of AKI may rise significantly in patients with COVID-19 following the onset of ARDS, pointing to lung-kidney interaction as a key cause of kidney injury (Ahmed et al., 2020).

Our systematic review that conducted during the first wave of COVID-19, revealed that a high incidence of AKI was primarily reported in cohorts where over 90% of patients had ARDS (Arentz et al., 2020, Ch et al., 2020, Grimaldi et al., 2020a,

Zangrillo et al., 2020a, Zheng et al., 2020, Zhou et al., 2020b, Fominskiy et al., 2020). Our meta-analysis revealed that AKI incidence was higher in patients with COVID-19 and ARDS compared to COVID-19 patients without ARDS (59% vs 6%, P< 0.001). This aligns with a multicentre study across nine European ICUs, which found that 50% of COVID-19 patients with ARDS developed AKI (Chaibi et al., 2020). We observed an increased need for RRT in patients with a high incidence of AKI, as reported by Ch et al. (2020) and Fominskiy et al. (2020). Gasparini et al. (2021) indicated that, irrespective of the existence of kidney dysfunction, 24% of patients who survived required RRT at a certain stage during their critical illness, which was even higher (46%) in patients who did not survive ($p < 0.001$). Furthermore, Torjesen (2021) revealed that even individuals who have experienced mild to moderate symptoms of COVID-19 a higher risk of AKI (adjusted Hazard Ratio (aHR): 1.94; 95% CI: 1.86 - 2.04) and major adverse kidney events (aHR:1.66; 95% CI 1.58-1.74). They also revealed that the risk of end-stage kidney disease alone was nearly 3-fold higher in those who had recovered from COVID-19 compared to the general population.

It is crucial to note that these findings were from the initial waves of the pandemic. A recent multi-centre observational cohort study examined 12,891 hospitalised patients with COVID-19 and found that over 50% of those patients had developed AKI (Tan et al., 2023).

The existing literature suggests that individuals with a pre-existing CKD are more prone to have several comorbidities that increase the risk for adverse outcomes, such as advanced age, diabetes mellitus, hypertension, and cardiovascular disease (Portolés et al., 2020). Similarly, age, pre-existing CKD, along with a high prevalence of other comorbidities like hypertension, diabetes, obesity, and heart failure, have all

been linked with worsened outcomes and an elevated risk of developing AKI among patients with COVID-19 (Nadim et al., 2020). These findings were in consistent with the study of Tan et al. (2023) that found also COVID-19 patients with AKI were more likely to be older, male sex, have severe COVID-19, CKD, hypertension, and Ischaemic heart disease.

Due to the heterogeneity of included studies in their samples, methodologies, and recruitment criteria, identifying associated risk factors with AKI development in the ARDS cohort was lacking. To explore this, we conducted a retrospective cohort study in chapter three, using real-world data from ARDS patients with and without COVID-19. We found a generally high incidence of AKI, particularly among those without COVID-19 (70%). The presence of CKD and elevated bilirubin levels were associated with a higher risk of AKI and MAKE-365 development in both cohorts. Other associated risk factors included older age and diabetes in the COVID-19 cohort and lower albumin levels in the non-COVID-19 cohort. These factors likely contribute to AKI development and could also be linked to worse long-term outcomes, thereby increasing morbidity and mortality in ARDS patients.

A recent study indicated that COVID-19 patients with elevated direct bilirubin levels faced an increased risk of complications such as shock and respiratory failure during hospitalisation (Chen et al., 2022). This could be due to liver dysfunction impacting the production of coagulation factors, albumin, and acute phase reactants, resulting in multisystem manifestations of COVID-19, including ARDS and multiple organ dysfunctions (Nardo et al., 2021). These systemic effects could exacerbate kidney damage, thus increasing the risk of AKI and MAKE-365.

Moreover, Bangash et al. (2020) suggested that patients with chronic liver diseases and cirrhosis are particularly at risk due to their compromised immune function and adverse outcomes from ARDS. The association between deranged liver markers and severe COVID-19 likely reflects collateral liver damage from virally induced cytotoxic T cells and a dysregulated innate immune response rather than primary liver damage.

Advanced age is associated with both functional and structural changes of the kidneys, potentially resulting in diminished renal function (Chou and Chen, 2021). Factors such as diabetes, hypertension, cardiovascular diseases, glomerulonephritis, and the inappropriate use of non-steroidal anti-inflammatory drugs (NSAIDs), can cause damage to ageing kidneys that already have decreased physiological resilience (Wang et al., 2018a). Moreover, the development of AKI during acute illnesses is emerging as a significant risk factor for subsequent development of CKD and end-stage renal disease (Chou et al., 2017a, Chou et al., 2017b).

In the early stages of kidney disease, small amounts of the blood protein albumin might leak into the urine, resulting in a condition known as microalbuminuria (Dabla, 2010). During this phase, the kidney's filtering capability typically remains unaffected. However, as the disease progresses, albumin leakage increases, leading to a stage known as macroalbuminuria or proteinuria (Dabla, 2010). This may reflect the progressive increase in glomerular and tubulointerstitial damage. Therefore, early identification of kidney damage could help decelerate the disease's progression and mitigate long-term major adverse kidney events. Moreover, this early identification could pave the way for new therapeutic interventions, such as angiotensin-converting

enzyme inhibitors, which have been indicated for their effects on reducing glomerular and tubular damage and dysfunction in diabetic patients (Nielsen et al., 2009).

5.2 MAJOR ADVERSE KIDNEY EVENTS IN PATIENTS WITH ARDS

AKI is a frequent complication in critically ill COVID-19 patients, dramatically increasing incidence in those with ARDS (Grimaldi et al., 2020b, Alenezi et al., 2021). Although several studies have investigated AKI in ARDS or COVID-19 patients, few have examined the long-term kidney outcomes associated with AKI development in COVID-19 patients with ARDS. Over the last decade, MAKE outcomes are increasingly known as valid long-term indicators of the impact of AKI on patient-related outcomes, especially in critically ill patients (Billings and Shaw, 2014). Therefore, in chapter three, a retrospective cohort study was conducted using data from ARDS patients with or without COVID-19 to assess the development of MAKEs at different timeframes (i.e., 30, 90, 180, and 365 days) from ICU admission and identify the associated risk factors with MAKEs. This study found that the incidence of MAKEs in both cohorts increased progressively across all timeframes. A higher incidence of MAKE-365 was primarily observed in the non-COVID-19 cohort. In keeping with this, Vinclair et al. (2020) revealed that the incidence of MAKEs at 30, 90, and 360 days was 59.9%, 60.5%, and 85.1%, respectively, in a cohort of patients receiving VA-ECMO.

In both ARDS cohorts, CKD and higher bilirubin levels were strongly associated with an increased risk of MAKE-365. Other associated risk factors included older age, diabetes in the COVID-19 cohort and lower albumin levels in the non-COVID cohort.

Although most risk factors for MAKEs remained consistent across different timeframes (i.e., 30, 90, 180, and 365 days), an increase in the odds ratio (OR) was observed for CKD in both cohorts and diabetes in the COVID-19 cohort.

Contrary to our findings, McKown et al. (2017) found no significant association between CKD and MAKE-30 (OR= 1.2, 95% CI= 0.95-1.51, P = 0.13). This variance could be due to the lower proportion of mechanically ventilated patients (28%) and fewer reported comorbidities in their population. As discussed in Chapter One, mechanical ventilation can potentially cause lung injury due to pulmonary overdistension and barotrauma, stimulating the release of inflammatory cytokines. This exacerbates systemic inflammation, potentially leading to dysfunction in distant end-organs such as the kidneys (Husain-Syed et al., 2016).

Although the non-COVID-19 cohort had a higher rate of RRT initiation at 30 days, we observed a consistent increase in mortality from day 30 to day 365. This observation aligns with Gaudry et al. (2018), who found no association between early initiation of RRT and a reduction in 60-day mortality.

A large multi-centre observational study included 85,687 hospitalised COVID-19 patients, Sullivan et al. (2021) indicated a positive association between dexamethasone use and RRT initiation (OR: 2.23; 95% CI: 1.09- 4.80). However, they found no association between dexamethasone use and AKI (OR: 0.90; 95% CI: 0.51-1.56). It's plausible that the increase in RRT initiation is reflective of disease severity, not the direct effect of dexamethasone, as the drug was typically administered to patients with severe pneumonitis. This could explain the higher incidence of RRT initiation within the COVID-19 cohort.

It's important to note that the decision to administer dexamethasone is based on individual patient conditions and the stage of the pandemic. During the early stages of the pandemic, some patients were deliberately kept fluid-depleted to avoid lung oedema, an approach that was later recognized as potentially detrimental. Notably, some of the COVID-19 patients included in our study were from this early stage and therefore did not receive dexamethasone. The World Health Organization has since updated their guidelines to recommend the use of glucocorticoids, including dexamethasone, for hospitalised patients with severe COVID-19 (Lamontagne et al., 2020).

Nonetheless, several studies indicate that dexamethasone can lower the risk of severe AKI and the need for RRT in critically ill COVID-19 patients (Bobot et al., 2022, Orieux et al., 2021). Also, the RECOVERY trial findings showed a reduced need for RRT and mortality rate in COVID-19 patients treated with dexamethasone (Horby et al., 2021). Most recent evidence investigating the early incidence of AKI (within 48 hours of IMV) in COVID-19 ARDS compared with non-COVID-19 ARDS cohorts found a higher incidence of AKI in the non-COVID-19 ARDS group (54% versus 21%; $P < 0.001$) (McNicholas et al., 2023). This discrepancy could be related to these cohorts' different aetiologies and clinical presentations during ICU admission. Specifically, patients with COVID-19 ARDS tend to present with single-organ failure, primarily impacting the lungs initially. In contrast, non-COVID-19 ARDS patients are more likely to be admitted with multi-organ failure, which raises the risk of kidney impairment and necessitates more frequent initiation of RRT (Mahida et al., 2020). These observations underline the importance of identifying those with AKI at risk of developing MAKEs in the non-COVID-19 ARDS cohort.

5.3 KIDNEY BIOMARKERS FOR PREDICTING MAKE-365

Various kidney biomarkers have been evaluated for their ability to predict AKI before serum creatinine. Some of these biomarkers have received clinical approval, including urinary and plasma NGAL and urinary [TIMP-2]*[IGFBP-7] (Vijayan et al., 2016a, Kashani et al., 2013, Albert et al., 2020). Recent studies have emphasised the use of kidney biomarkers for improved prediction of persistent AKI and MAKEs in critically ill patients (Flannery et al., 2021, Bagshaw et al., 2021). However, none of the previously published studies has evaluated kidney biomarkers for their capacity to predict MAKEs for up to 365 days in sepsis patients with or without ARDS.

Chapter Four initially planned to conduct a prospective study using biological samples from critically ill patients with ARDS. However, due to the time limitations of this PhD study, the research was refocused to a retrospective analysis utilising pre-collected biological samples from the "AM-ARDS study". The chapter's goal was to assess the association of kidney biomarkers (including plasma cystatin C, urinary NGAL, urinary [TIMP-2]*[IGFBP-7], and urinary CCL-14) with MAKE-365 in sepsis patients with AKI (within seven days) with or without ARDS. Furthermore, it aimed to test the effectiveness of combining the biomarker data with a clinical prediction model (including age and bilirubin levels) for predicting the risk of MAKE-365.

Chapter four revealed that MAKE-365 was commonly observed in sepsis patients with or without ARDS (75% and 50%, respectively). The leading cause of MAKE-365 in ARDS patients was the need for RRT, while in patients without ARDS, it was typically a reduction in eGFR of less than 75% from the baseline. These findings align with our results from chapter three, where the need for RRT was the most prevalent cause of MAKE-365 in the ARDS cohort.

Due to the small sample size of patients experiencing MAKE-365 in both cohorts, we decided to examine the incidence of MAKE-365 and its associations with kidney biomarkers in sepsis patients with AKI, irrespective of their ARDS status. Subsequently, the findings revealed that higher levels of urinary [TIMP-2]*[IGFBP-7] were associated with an increased risk of MAKE-365 in patients with sepsis and AKI (OR= 4.70; 95% CI= 1.22-44.9). Even when considering combining the biomarker data with a clinical prediction model, urinary [TIMP-2]*[IGFBP-7] was the only biomarker that significantly improved the predictive capacity of the clinical model for MAKE-365 occurrence (P= 0.036).

This thesis shows that neither urinary NGAL nor plasma cystatin C enhances the predictive performance of MAKE-365. In contrast, Flannery et al. (2021) showed significant improvement in the predictive power of MAKEs at hospital discharge when each serum cystatin C (AUC=0.941) and serum NGAL (AUC=0.873) were separately combined with a basic clinical model (P=0.001 and P=0.02, respectively). Potential explanations for these differences could be unreported the presence of sepsis, differing MAKEs reporting times, and different variables included in their clinical models, such as the Charlson Comorbidity Index (CCI) and APACHE II. Although current findings indicated that urinary [TIMP-2]*[IGFBP-7] could be a promising biomarker for predicting long-term consequences related to AKI (such as MAKE-365) in patients with sepsis, further research is needed to validate and expand these results.

5.4 STRENGTHS AND LIMITATION

5.4.1 STRENGTHS

The strengths of this thesis were primarily reflected in its robust design. The systematic review was prospectively registered, conducted, and reported following standardised methodologies (chapter 2). This comprehensive systematic review guided us in identifying the existing gaps in the literature and highlighting areas that required further investigation (Chapter 3). The study included a large sample of ICU patients with various underlying conditions such as AKI, hypertension, diabetes, obesity, and CKD. This helped identify the clinical predictors for MAKE-365 in non-COVID-19 and COVID-19 ARDS cohorts. Subsequently, we conducted the first retrospective cohort study that assessed the association between novel kidney biomarkers and MAKE-365 in critically ill sepsis patients, with or without ARDS (chapter 4). Using clinical variables obtained as part of routine care strengthens the clinical value of our results in this thesis. In addition, AKI and MAKEs outcomes were defined based on well-recognised and clinically accepted criteria (Kellum et al., 2012, Billings and Shaw, 2014).

5.4.2 LIMITATIONS

There were some limitations identified in this thesis. Most of the studies in the systematic review were from China and the United States, with a limited number from Africa and Europe (Chapter 2). This geographical concentration could limit the global applicability of the findings from the systematic review. High heterogeneity was observed between the studies. Hence most analyses were interpreted based on a random-effects model.

In chapter three, we carried out a retrospective cohort study using real-world data from a single centre, which may restrict the external validity of the study's findings. Different patient demographics and practices at other centres could influence the outcomes. Moreover, limited data on baseline eGFR measurements, particularly in COVID-19 patients, posed a challenge in identifying the MAKE outcome. Therefore, as current guidelines recommended, missing eGFR baseline values were estimated using the MDRD or CKD-EPI formula (Kellum et al., 2012).

In chapter four, we planned to conduct a prospective cohort study to assess the association between kidney biomarkers and the incidence of MAKEs for up to 365 days. However, due to the time limitations of this current PhD study, we decided to conduct a retrospective cohort study using biological samples collected initially under a previous study named “AM-ARDS”. This resulted in a few limitations, including a small sample size from a single centre, the inclusion of only critically ill sepsis patients, and the fact that all participants were of white ethnicity, limiting the generalizability of our findings. Furthermore, we only evaluated kidney biomarkers at a single time point.

5.5 SUGGESTIONS FOR FUTURE WORK

This thesis demonstrates that critically ill patients with non-COVID-19-related ARDS are at a higher risk of short-term and long-term kidney dysfunction, such as AKI and major adverse kidney events.

As described in this thesis, older age, pre-existing CKD, and high bilirubin were identified as clinical predictors for MAKE-365 in the ARDS cohort (Chapter 3). However, these findings require external validation to increase their generalizability. As highlighted in Chapter Four, the number of patients with ARDS in the sepsis cohort

was relatively small, which limited our ability to assess the association of clinical predictors with MAKE-365 in this population. Consequently, a multicentre prospective study, including a larger sample size of sepsis patients with or without ARDS, is recommended for future investigation.

Chapter Four also underlines the potential role of urinary [TIMP-2]*[IGFBP-7] in predicting MAKE-365 in sepsis patients (with or without ARDS). Moreover, combining urinary [TIMP-2]*[IGFBP-7] measurements with clinical variables improves the prediction accuracy of MAKE outcomes in sepsis patients with AKI. This could guide the development of more accurate predictive models, facilitating early intervention and improved patient outcomes. Importantly, these models should be validated in cohorts with diverse ethnic backgrounds to enhance their generalizability. A more comprehensive understanding of the exact role of the studied biomarkers in predicting MAKEs will refine our current predictive models and help advance patient care. The studied biomarkers could also provide new insights into the pathophysiology of kidney injury, thereby opening new avenues for therapeutic research.

Finally, considering that commercial biomarkers for AKI detection are still not accessible in many regions, there's a significant potential for developing a risk score system for predicting MAKE outcomes at varying timeframes (i.e., 30, 90, 180, and 365 days). This system could utilise routine clinical data and particularly benefit ICU patients with ARDS. It's worth noting that the development of similar risk prediction scores has been successfully achieved in different surgical cohorts, aiding in identifying patients at high risk of AKI development (Kheterpal et al., 2009, Malhotra et al., 2017, Thakar et al., 2005, Trongtrakul et al., 2020). Recently, both Sukmark et al. (2020) and Neyra et al. (2023) have developed scoring systems for predicting

MAKE within 28 and 120 days post-hospital discharge in ICU patients with AKI. However, there's a lack of reporting scoring system for predicting MAKE within 365 in ICU patients with ARDS and AKI, who generally have worse long-term outcomes due to their illness severity. Thus, the simplicity and cost-effectiveness of a scoring system based on routine clinical data could make it a valuable tool for early identification of high-risk patients in settings with limited resources. This could apply to ICU patients with ARDS and AKI and other clinical settings such as post-surgery and transplant patients. Thus, the development of such a scoring system could have wide-ranging applications and help reduce adverse outcomes across a broad spectrum of patient populations.

5.6 CONCLUSION

The presented thesis has demonstrated the serious impact of AKI in critically ill patients with ARDS and the increased risk of major adverse kidney events and mortality associated with AKI-related ARDS, especially in critically ill patients with older age, pre-existing CKD, or higher bilirubin levels. This thesis also underlined the association between elevated urinary [TIMP-2]*[IGFBP-7] and an increased risk of MAKE-365 in patients with sepsis. Furthermore, our research found that the accuracy in predicting MAKE-365 in sepsis patients with AKI significantly improved when clinical predictors were combined with urinary [TIMP-2]*[IGFBP-7] measurements.

These findings highlight the importance of early recognition of the MAKE-365 risk. This is comparable to management strategies in conditions like hypertension and diabetes, where active monitoring for macroalbuminuria, proteinuria, and other early signs of persistent damage often leads to therapeutic adjustments that significantly

enhance patient outcomes. Similarly, early identification of patients at risk of MAKE-365 may uncover modifiable risk factors. This could pave the way for new therapeutic interventions, such as angiotensin-converting enzyme inhibitors or other innovative treatments. By assessing these biomarkers in larger ARDS cohorts, we could facilitate the early identification of high-risk patients in clinical practice and potentially develop a current approach to managing MAKE-365 in critically ill patients.

These enhancements in early detection and intervention could improve patient outcomes and refine and shape future management strategies in critical care. Therefore, future research should focus on validating these findings in larger and more diverse ARDS cohorts.

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7 LIST OF APPENDICES

7.1. Published Article Renal Failure Journal

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CLINICAL STUDY

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Incidence and risk factors of acute kidney injury in COVID-19 patients with and without acute respiratory distress syndrome (ARDS) during the first wave of COVID-19: a systematic review and Meta-Analysis

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ABSTRACT

Background: Acute kidney injury (AKI) is common among patients with COVID-19. However, AKI incidence may increase when COVID-19 patients develop acute respiratory distress syndrome (ARDS). Thus, this systematic review and meta-analysis aimed to assess the incidence and risk factors of AKI, need for kidney replacement therapy (KRT), and mortality rate among COVID-19 patients with and without ARDS from the first wave of COVID-19.

Methods: The databases MEDLINE and EMBASE were searched using relevant keywords. Only articles available in English published between December 1, 2019, and November 1, 2020, were included. Studies that included AKI in COVID-19 patients with or without ARDS were included. Meta-analyses were conducted using random-effects models.

Results: Out of 618 studies identified and screened, 31 studies met the inclusion criteria. A total of 27,500 patients with confirmed COVID-19 were included. The overall incidence of AKI in patients with COVID-19 was 26% (95% CI 19% to 33%). The incidence of AKI was significantly higher among COVID-19 patients with ARDS than COVID-19 patients without ARDS (59% vs. 6%, $p < 0.001$). Comparing ARDS with non-ARDS COVID-19 cohorts, the need for KRT was also higher in ARDS cohorts (20% vs. 1%). The mortality among COVID-19 patients with AKI was significantly higher (Risk ratio = 4.46; 95% CI 3.31–6; $p < 0.00001$) than patients without AKI.

Conclusion: This study shows that ARDS development in COVID-19-patients leads to a higher incidence of AKI and increased mortality rate. Therefore, healthcare providers should be aware of kidney dysfunction, especially among elderly patients with multiple comorbidities. Early kidney function assessment and treatments are vital in COVID-19 patients with ARDS.

Abbreviations: ARDS: Acute respiratory distress syndrome; BAME: Black, Asian and minority ethnic; CKD: Chronic kidney disease; COVID-19: Coronavirus disease 2019; ICU: Intensive care unit; KDIGO: Kidney Disease: Improving Global Outcomes; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RR: Risk ratio; KRT: Kidney replacement therapy; BMI: Body mass index; NIH: National Institute of Health.

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Acute kidney injury; COVID-19; acute respiratory distress syndrome; kidney replacement therapy; mortality; systematic review; meta-analysis

Background

In December 2019, a novel coronavirus disease (COVID-19), was identified in Wuhan, China, which has spread quickly worldwide [1]. On March 11, 2020, the World Health Organization declared COVID-19 as a pandemic [2]. At the time of writing this review, over 32.7 million COVID-19 cases and 991,000 deaths have been reported. This rapid spread of COVID-19 across the world brought many challenges to global health care systems. COVID-19 leads to a wide range of clinical manifestations from asymptomatic, mild, moderate to severe health conditions. Symptomatic patients usually present with fever, dry cough, shortness of breath, myalgia, or fatigue [3]. COVID-19 is of clustering onset

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and mostly affects the respiratory system, with some patients rapidly progressing to acute respiratory distress syndrome (ARDS); these patients frequently require admission to the intensive care unit (ICU) [4]. Furthermore, it has been demonstrated that severe cases are mostly among the elderly and those with an underlying disease, which may progress to respiratory failure and increased risk of mortality [4].

A growing body of literature has exhibited that there are three potential mechanisms through which the kidney becomes involved in COVID-19 disease: cytokine-induced damage, systemic effects, and organ crosstalk [5]. These mechanisms are interrelated and have important implications for extracorporeal therapy [5]. Several risk factors may contribute to developing acute kidney injury (AKI) in severe cases; for example, most COVID-19 patients with AKI are older. Furthermore, they have comorbidities such as diabetes mellitus or hypertension, which are well-known to associate with kidney vulnerability [6]. ARDS has been identified as one of the prominent conditions that could lead to AKI development; this is also one of the primary reasons for admission in individuals with severe COVID-19 [4,7,8]. Additionally, some factors were associated with AKI development in patients with ARDS, such as impairment of gas exchange and severe hypoxemia [9].

Early reports from China suggested that the prevalence of AKI among patients with COVID-19 was low [6]. Guan et al. studied 1,099 Chinese patients with confirmed COVID-19; 93.6% of those patients were hospitalized, but only 5.3% of those were admitted to the ICU [7]. Across the hospital cohort, 3.4% developed ARDS and only 0.5% developed AKI. Notwithstanding, AKI is mostly common in critically ill patients with COVID-19, affecting 20–40% of patients admitted to ICU [10]. It is deemed a marker of disease severity and an adverse prognostic factor of survival [10]. A multicentre retrospective study from Wuhan investigated 239 critically ill COVID-19 patients and reported that the most common complications among those patients were ARDS, acute cardiac injury, and AKI (68.6%, 43.1%, and 49.8%, respectively) [1].

To date, most studies have revealed the incidence of AKI and ARDS in COVID-19 patients. However, none of these studies has compared AKI incidence in COVID-19 patients with and without ARDS. Therefore, this systematic review aimed to assess the incidence and risk factors of AKI among COVID-19 patients with and without ARDS. We also aimed to assess the necessity of kidney replacement therapy (KRT) in addition to the mortality rate.

Materials and methods

The protocol of this review has been registered prospectively in PROSPERO (CRD42020219460). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) guideline was used to report this systematic review and meta-analysis [11]. The PRISMA checklist is provided in Supplementary 1.

A comprehensive literature search was performed by searching MEDLINE and EMBASE databases *via* the Ovid portal to select studies that met the inclusion criteria. The search terms and strategy used were; (Adult*) AND ("Novel coronavirus.ti,ab." OR "New coronavirus.ti,ab." OR "Coronavirus 2019.ti,ab." OR "COVID-19.ti,ab." OR "SARS-CoV-2.ti,ab.") AND ("hospitalisation.ti,ab." OR "hospitalization.ti,ab." OR "oxygen therapy.ti,ab." OR "ventilation.ti,ab." OR "mechanical ventilation.ti,ab." OR "Positive Pressure Ventilation.ti,ab." OR "renal dialysis.ti,ab." OR "renal replacement therapy.ti,ab." OR "RRT.ti,ab"). AND ("acute kidney injury.ti,ab." OR "AKI.ti,ab." OR "acute renal injury.ti,ab." OR "acute kidney insufficiency.ti,ab." OR "acute renal insufficiency.ti,ab." OR "acute kidney failure.ti,ab." OR "acute renal failure.ti,ab." OR "respiratory distress syndrome.ti,ab." OR "respiratory failure.ti,ab.") (Supplementary 2). The search was limited to original research published between December 1, 2019 and November 1, 2020 with full text available in English.

Study selection

Two authors independently screened the abstracts, and any disagreements were resolved by consensus or by a third reviewer. The studies were initially screened by title and abstract to assess articles for relevance. The following populations were excluded: pediatric, end-stage kidney disease, kidney transplant, pregnant, or patients who have cancer. Additionally, case reports, reviews, and case series with less than ten patients were excluded. The full texts for the remaining studies were assessed for the following inclusion criteria: observational cohort studies, cross-sectional studies, and case series, with extractable quantitative data on patient demographics and data on AKI, ARDS, need for KRT, and mortality rate. Retrieved full-texts were independently assessed for eligibility by two authors, and disagreements were resolved through consensus.

Data extraction and quality assessment

The following information was extracted from each included study: authors' names, study sites, study design, sample size, cohort demographics (age and

sex), the prevalence of comorbidities, and ICU admission. All clinical information related to AKI incidence, ARDS, need for KRT, and the mortality rate was extracted. The primary outcome was the incidence of AKI in COVID-19 patients with and without ARDS. The secondary outcomes were the need for KRT and the mortality rate of COVID-19 patients with AKI and ARDS as well as AKI without ARDS. All studies were qualitatively evaluated based on the National Institute of Health (NIH) quality assessment tools for observational cohort/cross-sectional studies and case series studies with the quality classified as good, fair, and poor. Two independent reviewers assessed the quality of included studies (FA and MAA). Disagreement was resolved through discussion.

Data synthesis and analysis

Random-effects meta-analyses were performed to obtain pooled incidence, Risk Ratio (RR) estimates, and 95% confidence intervals (CIs) for categorical variables. The Metan and Metaprop command tools were used to analyze the incidence of AKI [12]. After the initial analysis, heterogeneity in incidence and mortality outcomes were investigated. All analyses were performed using Stata 16 and Revman 5 (Cochrane). Funnel plot were used to assess publication bias.

Results

Study selection

A total of 618 abstracts were obtained and screened, of which 63 full-text articles were assessed for eligibility and 31 met the inclusion criteria (Figure 1 shows the PRISMA flow diagram). Only two studies were cross-sectional in design [13,14], fifteen studies were cohort studies [15–29], and fourteen studies were case series [7,8,30–41].

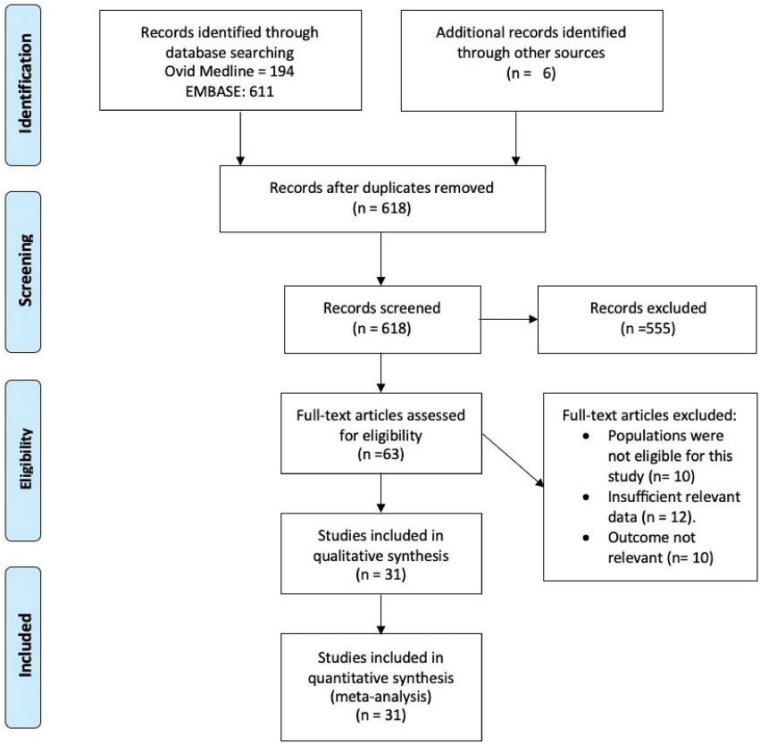


Figure 1. PRISMA flow diagram.

Study characteristics

The included studies covered 27,500 patients from hospitals in China, United States (US), United Kingdom (UK), Morocco, Italy, France, and Belgium. All studies included hospitalized patients, except Guan et al. [7], who included both inpatients and outpatients. Seven studies included only patients admitted to the ICU. All included studies reported the incidence of AKI and mortality rate; twenty-four studies reported the need for KRT; twenty-one studies reported the development of ARDS in COVID-19 patients.

The majority of patients were male (55.9%, 15378/27500). Twenty-one per cent (5934/27500) were admitted to the ICU, and 16.8% of all patients (4617/27128) died. The most common comorbidities reported were hypertension (40%) and diabetes (26%). 5.8% of patients had evidence of chronic kidney disease (CKD) at baseline. Two studies from United States [30,37] and one from Italy [27] reported CKD prevalence between 28.6% to 47.6% (See Table 1).

Definitions of AKI and ARDS were consistent among the included studies, and the same definitions were used in this review. AKI was defined based on the Kidney Disease: Improving Global Outcomes criteria (KDIGO) [42] and ARDS was defined based on Berlin definition [43].

Quality assessment and risk of bias

As the studies were case-series and cohort/cross-sectional studies, all included articles were evaluated using the NIH quality assessment tools. Domains 5 of the NIH quality assessment tool of case series and also the domain 5, 8, and 12 of the NIH quality assessment tool of observational cohort/cross-sectional studies were not applicable as they relate to the intervention, power calculation, exposure measure overtime and blinding of outcome assessment and these were not applicable to the included studies (Supplementary 3). Out of the 31 studies, 27 were judged as good quality, 3 as fair [15,19,28] and 1 as poor quality [24]. A funnel plot did not indicate major publication bias (Figure 2).

Results of individual studies

Across all 31 studies, a total of 27,500 patients were included in this review. Overall pooled AKI incidence was 26% (95% CI 19–33). Across eight studies that only included COVID-19 patients admitted to the ICU ($n = 1540$), AKI incidence was 50% (95% CI 35–65) [13,14,22,23,30,32,39,40]. Only three studies included hospitalized patients who were not admitted to the ICU, across which the pooled AKI incidence was only 25% (95% CI 21–29) [27,28,38]. In Table 2, the overall study outcomes are reported.

The majority (68.6%) of patients admitted to ICU had ARDS [13,14,22,23,26,32,39,40]. Suleyman et al. [37] carried out a case series of 463 consecutive patients with COVID-19. The mean age was 57.5 ± 16.8 years and the majority were female (55.9%), and African American (72.1%). The most common comorbidities in this cohort included hypertension (63.7%), CKD (39.3%), and diabetes (38.4%). Of these patients, 355 required hospital admission; 214 were treated in the general practice unit and 141 required ICU management. The AKI incidence was significantly higher among patients in the ICU than patients in the general practice unit (69.5% vs 28.5%. $p < 0.001$). In the UK, Gasparini et al. [14] conducted a multicentre observational study, aiming to examine the association between acute and chronic kidney disease with clinical outcomes in 372 patients with COVID-19 and admitted to ICU. The median age of this cohort was 59 (51–65) years. Most of them were male (72%) and the majority of patients were from a Black, Asian and minority ethnic (BAME) background (76%). Most patients (91%) required mechanical ventilation. A total of 168 patients (45%) developed AKI and had a high mortality rate (48%) (95% CI 41–56).

AKI incidence rate in non-ARDS COVID-19 patients

After excluding all studies that reported the presence of ARDS among their cohorts, the pooled AKI incidence across eight studies with a total of 18,185 patients, was 23% (95% CI 13–35) [14,18,19,21,27,33–36]. There was a high rate of comorbidities in these cohorts including hypertension (42%) (95% CI 35–49) [18,19,27,33–36], obesity (33%) (95% CI 26–40) [21,34,36], and diabetes (23%) (95% CI 18–28) [18,19,21,27,33–35].

Hirsch et al. [34] and Richardson et al. [36] studied 11,149 hospitalized COVID-19 patients with a mean age of 63.5 (52–75) years. Both cohorts had a high prevalence of hypertension (55.7%–56.6%) and obesity (27.1%–41.7%). Both studies reported a high incidence of AKI (24%–36.6%) and a high mortality rate in those patients who developed AKI (25.3%–35%).

Furthermore, Cheng et al. [18] studied 1392 COVID-19 patients retrospectively, aiming to assess AKI incidence. The median age of this cohort was 63 years, and they had fewer comorbidities compared to previous studies: hypertension (36%), diabetes (17%) and CKD (1.5%). Only 7% (99 patients) of this cohort developed AKI, and no patient needed KRT. Later, the same authors conducted a prospective cohort study on 701

Table 1. Characteristics of the included studies in patients with COVID-19.

Study name	Country	Study design	Demographics			Comorbidities (%)			
			N	Mean/median age (years)	Male (%)	Hypertension	Diabetes	CKD	Obesity
Aggarwal et al. [15]	US	Single-centre, retrospective cohort study	16	67 (38–95)	12 (75)	9 (57)	5 (31)	6 (38)	8 (50)
Arentz et al. [30]	US	Single-centre, retrospective case series	21	70 (43–92)	11 (52)	—	7 (33.3)	10 (47.6)	—
Argenziano et al. [31]	US	Single-centre, retrospective case series	1000	63 (50–75)	596 (59.6)	601 (60.1)	372 (37.2)	137 (13.7)	52/841 (48.3)
Ch et al. [32]	US	Multicentre, Retrospective case series	300	58.2 ± 12.6	182 (60.7)	200 (66.7)	134 (44.7)	39 (13)	163 (54)
Chen, Bai et al. [16]	China	Multicentre, Retrospective Cohort study	3309	62 (49–69)	1642 (49.62)	988 (29.9)	464 (14)	57 (1.7)	—
Chen, Liu et al. [17]	China	Multicentre, Retrospective Cohort study	792	55 (36-68)	432 (55)	215 (27)	142 (18)	26 (3.3)	—
Cheng et al. [18]	China	Single-centre, retrospective cohort study	1392	63 (50–71)	711 (51)	499 (36)	241 (17)	21 (1.5)	—
Cheng et al. [33]	China	Single-centre, Prospective case series	701	63 (50–71)	367 (52.4)	233 (33.4)	100 (14.3)	14 (2)	—
Cui et al. [19]	China	Multicentre, Retrospective cohort study	116	59	66 (56.9)	38 (32.27)	28 (24.1)	5 (4.3)	—
El Aidaoui et al. [20]	Morocco	Single-centre, retrospective cohort study	134	53 (36–64)	73 (54.5)	36 (26.9)	19 (14.2)	3 (2.2)	—
Fisher et al. [21]	US	Multicentre, Retrospective cohort study	3345	64.4 ± 16.4	1776 (53.1)	—	906 (27.1)	409 (12.1)	1351 (42.9)
Fominskiy et al. [22]	Italy	Single-centre, Prospective cohort study	99	61	83 (83.8)	34 (52.9)	12 (13.6)	5 (5)	22 (22.2)
Gasparini et al. [14]	UK	Multicentre, Retrospective cross-sectional study	372	59 (51–65)	269 (72)	—	—	—	—
Grimaldi et al. [23]	France/Belgium	Multicentre, Retrospective cohort study	415	64 ± 10	321 (77)	235 (57)	—	33 (7.9)	—
Guan et al. [7]	China	Multicentre, Retrospective case series	1099	47 (35–58)	640 (58.2)	165 (15)	81 (7.4)	8 (0.7)	—
Hirsch et al. [34]	US	Multicentre, Retrospective case series	5449	64 (52 − 75)	3317 (60.9)	3037(55.7)	1797 (33)	—	1475 (27.1)
Hong et al. [24]	China	Single-centre, retrospective cohort study	98	55.4 ± 17.1	38 (38.8)	30 (30.6)	9 (9.2)	—	—
Huang et al. [8]	China	Single-centre, Prospective case series	41	49 (41–58)	30 (73.2)	6 (15)	8 (20)	—	—
Okoh et al. [25]	US	Single-centre, retrospective cohort study	251	62 (49–74)	129 (51)	175 (70)	115 (46)	46 (18)	120 (48)
Pei et al. [35]	China	Single-centre, retrospective case series	333	56.3 ± 13.4	182 (54.7)	107 (32.2)	76 (22.9)	—	—
Qian et al. [26]	China	Single-centre, retrospective cohort study	37	55 (48–68)	26 (68.4)	14 (36.8)	8 (21.1)	1 (2.7)	—
Richardson et al. [36]	US	Multicentre, Retrospective case series	5700	63 (52–75)	3437 (60.3)	3026 (56.6)	1808 (33.8)	268 (4.7)	1737 (41.7)
Russo et al. [27]	Italy	Single-centre, retrospective cohort study	777	70 ± 16	59 (7.6)	385 (49.5)	123 (15.8)	222 (28.6)	—
Suleyman et al. [37]	US	Single-centre, retrospective case series	463	57.5 ± 16.8	204 (44)	295 (63.7)	178 (38.4)	182 (39.3)	262 (57.6)
Yang et al. [38]	China	Single-centre, retrospective case series	52	59.7 ± 13.3	35 (67)	—	9 (17)	—	—
Yu et al. [13]	China	Multicentre, Prospective cross-sectional study	226	64 (57–70)	139 (61.5)	96 (42.5)	47 (20.8)	—	—
Zahid et al. [28]	US	Single-centre, retrospective cohort study	469	66 (55 − 75)	268 (57.1)	232 (68.6)	219 (46.7)	50 (11)	—
Zangrillo et al. [39]	Italy	Single-centre, retrospective case series	73	61 (54–69)	61 (83.6)	39 (52.9)	10 (13.6)	—	—
Zheng et al. [40]	China	Single-centre, retrospective case series	34	66 (58 − 76)	23 (67.6)	22 (64.7)	8 (23.5)	2 (5.9)	—
Zhou, Yang et al. [41]	China	Multicentre, Retrospective case series	195	66 (56–76)	130 (66.7)	89 (45.6)	55 (28.2)	—	—
Zhou, Yu et al. [29]	China	Multicentre, Retrospective Cohort study	191	56 (46–67)	119 (62)	58 (30)	36 (19)	2 (1)	—

Values are median (IQR), mean (SD) or number (proportion).
N: number; CKD: Chronic kidney disease.

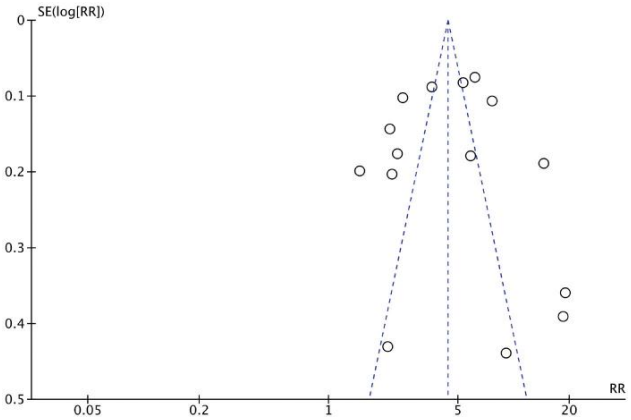


Figure 2. Funnel plot for detection of publication bias.

Table 2. Outcomes of the included studies in patients with COVID-19.

Study name	Country	N	Admitted to ICU	Incidence AKI	ARDS	Need for KRT	Mortality Overall mortality	AKI	ARDS	KRT
Aggarwal et al. [15]	US	16	8 (50)	11 (69)	5 (31)	–	3 (19)	–	–	–
Arentz et al. [30]	US	21	–	4 (19.1)	20 (95.2)	–	11 (52.4)	–	–	–
Argenziano et al. [31]	US	1000	236 (23.6)	288/850 (33.9)	299/850 (35.2)	117/850 (13.8)	211 (21.1)	–	–	–
Ch et al. [32]	US	300	300 (100)	230 (76.7)	275 (91.7)	133 (44.3)	157(52.3)	138 (60)	155 (56.4)	82 (61.7)
Chen, Bai et al. [16]	China	3309	1036 (31.3)	401 (12.1)	1325 (40)	–	307 (9.3)	–	–	–
Chen, Liu et al. [17]	China	792	94 (12)	46 (6)	104 (13)	11 (1.4)	68 (8.6)	32 (69.6)	61 (58.6)	11 (100)
Cheng et al. [18]	China	1392	140 (10)	99 (7)	–	–	199 (14)	71 (71.7)	–	–
Cheng et al. [33]	China	701	73 (10.4)	36 (5.1)	–	–	113 (16.1)	–	–	–
Cui et al. [19]	China	116	NA	21 (18.1)	–	–	18 (15.5)	12 (57.1)	–	–
El Aidaoui et al. [20]	Morocco	134	45 (33.6)	8 (6)	13 (9.7)	8 (6)	14 (10.4)	8 (100)	4 (30.8)	–
Fisher et al. [21]	US	3345	438 (13.1)	1903 (56.9)	–	164 (4.9)	775 (23.2)	641 (33.7)	–	–
Fominskiy et al. [22]	Italy	99	99 (100)	72 (72.7)	–	17 (17.7)	33 (33.3)	28 (38.9)	–	9 (52.9)
Gasparini et al. [14]	UK	372	372 (100)	168 (45)	–	121 (32.5)	139 (37)	81 (48)	–	–
Grimaldi et al. [23]	France /Belgium	415	415 (100)	231 (56)	415 (100)	82 (19.76)	166 (40)	121 (52.4)	166 (40)	49 (59.7)
Guan et al. [7]	China	1099	33 (16.2)	6 (0.5)	37 (3.4)	9 (0.8)	15 (1.4)	–	–	–
Hirsch et al. [34]	US	5449	1395 (25.6)	1993 (36.6)	–	285 (5.2)	888 (16.3)	694 (34.8)	–	157 (55.1)
Hong et al. [24]	China	98	13 (13.3)	9 (9.2)	18 (18.4)	3 (3.1)	5 (5.1)	–	–	–
Huang et al. [8]	China	41	13 (32)	3 (7)	12 (29)	3 (7)	6 (14.6)	–	–	–
Okoh et al. [25]	US	251	82 (33)	52 (21)	82 (33)	52 (21)	97 (38.6)	–	–	–
Pei et al. [35]	China	333	189 (56.8)	35 (10.5)	–	6 (1.8)	29 (8.7)	20 (57.1)	–	–
Qian et al. [26]	China	37	37 (100)	8 (21.6)	11 (29.7)	3 (8.1)	1 (2.7)	–	–	–
Richardson et al. [36]	US	5700	373 (6.5)	1370 (24)	–	225 (3.9)	553 (9.7)	347 (25.3)	–	78 (34.7)
Russo et al. [27]	Italy	777	–	176 (22.6)	–	21 (2.8)	275 (35)	111 (63.1)	–	–
Suleyman et al. [37]	US	463	141 (39.7)	159/355 (44)	111/355 (31.3)	25/355 (7)	72 (16)	–	–	–
Yang et al. [38]	China	52	–	15 (29)	35 (67)	9 (17)	32 (61·5)	12 (80)	26 (74.3)	8 (88.9)
Yu et al. [13]	China	226	226 (100)	57 (25.2)	161 (71.2)	24 (10.6)	87 (38.5)	–	–	–
Zahid et al. [28]	US	469	–	128 (27.3)	206 (44)	22 (4.7)	188 (40.1)	91 (71.1)	–	18 (81.8)
Zangrillo et al. [39]	Italy	73	73 (100)	55 (75.3)	73 (100)	16 (21.9)	19 (26)	–	19 (26)	–
Zheng et al. [40]	China	34	34 (100)	7 (20.6)	33 (97.1)	5 (14.7)	0 (0)	–	–	–
Zhou, Yang et al. [41]	China	195	19 (9.8)	58 (29.7)	162 (83.1)	26 (13.3)	82 (42)	–	–	–
Zhou, Yu et al. [29]	China	191	50 (26)	28 (15)	59 (31)	10 (5)	54 (28.3)	27 (96)	50 (84.7)	10 (100)

Values are number (proportion).
N: number; ICU: Intensive care unit; AKI: Acute Kidney Injury; ARDS: Acute respiratory distress syndrome; KRT: Kidney Replacement Therapy.

COVID-19 patients [33]. The median age was 63 years, and 33.4% of those patients had hypertension, 17% had diabetes, and only 2% had CKD. The incidence of AKI among those patients was 5.1%, and the overall mortality was 16.1%.

AKI incidence rate in ARDS COVID-19 patients

Twenty-two studies included COVID-19 patients with ARDS. While these cohorts included >90% of patients with ARDS, the pooled AKI incidence was 67% (95% CI 57–76) [22,23,28,32,39,40]. Grimaldi et al. [23] examined 415 COVID-19 patients with moderate-to-severe ARDS who were invasively ventilated and treated with different antiviral strategies. Patients were aged between 50 and 70 years. Most were males ($n = 321$, 77%) with mean body mass index (BMI) (30 ± 5 kg/m2), and hypertension was the most frequent comorbidity among the cohort ($n = 235$ patients; 57%). The findings of this study showed that 56% of patients developed AKI. However, these findings might be affected by the different antiviral therapies being used. Zangrillo et al. [39] also assessed 73 COVID-19 patients with ARDS; they were mostly male (83.6%) with a median age of 61 years. The authors revealed that 75.3% of the population developed AKI. The most frequent comorbidities were hypertension (52.9%), obesity (>25%) and diabetes (13.6%). Fominskiy et al. [22] studied 99 confirmed COVID-19 patients who were admitted to ICU and invasively ventilated. The aim was to assess the clinical characteristics, predictors of AKI, and KRT need. The median age was 61 years, and the most frequent comorbidities were hypertension (52.9%) and obesity (22.2%). Since all patients were invasively ventilated, it is likely that a substantial proportion of these patients had ARDS. A total of 72.7% of those patients developed AKI.

Ch et al. [32] studied 300 COVID-19 patients admitted to the ICU with a mean age (+SD) of 58.2 ± 12.6 years. The majority (91.7%) of participants had ARDS, and 76.7% of patients presented either with AKI on admission or developed AKI during the course of illness. Increasing age (RR: 1.02; 95% CI 1.01–1.03)) and male sex (48.4% vs. 23.8%; RR: 1.68; 95% CI 1.2–2.3) were also risk factors for presentation with AKI. Both Arentz et al. [30] and Zheng et al. [40] carried out similar case series that included 55 participants to assess the clinical characteristics and outcomes of confirmed COVID-19 patients admitted to the ICU. The mean age was between 66 to 70 years. Although the majority (96.36%) of participants in both studies had ARDS, AKI incidence was ranged from 19.1% to 20.6%. The most common comorbidities reported by Arentz et al. [30] were CKD (47.6%) and congestive heart failure (42.9%), and the most frequent comorbidity reported by Zheng et al. [40] was hypertension (64.7%).

Need for KRT

Twenty-five studies reported the need for KRT and only 6% of all patients required KRT (Table 2). After analyzing the studies that reported patients with ARDS, we found that 10% of patients required KRT across nineteen studies. Nevertheless, the need for KRT was only 5% among studies that did not report ARDS incidence [14,21,27,34–36]. A higher incidence of AKI (76.7%) and need for KRT (44.3%) were reported by Ch et al. [32] who only included patients who were admitted to the ICU, of which >90% developed ARDS.

Mortality

The overall mortality across all cohorts was 16.9%. However, the mortality was higher (38.7%) when the studies enrolled only COVID-19 patients admitted to the ICU [13,14,22,23,26,32,39,40]. The mortality rate was significantly higher among cohorts comprising >90% of ARDS patients. For instance, ARDS patients comprised >90% of cohorts studied by both Ch et al. [32] and Arentz et al. [30], and the mortality was 52.3 and 52.4%, respectively. AKI mortality was reported across eighteen studies. Across eight studies that included patients with ARDS, AKI mortality was 60.3% (range, 52.4%–100%) [13,17,20,22,23,29,32,39]. The remaining eight studies did not report ARDS incidence and revealed that AKI mortality was 34.2% (range, 25.3%–63%) [14,18,19,21,27,34–36].

Synthesis of results

A total of 27,500 patients from 31 studies were included in the meta-analysis of AKI incidence amongst all COVID-19 cohorts. By using a random-effects model, the pooled incidence of AKI was 26% (95% CI 19–33; $I^2 = 99.38\%$; $p < 0.001$; Figure 3).

A total of 808 COVID-19-ARDS patients from five studies were included. The pooled incidence of AKI in ARDS patients was 59% (95% CI 46–71; $I^2 = 90.26\%$; $p < 0.001$; Figure 4A). A total of 174 COVID-19 patients without ARDS were included from three studies. The pooled incidence of AKI in this population was 6% (95% CI 0–31; $I^2 = 93.30\%$; $p < 0.001$; Figure 4B).

The pooled need for KRT was assessed on a total of 590 ARDS patients from four studies and 174 non-ARDS patients from three studies. In ARDS patients, the pooled need for KRT was 20% (95% CI 17–23; $I^2 = 0$; $p = 0.84$; Figure 5A) and only 1% (95% CI 0–5; $I^2 = 56.41\%$; $p = 0.10$; Figure 5B) in non-ARDS patients.

The AKI mortality was analyzed based on the data of 19,888 patients available from 16 studies. Development

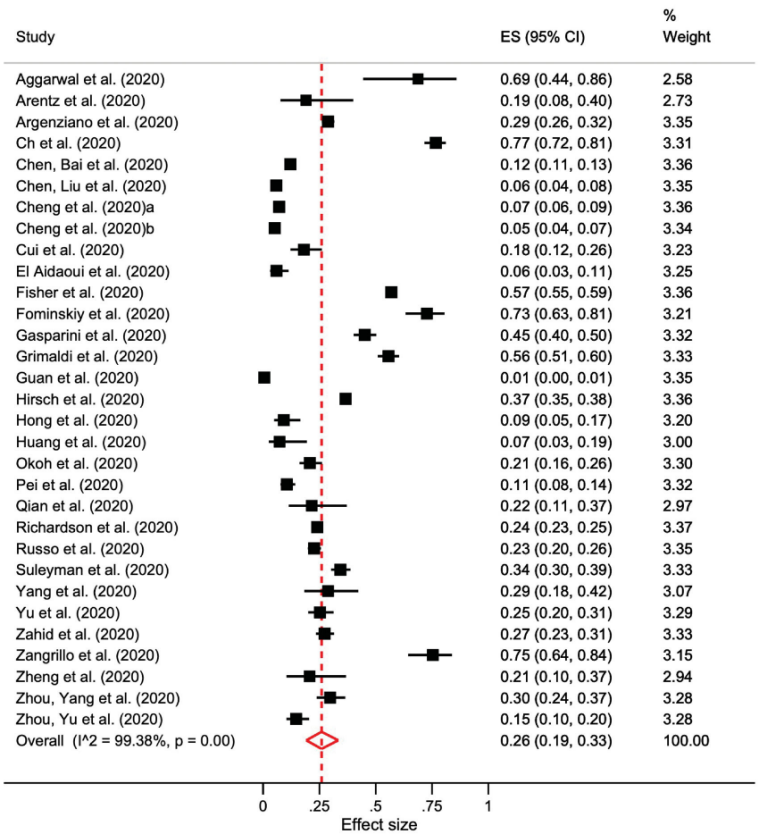


Figure 3. Forest plot of pooled AKI incidence in overall cohorts.

of AKI was associated with significantly higher mortality among COVID-19 patients, with RR of 4.46 (95% CI 3.31–6; $I^2 = 95\%$; $p < 0.00001$; Figure 6) in a random-effects model.

Discussion

To the authors' knowledge, this is the first systematic review to assess and compare the incidence of AKI between COVID-19 patients with and without ARDS. Based on the literature, the incidence of AKI in ARDS patients prior to the emergence of COVID-19 was approximately 35–50%, and was associated with a high mortality rate which significantly increased by almost two-fold in the ICU [44,45]. For instance, a retrospective study examined a cohort of 634 ARDS patients and revealed an AKI incidence rate of 68.3% after ARDS onset [46]. However, AKI incidence may increase significantly in COVID-19 patients after the onset of ARDS, suggesting lung-kidney crosstalk as the dominant cause of kidney injury [47].

This review shows that most of the included studies reported a higher incidence of AKI in COVID-19 patients who developed ARDS. Across all cohorts with confirmed COVID-19 infection from China, US, UK, Morocco, Italy, France, and Belgium, we identified a wide range of AKI incidence which ranged from 0.5% to 76.7%. However, this may reflect the variety of disease severity thresholds for hospitalization all over the world and potential

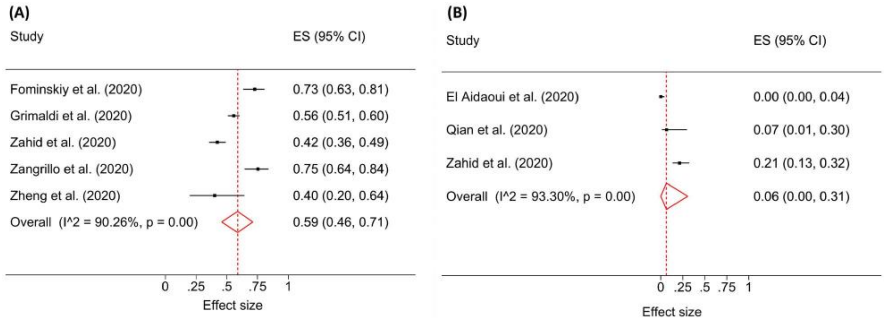


Figure 4. Forest plot of the pooled AKI incidence showing the increased rate in ARDS (A) compared to non-ARDS (B) cohorts.

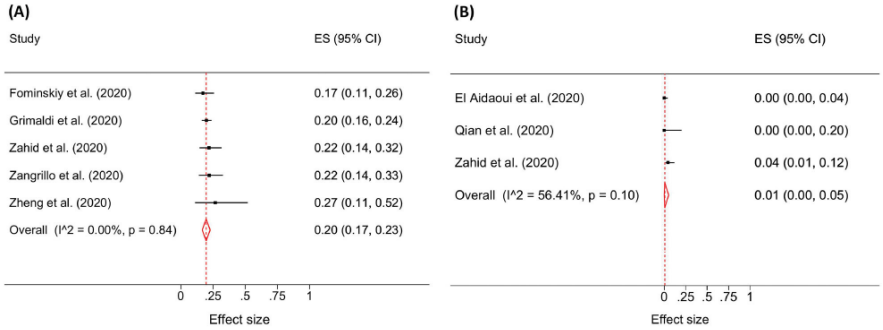


Figure 5. Forest plot demonstrating the need for KRT in ARDS (A) compared with non-ARDS (B) COVID-19 cohort.

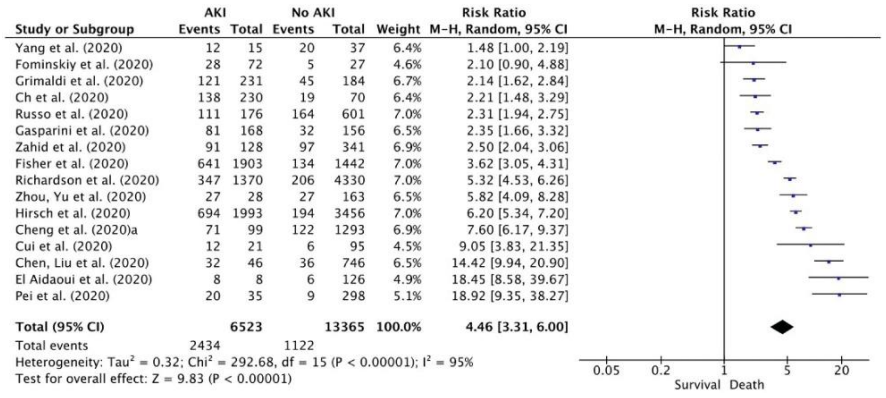


Figure 6. Forest plot for mortality risk among patients with AKI associated with COVID-19.

differences in clinical practice for monitoring kidney dysfunction.

Our findings show that COVID-19 patients admitted to the ICU had a higher incidence of AKI; however, most (68.6%) of those patients also had ARDS. This finding is consistent with that of Xu et al. [1] who studied 239 critically ill COVID-19 patients admitted to the ICU and found that 49.8% of those patients developed AKI, and 68.6% had ARDS.

We identified that a high AKI incidence was most commonly reported when >90% of patients in the cohort had ARDS [22,23,30,32,39–41]. Additionally, this meta-analysis comparing ARDS with non-ARDS COVID-19 cohorts revealed that AKI incidence was significantly higher among COVID-19 patients with ARDS (59% vs 6%, $p < 0.001$). These findings are consistent with a multicentre study conducted in nine ICUs located in Europe, which found that 50% of COVID-19 patients with ARDS developed AKI [48].

Although some studies did not enroll COVID-19 patients with ARDS, a few studies demonstrated a high incidence of AKI that ranged from 5.1% to 56.9% [14,18,21,27,33–36]. Based on the literature, patients with a history of CKD are more likely to have comorbidities that have been identified as risk factors for poor outcomes, such as older age, hypertension, diabetes mellitus, cardiovascular disease, and this may be explained by our findings [49]. Additionally, Nadim et al. suggested that the advanced age, CKD, and high prevalence of other comorbidities (e.g., hypertension, diabetes, obesity, and heart failure) are all linked to worse outcomes and are risk factors for the development of AKI in patients with COVID-19 [50].

The metabolic syndrome is a cluster of risk factors (diabetes mellitus, hypertension, obesity) for developing cardiovascular disease and kidney abnormalities [51]. The consequences of the metabolic syndrome on kidney functions in COVID-19 patients are poorly descried Lohia et al. [52] investigated the association between metabolic syndrome and severe disease outcomes among 1871 patients with confirmed COVID-19 diagnosis. Author found that patients with metabolic syndrome had significantly increased in the ICU admission (odds ratio [OR], 1.68; 95% CI, 1.36-2.08; $p < .001$), and need for mechanical ventilation (OR, 1.90; 95% CI, 1.52-2.37; $p < .001$), and mortality rate (OR, 1.40; 95% CI, 1.11-1.75; $p = .004$). Patients with CKD were higher in the metabolic syndrome cohort compared to the none-metabolic syndrome cohort (14.7% vs. 9%; $p < .001$). Metabolic syndrome cohort may be at higher risk of developing AKI if they contract COVID-19, and this risk may be by background CKD. Chen et al. [53] recruited >6000 participants to examine the association between the metabolic syndrome and kidney impairment, and they found that the multivariate-adjusted risk for both CKD (defined as a GFR of <60 mL/min per 1.73 m2) and microalbuminuria was significantly higher in those with the metabolic syndrome compared to participants without metabolic syndrome (Odds ratio 2.60, 95% CI 1.68–4.03 and 1.89, CI 1.34–2.67, respectively). Also, they revealed that risk increased progressively with the number of the metabolic syndrome's components observed in each patient.

A meta-analysis comparing ARDS with non-ARDS COVID-19 cohorts showed the need for KRT was also higher in ARDS cohorts (20% vs 1%). Across all studies which reported the need for KRT, we observed a higher need for KRT among patients with a high incidence of AKI as reported by Ch et al. [32] and Fominskiy et al. [22]. However, it is unclear from these studies whether KRT was used to treat fluid overload, end-stage kidney disease, or patients with AKI alone.

The mortality rate was significantly increased in critically ill patients if they had a high incidence of AKI or ARDS [23,32]. In our meta-analysis, the overall mortality among patients with AKI was significantly higher than those without AKI ($p < 0.00001$). In both Ch et al. [32] and Arentz et al. [30], AKI and ARDS development was associated with a high mortality rate. Ch et al. [32] found that the AKI incidence was associated with a 25% increased risk of death (RR: 1.25; 95% CI: (1.02, 1.52)). These findings are consistent with previously published research, which found that severe AKI in patients with COVID-19 is associated with a high mortality rate [54]. Additionally, in the population of Ch et al. [32] high rates of comorbidities such as obesity (85.7% with BMI >25) and hypertension (66.7%) were also linked with increased mortality rate. Both Gasparini et al. [14] and Fominskiy et al. [22] also found that patients with AKI had a higher mortality rate compared to patients without AKI. A possible explanation for the higher mortality rate in the previous two studies is that each study recruited >90% critically ill individuals who were invasively ventilated in ICU.

Limitations

The main limitation of this study is that most of the selected studies were of the retrospective design, making them susceptible to selection bias. There was limited data on AKI patients' characteristics among included studies, such as urine output status, the need for KRT and the grade of AKI. This information is essential to define the severity and recoverability of AKI.

Moreover, most cohorts were from China and the United States, and a small amount from Africa and Europe, which does reduce the generalization to other countries. The heterogeneity between studies was high; consequently, most of the analyses were interpreted based on a random-effects model. Furthermore, given the rapid, constant expansion of COVID-19 research, several studies had limitations in their description of details and relatively short periods of follow-up. Finally, we cannot be certain that all relevant studies were captured, despite a detailed, comprehensive search strategy.

Conclusion

A higher incidence of AKI was most common among COVID-19 cohorts admitted to the ICU and was associated with the development of ARDS. Also, increased age, male sex, and preexisting comorbidities (e.g., hypertension, diabetes, obesity, and CKD) were associated with significantly worse outcomes, which may be considered risk factors for developing AKI and increased mortality among COVID-19 patients. Therefore, healthcare providers should be aware of kidney dysfunction among those patients, especially those who are elderly with multiple comorbidities. This may ultimately lead to using appropriate diagnostic tools and treatment strategies to avoid additional damage to the kidneys and providing adequate kidney support when needed.

Author contributions

FA and JP conceived, planned and analyzed the data, and made a major contribution in writing the manuscript. FA and MAA performed abstract screening, full-text screening and quality assessment. FA and RM planned and performed searching strategy and data synthesis. MAA and RM contributed to data analysis and writing the manuscript. MNB and DRT reviewed the manuscript. All authors have read and approved the manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

All data relevant to the study are included in the article or uploaded as supplementary information.

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7.2. Protocol Registry In PROSPERO

PROSPERO
International prospective register of systematic reviews

NHS
National Institute for
Health Research

UNIVERSITY of York
Centre for Reviews and Dissemination

Systematic review

A list of fields that can be edited in an update can be found here

[1.* Review] title.

Give the title of the review in English

The incidence of Acute Kidney Injury among adult COVID-19 patients with and without Acute Respiratory Distress Syndrome: systematic review

2. Original language title.

For reviews in languages other than English, give the title in the original language. This will be displayed with the English language title.

3. * Anticipated or actual start date.

Give the date the systematic review started or is expected to start.

01/11/2020

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

01/03/2021

5. [1.* Stage] of review at time of this submission.

This field uses answers to initial screening questions. It cannot be edited until after registration.

Tick the boxes to show which review tasks have been started and which have been completed.

Update this field each time any amendments are made to a published record.

The review has not yet started: No

Review stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Provide any other relevant information about the stage of the review here.

6.1 * Named contact.

The named contact is the guarantor for the accuracy of the information in the register record. This may be any member of the review team.

Faraj K Alenezi

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Mr Alenezi

7. * Named contact email.

Give the electronic email address of the named contact.

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Give the full institutional/organisational postal address for the named contact.

294 Orion Building, 90 Navigational Street, Birmingham, UK, B5 4AE

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

07988887693

10.1 * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

University of Birmingham

Organisation web address:

https://www.birmingham.ac.uk

11. * Review team members and their organisational affiliations.

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong. **NOTE: email and country now MUST be entered for each person, unless you are amending a published record.**

Mr Faraj Alenezi. University of Birmingham
Mr Mohammed Almeshari. King Saud University
Dr Raul Mahida. University of Birmingham
Dr Mansoor N. Bangash. University Hospital of Birmingham NHS Foundation Trust
Professor David Thickett. University of Birmingham
Dr Jaimin Patel. University of Birmingham

12. * Funding sources/sponsors.

Details of the individuals, organizations, groups, companies or other legal entities who have funded or sponsored the review.

King Saud bin Abdulaziz University for Health Sciences

University of Birmingham

Grant number(s)

State the funder, grant or award number and the date of award

13. * Conflicts of interest.

List actual or perceived conflicts of interest (financial or academic).

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country must be completed for each person, unless you are amending a published record.**

15. * Review question.

State the review question(s) clearly and precisely. It may be appropriate to break very broad questions down

.

into a series of related more specific questions. Questions may be framed or refined using PI(E)COS or similar where relevant.

What is the incidence rate of acute kidney injury among adult COVID-19 patients with and without ARDS?

16. Searches.

State the sources that will be searched (e.g. Medline). Give the search dates, and any restrictions (e.g. language or publication date). Do NOT enter the full search strategy (it may be provided as a link or attachment below.)

Literature search will be conducted using Medical Subject Heading (MeSH) terms and free text words related to incidence rate of acute kidney injury among adult COVID-19 patients. We will search MEDLINE (OVID interface, 1948 onwards) and EMBASE (OVID interface, 1974 onwards).

The recently completed and ongoing clinical trials will also be searched through ClincalTrials.gov. In addition, PROSPERO will be searched for ongoing and recently completed systematic reviews.

A snowballing technique will be adopted, which involves scanning reference lists of relevant reviews and included studies in order to ensure literature saturation and to gather the most relevant studies.

The search strategy will be specifically designed to obtain all available published and unpublished evidence through the databases and sources mentioned above. The search will be limited to December 2019 onwards. The specific search strategy will be created by the systematic review team, with assistance from the medical school librarian at the University of Birmingham.

17. URL to search strategy.

Upload a file with your search strategy, or an example of a search strategy for a specific database, (including the keywords) in pdf or word format. In doing so you are consenting to the file being made publicly accessible. Or provide a URL or link to the strategy. Do NOT provide links to your search **results**.

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied in your systematic review.

Acute kidney injury in adults patients hospitalized with COVID-19 and ARDS or none ARDS

19. * Participants/population.

Specify the participants or populations being studied in the review. The preferred format includes details of both inclusion and exclusion criteria.

Adults (18 years) with AKI and COVID-19 , either with ARDS or none ARDS

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the interventions or the exposures to be reviewed. The preferred format includes details of both inclusion and exclusion criteria.

COVID-19 patients with AKI and ARDS. The term "ARDS" was defined based on Berlin criteria.

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the intervention/exposure will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

Incidence of AKI among adult COVID-19 patients without ARDS

22. * Types of study to be included.

Give details of the study designs (e.g. RCT) that are eligible for inclusion in the review. The preferred format includes both inclusion and exclusion criteria. If there are no restrictions on the types of study, this should be stated.

Included studies:

Cross-sectional

Longitudinal

Case-series 10 patients

Excluded studies:

Studies on pediatric, pregnant, kidney transplant, and cancer patients or patients with end-stage kidney disease.

Case report

Review articles

Background articles

23. Context.

Give summary details of the setting or other relevant characteristics, which help define the inclusion or exclusion criteria.

24. *Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

Primary outcome of interest is Incidence of acute kidney injury in both groups (those COVID-19 patient who develop ARDS versus those COVID-19 patients who do not develop ARDS.

Measures of effect

Please specify the effect measure(s) for you main outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

Relative risk

25. *Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state ‘None’ or ‘Not applicable’ as appropriate to the review

Need for Renal Replacement Therapy (RRT).Mortality rate.

Measures of effect

Please specify the effect measure(s) for you additional outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

Relative risk

26. *Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

Studies abstracts and full texts will be screened by 2 reviewers independently using the predefined criteria of

Data will be extracted using a piloted form by the first reviewer and checked="checked" value="1" for accuracy by the second reivewer.

The main data will be extracted:

Baseline characteristics data (age and sex)

Comorbidities (such as hypertension, diabetes, chronic obstructive pulmonary disease (COPD) , cardiovascular disease and Kidney disease),

Incidence of acute kidney injury (AKI)

presence of acute respiratory distress syndrome (ARDS)

Need for Renal Replacement Therapy (RRT).

Mortality rate.

17. * Risk of bias (quality) assessment.

State which characteristics of the studies will be assessed and/or any formal risk of bias/quality assessment tools that will be used.

All studies selected for inclusion will be assessed for risk of bias using a pre-specified tool depending on the study design.

The reviewers will independently check each selected article to minimize bias, and any disagreements will be resolved by a third reviewer.

Information from the risk of bias assessments will be utilized when synthesising the data to explain any differences in study results, and to comment on the reliability of the conclusions that arise from the analysis.

18. * Strategy for data synthesis.

Describe the methods you plan to use to synthesise data. This **must not be generic text** but should be **specific to your review** and describe how the proposed approach will be applied to your data. If meta-analysis is planned, describe the models to be used, methods to explore statistical heterogeneity, and software package to be used.

The recommendations of Cochrane collaboration will be followed in data synthesis.

Studies will be grouped based on presence of ARDS among COVID-19 patients with AKI. A narrative synthesis will be carried out to assess the incidence of AKI in both groups (those COVID-19 patient who develop ARDS versus those COVID-19 patients who do not develop ARDS. This will help in getting more

insight on the impact of developing ARDS with COVID-19 patients on kidney function.

Descriptive analyses will be reported, whereas a meta-analysis will be conducted only if possible.

Risk ratio will be reported as the main outcome using Revman 5. I^2 will be used to assess and report statistical heterogeneity. .

29. * Analysis of subgroups or subsets.

[29.change]

State any planned investigation of 'subgroups'. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach.

If the necessary data are available, subgroup analysis will be conducted as appropriate.

30. * Type and method of review.

Select the type of review, review method and health area from the lists below.

Type of review

Cost effectiveness

No

Diagnostic

No

Epidemiologic

No

Individual patient data (IPD) meta-analysis

No

Intervention

No

Living systematic review

No

Meta-analysis

No

Methodology

No

Narrative synthesis

No

Network meta-analysis

No

Pre-clinical

No

Prevention
No

Prognostic
No

Prospective meta-analysis (PMA)
No

Review of reviews
No

Service delivery
No

Synthesis of qualitative studies
No

Systematic review
Yes

Other
No

Health area of the review

Alcohol/substance misuse/abuse
No

Blood and immune system
No

Cancer
No

Cardiovascular
No

Care of the elderly
No

Child health
No

Complementary therapies
No

COVID-19
Yes

For COVID-19 registrations please tick all categories that apply. Doing so will enable your record to appear in area-specific searches

Chinese medicine
Diagnosis
Epidemiological
Genetics
Health impacts
Immunity
Long COVID
Mental health
PPE
Prognosis
Public health intervention
Rehabilitation
Service delivery
Transmission
Treatments
Vaccines
Other

Crime and justice
No

Dental
No

Digestive system
No

Ear, nose and throat
No

Education
No

Endocrine and metabolic disorders
No

Eye disorders
No

General interest
No

Genetics
No

Health inequalities/health equity
No

Infections and infestations
No

International development

No

Mental health and behavioural conditions
No

Musculoskeletal
No

Neurological
No

Nursing
No

Obstetrics and gynaecology
No

Oral health
No

Palliative care
No

Perioperative care
No

Physiotherapy
No

Pregnancy and childbirth
No

Public health (including social determinants of health)
No

Rehabilitation
No

Respiratory disorders
Yes

Service delivery
No

Skin disorders
No

Social care
No

Surgery
No

Tropical Medicine

No

Urological

No

Wounds, injuries and accidents

No

Violence and abuse

No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.

English

There is an English language summary.

32. * Country.

Select the country in which the review is being carried out. For multi-national collaborations select all the countries involved.

England

33. Other registration details.

Name any other organisation where the systematic review title or protocol is registered (e.g. Campbell, or The Joanna Briggs Institute) together with any unique identification number assigned by them. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

34. Reference and/or URL for published protocol.

If the protocol for this review is published provide details (authors, title and journal details, preferably in Vancouver format)

Add web link to the published protocol.

Or, upload your published protocol here in pdf format. Note that the upload will be publicly accessible.

No I do not make this file publicly available until the review is complete

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

.

Do you intend to publish the review on completion?

Yes

Give brief details of plans for communicating review findings.?

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords help PROSPERO users find your review (keywords do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

Acute Kidney Injury; Adults; COVID-19; SARS-CoV-2, Acute respiratory distress syndrome.

37. Details of any existing review of the same topic by the same authors.

If you are registering an update of an existing review give details of the earlier versions and include a full bibliographic reference, if available.

38. Current review status.

[38. Changes]

Update review status when the review is completed and when it is published.New registrations must be ongoing so this field is not editable for initial submission.

Please provide anticipated publication date

Review_Completed_published

39. Any additional information.

[39. Changes]

Provide any other information relevant to the registration of this review.

40. Details of final report/publication(s) or preprints if available.

[40. Details]

Leave empty until publication details are available OR you have a link to a preprint (NOTE: this field is not editable for initial submission). List authors, title and journal details preferably in Vancouver format.

Give the link to the published review or preprint.

https://www.tandfonline.com/doi/full/10.1080/0886022X.2021.2011747

7.3. PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4

Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	2
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	2
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	3
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	4

Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	11

7.4. Quality assessment of included studies



Figure 7.5.1: Quality assessment of included studies based on the NHLBI Observational Cohort/ Cross-Sectional Studies Quality Assessment Tool.

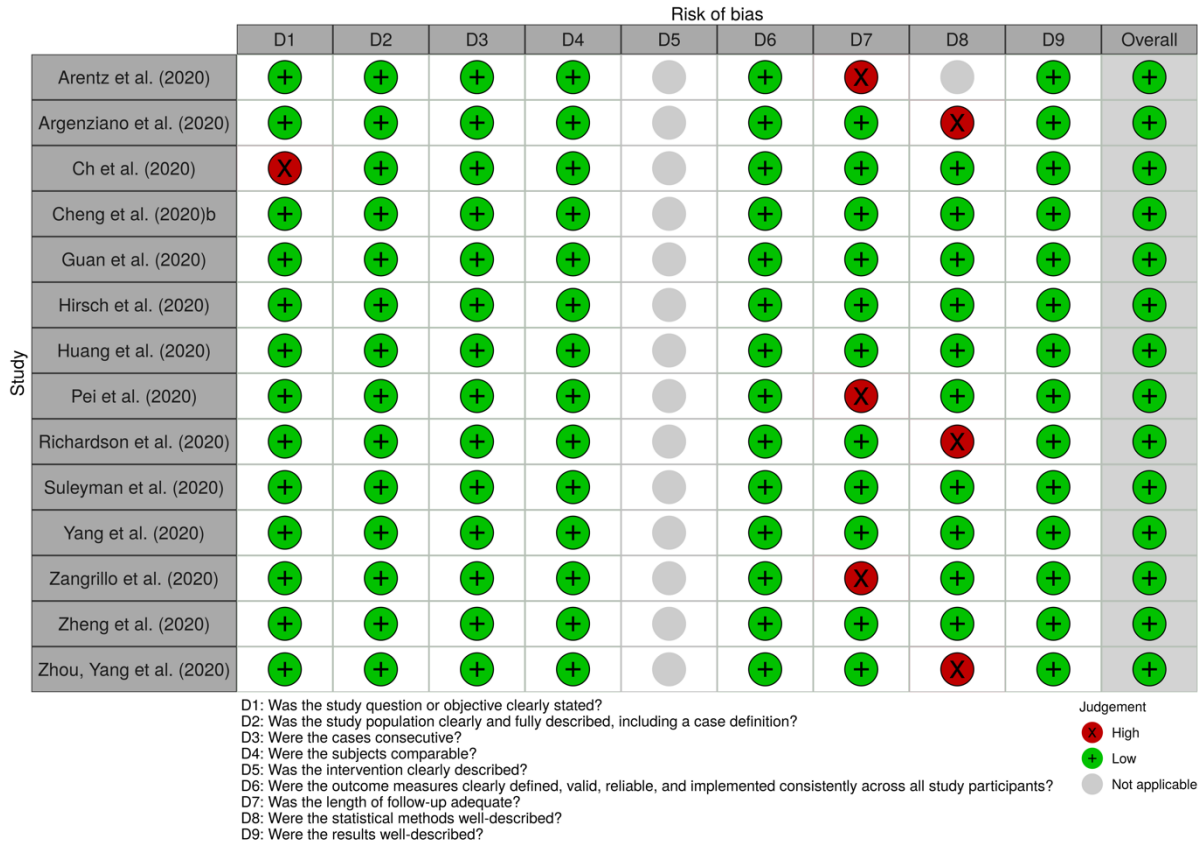
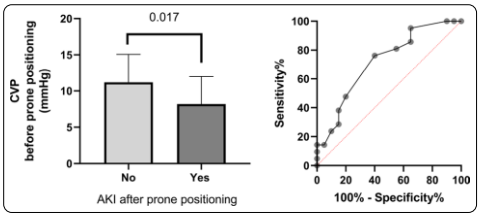


Figure 7.5.2: Quality assessment of included studies based on the NHLBI Case Series Quality Assessment Tool.

7.5. Published Abstract in Intensive Care Medicine Experimental Journal.

Results: We analyzed data from 41 patients. No patient had kidney diseases before ICU. Twenty/41 patients (48%) developed AKI according to the KDIGO criteria, and the diagnosis was made at 27.8 (± 19.6) hours after starting PP. No statistically significant differences were found among the two groups in age, BMI, SAPS-II, PaO2/FiO2 ratio at admission, nor in serum lactates, Hgb, fluid balance and diuresis at admission and 24 h before pronation. Nevertheless, CVP was different between the groups (AKI patients: 8.2 ± 3.7; non-AKI patients: 11.2 ± 3.9) and the difference was statistically significant (p = 0.017). A logistic regression was performed to evaluate the impact of prepronation serum lactates, CVP, total fluid balance and Hct on AKI development. The model was statistically significant (p < 0.05) and correctly classified 73.2% of cases with CVP having the best contribution in the model (p = 0.04). The ROC analysis for CVP revealed a good classifying capability, with an AUC of 0.72 (p = 0.012) (Fig. 1, right panel).



Conclusion: AKI can be temporally associated to PP in COVID-19 ARDS patients undergoing IMV and may be related to hypovolemia. The CVP before PP can potentially predict PP-related AKI with a good accuracy.

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001162

The Risk Factors of Major Adverse Kidney Events at 6-months among COVID-19 Patients with ARDS

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Introduction: Acute kidney injury (AKI) is one of the most common complications among hospitalised COVID-19 patients who develop acute respiratory distress syndrome (1, 2). Major adverse kidney events (MAKEs), a composite of renal replacement therapy (RRT), or decline in eGFR of < 75% of baseline, or all-cause mortality, is a validated long term measure of the impact of AKI on patient-related outcomes (3). To date, this has not been investigated in patients with COVID-19 related ARDS or non-COVID ARDS. This study aimed to identify the MAKEs at 180 days after intensive care unit (ICU) admission in non-COVID and COVID-ARDS.
Methods: This retrospective observational study was conducted at the Queen Elizabeth Hospital Birmingham (QEHB). COVID-ARDS patients admitted to ICU between 11 March 2020 and 17 January 2021 and ICU patients diagnosed with ARDS between 1 January 2017 and 1 November 2019 were included (non-COVID group). All data were routinely collected on the hospital's electronic patient records. The primary outcome was the incidence of MAKE at 180-days (MAKE-180) after ICU admission. Secondary outcomes included the risk factors for MAKE-180 and renal recovery at hospital discharge (defined as eGFR of ≥ 60 ml/min/1.73 m^2) (4). Chi-squared test, unpaired t-test, or Wilcoxon rank-sum test was used for multiple comparisons among groups. Univariate and multivariate analysis with logistic regression was performed to determine independent risk factors for MAKE-180.
Results: 519 ARDS patients were included in this study, 262 COVID-19 patients and 257 non-COVID patients. Both groups demonstrated a male predominance (70.2% vs 60.3%) however, the non-COVID group were older (61.0 (IQR, 49.0–71.0) vs 57.0 years (IQR, 48.0–63.8), P < 0.001). The incidence of AKI was higher in the non-COVID group (180 (70.0%) vs 136 (51.9%); P < 0.001). The incidence of MAKE-180 outcomes was significantly greater in the non-COVID group (170 (66.1%) vs 112 (42.7%); P < 0.001). In terms of the individual MAKE-180 outcome, there were overlaps between the classifiers. In non-COVID group, RRT = 123, decline in eGFR = 87, deaths = 104 compared to COVID group, RRT = 89, decline in eGFR = 84, deaths = 65. Only one patient in each group still required an RRT at 180 days. There were no differences in the rate of complete renal recovery between the two groups (36.8% vs 26.7%, P = 0.526). The strongest independent risk factors for MAKE-180 in both groups were CKD and high bilirubin. Other independent risk factors for MAKE-180 were age (OR = 1.04, CI:1.01–1.07, P = 0.007) in COVID group and obesity (OR = 2.20, CI:1.17–4.27, P = 0.017) and low albumin (OR = 0.93, CI:0.89–0.97, P = 0.001) in non-COVID group.
Conclusion: MAKE-180 is common in both groups but higher in those with non-covid ARDS. This is an important long-term patient-centred outcome, and interventions should be targeted at reducing it, especially in critically ill patients. Recognition of factors associated with MAKE-180 might help guide future practice and management strategies in critical care.

References

1. 1. Lumlertgul N, Pirondini L, Cooney E, Kok W, Gregson J, Camporota L, et al. Acute kidney injury prevalence, progression and long-term outcomes in critically ill patients with COVID-19: a cohort study. Annals of Intensive Care. 2021;11(1):123.
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