INVESTIGATING PATIENTS WITH ACUTE KIDNEY INJURY AND SEPSIS IN GENERAL WARDS

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DECLARATION

I hereby declare that this submission is my own work and to the best of my knowledge it contains no materials previously published or written by another person, or substantial proportions of material which have been accepted for the award of any other degree or diploma at Macquarie University or any other educational institution, except where due acknowledgement is made in this thesis. Any contribution made to the research by others, with whom I have worked with at Macquarie University or elsewhere, is explicitly acknowledged in the thesis.

I also declare that the intellectual content of this thesis is the product of my own work, except to the extent that the assistance from others in the project's design and conception or in style, presentation and linguistic expression is acknowledged.

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ABSTRACT

Introduction. Acute kidney injury (AKI) and sepsis are associated with a poor prognosis, but little research about their presence among hospital general ward patients has been conducted. This thesis aimed to review the current evidence and examine patient characteristics, variation of incidence, and outcomes of AKI and sepsis in general wards.

Method. A systematic review on AKI and sepsis patients in general wards and a retrospective observational cohort study of 192,133 patients at one regional and three metropolitan hospitals in New South Wales, Australia, in 2009-2013 were conducted.

Results. There was limited evidence about patients with AKI and sepsis in general wards in the literature, none from Australia. The observational study found that AKI and sepsis patients were older (median age: 72), had more with multiple comorbidities and had seven times longer length of stay (median:16.9 days) than patients without AKI and sepsis ($p<0.001$). During the study period, the incidence varied (1.62%-1.76%) across hospitals, was slightly higher in metropolitan (1.70%) than in regional (1.05%) hospitals, and AKI and sepsis admissions had tripled.

Conclusions. There was little variation in the incidence of AKI and sepsis in the four Australian general wards. Patients with AKI and sepsis were associated with poor outcomes (longer hospital stays) compared to patients without AKI and sepsis. More studies on patients with AKI and sepsis in general wards from different hospitals and population groups are needed to improve the patient outcomes in Australia.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACCP-SCCM	American College of Chest Physicians and the Society Critical Care Medicine
ADQI	Acute Dialysis Quality Initiative
AKI	Acute Kidney Injury
AKIN	Acute Kidney Injury Network
ANZICS	Australian and New Zealand Intensive Care Society
ARF	Acute Renal Failure
BEST Kidney	Beginning and Ending Supportive Therapy for the Kidney
CIMC	College of Intensive Care Medicine
eGFR	Estimated Glomerular Filtration Rate
EPHPP	Effective Public Health Practice Project
ESKD	End-Stage Kidney Disease
GFR	Glomerular Filtration Rate
HREC	Human Research Ethics Committee
ICD-9-CM	The International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10-CM	The International Classification of Diseases, Tenth Revision, Clinical Modification
ICD-10-AM	The International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification
ICU	Intensive Care Unit
IQR	Interquartile range
KDIGO	Kidney Disease Improving Global Outcomes
KHA-CARI	Kidney Health Australia-Caring for Australasians with Renal Impairment
LIS	Laboratory Information Systems
LOS	Length of stay
NIS	National Inpatient Sample
PAS	Patient Admission Systems
PICARD	Program to Improve Care in Acute Renal Disease
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
RIFLE	Risk, Injury, Failure, Loss, and End-stage of kidney disease

RRT	Renal Replacement Therapy
SD	Standard deviation
SESLHD	South Eastern Sydney Local Health District
SIRS	Systemic Inflammatory Response Syndrome
SOFA	Sepsis-related Organ Failure Assessment
STROBE	Strengthening the reporting of observational studies in epidemiology

CHAPTER 1. INTRODUCTION

Acute kidney injury (AKI) and sepsis cases are commonly found in hospitals but are potentially preventable by early detection (1, 2). AKI and sepsis have been studied in various populations, such as post-surgical, dialysis, or trauma patients (2-6). Previous studies have focused on the development of AKI and sepsis in a specific high-risk population, such as in older people, males, and those with specific pre-existing conditions (such as chronic kidney disease, diabetes mellitus, heart failure, or liver disease) in different hospital settings (ICU or general wards) (4, 7, 8). However, findings from a specific population could not be extrapolated to a heterogeneous population.

The characteristics, incidence, and outcomes of patients with AKI and sepsis in general wards are not very well understood and need further research. A better understanding of the current characteristics, incidence, and outcomes of patients with AKI and sepsis in general wards could help develop strategies to prevent life-threatening conditions caused by AKI and sepsis. This thesis presents a systematic review to summarise the current knowledge of patients with AKI and sepsis in general wards, and a retrospective observational cohort study to investigate four general wards in Australia over a 5-year period.

The present chapter provides the background of the study and investigates the research gap in the literature about patients with AKI and sepsis and describes the aims of the research project. The last part of this chapter outlines the thesis structure.

1.1 Background

Worldwide, AKI has been reported in around one in ten general ward patients and one in five ICU patients (9-11). AKI, previously known as acute renal failure (ARF), is defined as an acute impairment in kidney function (12). Even if the impairment in kidney function is managed in a timely fashion, it still can lead to chronic kidney disease, end-stage kidney disease (ESKD), which may lead to long term renal replacement therapy (RRT), or death (13, 14). The reported mortality rate of patients with AKI ranges from 15 to 60% (12). Sepsis itself is defined as “a life-threatening condition with organ dysfunction due to the body’s response to infection” (15). In contrast to AKI, sepsis was found in around 37% of ICU patients and approximately 50% of patients with sepsis were treated in general wards (16-18). Sepsis was also reported to have a high mortality rate. Around 50% of in-hospital deaths were due to sepsis (16-18).

Patients with AKI and sepsis represent a significant risk of poor prognosis (high morbidity and mortality) with poor long-term outcomes such as chronic kidney disease (17, 19). The combination of AKI and sepsis is also often associated with prolonged length of hospital stay and higher health care costs (6, 7, 20-24). This is presumably due to complicated treatments and high rehospitalisation for patients with AKI and sepsis (7). It has been reported that patients with AKI and sepsis stayed two times longer in the ICU compared to patients without AKI and sepsis (6). In the US, the cost for sepsis has been estimated to be USD 22,100 per case and around USD 9,000 more for AKI patients compared to patients without AKI (21, 22). In Australia, it is estimated that the cost of AKI is around AUD 55,998 per hospitalisation and around AUD 846 million annually for sepsis treatment, with the total economic burden is around AUD 1.5 billion (23, 24).

The incidence of patients with both AKI and sepsis varied around 2.9%-16% across different hospital settings globally (2, 4-6). It was also reported that the incidence of AKI and sepsis has been increasing by around 10% per year, especially in older patients with specific conditions, such as post-surgery, heart failure, chronic kidney disease, hypertension, liver disease, and diabetes mellitus (4, 17). The variation of incidence of AKI and sepsis is dependent on the definition of AKI and sepsis, the underlying disease, whether sepsis was developed from AKI or AKI was developed from sepsis, and patient populations in different settings (2, 4-6, 17, 25-33). These factors will be discussed separately in the following sections.

1.1.1. *A brief history of AKI and sepsis*

1.1.1.1 AKI guidelines

Before 2004, there were more than 35 definitions of AKI in the literature because of the lack of consensus on how to diagnose AKI (12). In 2004, the Acute Dialysis Quality Initiative (ADQI) initiated a consensus exercise (34). From this consensus, the ARF definition was changed to AKI with the Risk, Injury, Failure, Loss, and End-stage of kidney disease (RIFLE) diagnosis criteria, which was based on an increase in serum creatinine from the baseline (the known value of patient's serum creatine before the development of AKI) (35) and a decreased in the glomerular filtration rate (GFR) (34). This definition was further modified in 2007 by the Acute Kidney Injury Network (AKIN) based on the discovery that small increases in serum creatinine can influence patient outcomes (36). The latest definition was proposed by the International

Kidney Disease: Improving Global Outcomes group (KDIGO) in 2012 as a modification from the RIFLE and AKIN guidelines (11) followed by a standardised calculation of the baseline serum creatinine value in 2015 (37). Differences between the RIFLE, AKIN, and KDIGO in defining AKI are provided in Table 1.1.

Table 1.1 Differences between guidelines in AKI definition and diagnosis criteria

AKI Guideline	GFR	Serum Creatinine	Urine Output
RIFLE (2004)	Decrease >25%	Increase ≥0.5 mg/dl or 1.5 times the baseline within 1-7 days	<0.5 ml/kg/h for 6 hours
		• A Modification of Diet in Renal Disease (MDRD) with estimated glomerular filtration rate (eGFR) of 75-100 ml/min/1.73m^2 (baseline) when creatinine is missing	
		• 5 stages of classification	
AKIN (2007)	-	Increase ≥0.3 mg/dl (26.4 µmol/l) or 1.5-2 times the baseline within 48 hours	<0.5 ml/kg/h for 6 hours
		• The baseline is unnecessary, as long as the measures occur over 48 hours	
		• 3 stages of classification	
KDIGO (2012)	-	Increase ≥0.3 mg/dl (26.4 µmol/l) or 1.5-1.9 within hours-days	<0.5 ml/kg/h for 6 hours
		• 3 stages of classification	

RIFFLE = Risk, Injury, Failure, Loss, and End-stage of kidney disease; AKIN = Acute Kidney Injury Network; KDIGO = Kidney Disease Improving Global Outcomes; GFR = Glomerular Filtration Rate

1.1.1.2 Sepsis definitions

Similar to AKI, before 1992 there was no consensus regarding the definition of sepsis. Initially, sepsis was defined as a syndrome associated with an infection. In 1992, the first definition for sepsis (Sepsis-1 definition) was proposed by the American College of Chest Physicians and the Society Critical Care Medicine (ACCP-SCCM) (38). Later in 2001, the International Sepsis Definitions Conference updated the definition with the Sepsis-2 definition (39). As more research on the underlying cause, epidemiology, and management of sepsis evolved, the European Society of Intensive Care Medicine revised the definition and diagnostic criteria of sepsis and septic shock in 2015, formulating the Sepsis-3 definition (15) (details in Table 1.2).

Table 1.2 Sepsis definitions based on different guidelines

Sepsis Category	Sepsis-1 (1992)	Sepsis-2 (2001)	Sepsis-3 (2016)
Sepsis	Infection-induced SIRS	2 of 4 SIRS criteria with suspected infection	SOFA score ≥2 with suspected infection
Severe sepsis	Sepsis with organ dysfunction, hypoperfusion or hypertension	Sepsis with organ dysfunction (SOFA-score), hypoperfusion or hypertension	N/A
Septic shock	Sepsis-induced arterial hypotension or with a reduction in systolic blood pressure even though with adequate fluid resuscitation and the presence of perfusion abnormalities	Sepsis-induced hypotension even after adequate IV fluid resuscitation with the presence of perfusion abnormalities or organ dysfunction	Sepsis with persisting hypotension and a vasopressor dependent (require maintaining mean arterial pressure ≥65 mmHg and serum lactate level >2 mmol/L without hypovolemia)

SIRS = systemic inflammatory response syndrome; SOFA = sepsis-related organ failure assessment

1.1.2. *The bi-directional relationship between AKI and sepsis*

The strong relationship between AKI and sepsis was proven by several experimental studies from animal models and clinical studies in humans that identified the relationship between the harmful effect of cross organ dysfunction in AKI and the systemic inflammatory response in sepsis (40-44).

1.1.2.1 AKI as a predisposing factor for sepsis

Several studies reported that patients with AKI were also susceptible to developing sepsis compared to patients without AKI (41, 45). The susceptibility of AKI patients in developing sepsis was predicted due to the impact of AKI in distant organ function (organ cross-talk) that can reduce the immune system (14). However, the pathophysiologic mechanism to explain how AKI increases the risk of sepsis is still unclear (46). Several studies suggested that the high sensitivity of patients with AKI in acquiring new infections or sepsis is due to immune dysregulation through leukocyte migration and apoptosis of the tubular cell in the kidney, changes in oxidative stress metabolism and gene regulation, inflammation, and the effect of distal organ injury (44, 46, 47). In a clinical multicentre study in 2011 performed by the Program to Improve Care in Acute Renal Disease (PICARD), it was identified that 40% of AKI

patients who were sepsis-free at the time of AKI was diagnosed, had sepsis during their period of hospitalisation (in around 5 days after AKI was diagnosed in 50% of patients) (48).

1.1.2.2 Sepsis resulting in AKI

Sepsis was reported as the most common cause of AKI development and associated with an increased need for RRT and a higher in-hospital mortality rate (4, 49-51). For instance, a study from the Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) trial that involved 54 ICUs from 23 countries, including Australia, found that approximately 47.5% of patients developed AKI due to sepsis (50). The development of sepsis can also worsen AKI, where most of the patients with AKI and sepsis were found in AKI stage 3 (52). However, the mechanism of how sepsis can trigger AKI is still unknown. Several theories based on studies in human and animal suggest that: 1) sepsis could reduce the total renal blood flow which triggers the development of AKI, 2) AKI develops from the kidney's response to systemic inflammation injury in sepsis, and 3) both circulatory dysfunction and renal inflammation simultaneously enhance the development of AKI in patients with sepsis (44, 53).

1.2 Research gap

Due to various AKI and sepsis definitions, it is difficult to compare the incidence and outcomes of patients with AKI and sepsis across different studies. For example, in Australia the KDIGO guideline has been adapted by the Kidney Health Australia-Caring for Australasians with Renal Impairment (KHA-CARI) in 2014 (54), but in the United Kingdom another AKI guideline was introduced in 2013 by the National Institute for Health and Care Excellent, which was the NICE guidelines (55). Similar to the inconsistency in AKI guidelines, the latest Sepsis-3 definition continues with a lack of consistent uptake in several countries (56). For example, in Australia, the Sepsis-3 definition was recommended by the Australian and New Zealand Intensive Care Society Centre (ANZICS), but not by the College of Intensive Care Medicine of Australia and New Zealand (CIMC) and the Australian College for Emergency Medicine (57).

The difference in the incidence rate of AKI and sepsis was also related to the coexistence between AKI and sepsis (4, 58). For example, it was reported that the incidence of AKI and sepsis was around 45.5%-53.5% in severe sepsis or septic shock patients who developed AKI during their hospitalisations (58). Another multicentre study from Australia also identified the incidence of AKI and sepsis was 42.1% of sepsis patients in the ICU who later on developed AKI or around 32.4% of AKI patients who had sepsis in their hospitalisations (4).

There are also several factors that contribute to the variation in the incidence and outcomes of AKI and sepsis. These include patient characteristics (age and gender), the geographic area of the studied population (e.g., metropolitan or regional), and the population studied (e.g., ICU or general ward patients) (2, 4-6). These factors will be discussed in the following sections.

1.2.1. *The variation in the incidence and outcomes of patients with AKI and sepsis*

1.2.1.1 Age and gender

There is variation in the reported age and gender for patients with AKI and sepsis. For example, two ICU studies for patients with AKI and sepsis have reported different mean age for the characteristics of patients with both conditions. Bagshaw et al. reported that the mean age of patients with both conditions was 66.7, while Zhang et al. reported AKI and sepsis in younger patients (mean age was 52.41) (4, 28). It is still unclear whether the high risk of development of AKI and sepsis is related to older age or not (59). There has been a discussion about the ageing process that could change the structure of kidney cells or the function of glomeruli in the kidney, which could reduce the kidney's overall function of glomerular filtration rate (GFR) and immune system function (59, 60). Several studies also suggest that older patients with several comorbidities (e.g., diabetes, atherosclerosis, or hypertension) were more likely to develop AKI and sepsis (59, 60).

There was also inconsistency in the incidence of AKI and sepsis between male and female patients. Bagshaw et al. identified a higher proportion of male (54.6%) patients with AKI and sepsis than female patients (4). In contrast, Zhang et al. reported more female patients (73.27%) with AKI and sepsis than male patients (28). Several studies reported that AKI was more common in males due to prostate enlargement with ageing that could increase the risk of urinary obstructions (61, 62). However, Funk et al. reported a lower mortality rate for female patients with AKI than in male patients despite female patients being older (59).

1.2.1.2 The geographic area of the studied population

A multicentre study in the U.S in 2015 identified that there were differences in the incidence and outcomes for patients with AKI and sepsis depending on the location of the population studied (metropolitan or regional areas) and the hospital volume (small, medium, or large hospitals) (27). They reported that the range of the incidence of patients with AKI and severe sepsis ranged from 11.1% in small hospitals to 64.3% in large hospitals (27). This could be

caused by different resources in the hospital (metropolitan or regional) (27). It was predicted that the variation was dependent on the resources of the hospital in managing the underlying conditions and the criteria used in diagnosing AKI and sepsis in each hospital (63, 64).

1.2.1.3 Hospital settings (the ICU vs. general ward) of the studied population

Another factor associated with the incidence and outcomes of patients with AKI and sepsis is the hospital setting where patients were studied:

a) ICU setting

There was a significant variation in the incidence and outcomes across the study populations. The incidence of patients with AKI and sepsis in the ICU was reported ranging from 0.7%-53.9% (4, 28). The mortality rate for patients with AKI and sepsis also varied significantly in the ICU setting (19.8%-54.4%), whereas the in-hospital mortality rate was found to be 29.7% (4). Previous studies also reported that ICU patients with AKI and sepsis had a higher mortality rate and were approximately three times more likely to die compared to patients without AKI or sepsis (29, 30).

The variation in the mortality rate of ICU patients with AKI and sepsis has been associated with the degree of severity of AKI or sepsis (28-30, 65). For example, Zhang et al. identified that the high mortality of ICU patients with AKI and sepsis corresponded to the severity of the primary disease (28). They found that the mortality rate of patients with the lowest severity of sepsis and AKI was around 14.5%, while the mortality rate was even higher in patients with severe sepsis and AKI (27.4%), and for patients with septic shock and AKI the mortality rate was the highest (57.4%) (28).

b) General ward setting

The majority of studies for patients with AKI and sepsis in the literature are in ICU patients, with few studies on patients with AKI and sepsis in general wards. Two studies have reported the incidence of patients with AKI and sepsis in general wards (31, 32). In 2013, Singh et al. found that the incidence of AKI and sepsis in ICU and general wards were 0.1% and 0.7%, respectively (32). In contrast, a study in 2016 by Pan et al. identified that the incidence of AKI and sepsis in general wards was 35.8%, with the mortality rate was around 33.3% (31). This finding suggests that patients with AKI and sepsis may have poor outcomes in a general ward setting, but there is very

limited data about patients with AKI and sepsis in general wards. None of the studies reported the characteristics of patients with AKI and sepsis.

Until recently, little has been known about the incidence, outcomes, and characteristics of patients with AKI and sepsis in general wards (2, 6, 66). Most research on patients with AKI and sepsis has focused on ICU patients or patients with specific clinical conditions (e.g., post-cardiac surgery, coronary intervention, etc.) (2, 6). The characteristics of ICU patients were significantly different from general ward patients (32, 33). ICU patients are more likely to have advanced comorbidities and deteriorating or life-threatening conditions, compared to general ward patients (32, 33). The Australian Institute of Health and Welfare (2014-2015) also reported that ICU patients only represented 1.3% of all hospitalisations, suggesting that findings from the existing literature cannot be reliably extrapolated to the general ward setting (67, 68). Selby et al. also reported that data from different clinical settings could yield a variety of outcomes, which could be seen in a wide variation of the mortality rate of AKI and sepsis (66).

The variability in the reported incidence, outcomes, definitions, and limited available data highlights a clear need for an in-depth study of patients with AKI and sepsis in general wards. A review to examine the research gap for general ward patients with both conditions and a study that includes data from general wards in both metropolitan and regional hospitals over a period of time will provide more reliable insights into the epidemiology and the outcomes of patients with AKI and sepsis. As more information on the patient outcomes becomes available from the study, the results will help health organisations and professionals develop timely identification and management of AKI and sepsis patients.

1.3 Aims

This thesis aims:

1. To review the current evidence on the incidence and outcomes of patients with AKI and sepsis in general wards.
2. To investigate the patient characteristics such as age, gender, and comorbidities associated with AKI and sepsis in four hospitals in New South Wales, Australia.
3. To investigate the variation of patient characteristics and the trend of incidence and outcomes of patients with AKI and sepsis across four hospitals over time (2009 to 2013).

The aims were addressed using a systematic review in combination with a retrospective observational cohort study of four hospitals in metropolitan and regional areas in New South Wales, Australia, from 2009 to 2013. For the first aim, the systematic review was performed to synthesise the existing evidence and identify the knowledge gap for patients with AKI and sepsis in the general wards. Although a systematic review should be conducted by two or more reviewers, this thesis presents the work of the MRes candidate who is responsible for conducting the systematic review to fulfill the requirement of the degree. In order to address the second and third aims, a cohort study was performed to investigate the characteristics and outcomes of patients with both AKI and sepsis admitted to general wards in four different hospitals in New South Wales, Australia.

1.4 Ethics

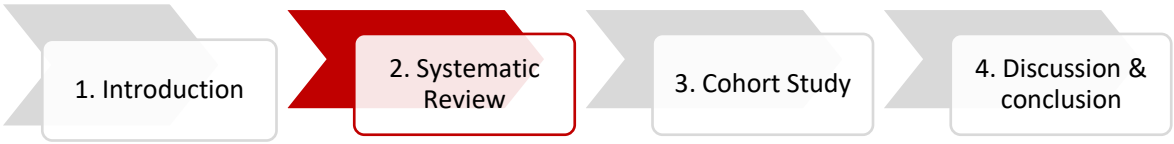
Ethics approval was granted by the South Eastern Sydney Local Health District (SESLHD) Human Research Ethics Committee (HREC) [16/041 (HREC/16/POWH/412) (NEAF approval)] prior to the study in 2017 (see Appendix 1 and 2). The systematic review and cohort study were conducted in 2019 (MRes year 2) as an extension of the MRes year 1 research project with different research questions and aims.

1.5 Outline of the thesis

The structure of this thesis is shown in Figure 1.1. Chapter 1 describes the introduction (background) of the research project. A systematic review to address the first aim in identifying the current evidence in the literature for patients with AKI and sepsis in general wards is presented in Chapter 2. Chapter 3 presents a cohort study of patients with AKI and sepsis from four different hospitals in New South Wales, Australia, over a 5-year period to achieve the second and third aims. The method, results, and discussion are presented separately in Chapters 2 and 3 for the systematic review and cohort study. Finally, a summary of findings, strengths, limitations, and future directions are discussed in Chapter 4.

Figure 1. 1 Thesis structure diagram

CHAPTER 2. A SYSTEMATIC REVIEW OF PATIENTS WITH AKI AND SEPSIS IN GENERAL WARDS



2.1 Overview of Chapter 2

Chapter 2 provides a systematic review of the literature to address the first aim of this thesis, i.e., examining the characteristics, incidence, and outcomes of patients with AKI and sepsis in general wards.

2.2 Background

Sepsis and AKI occur together in a number of hospitalised patients (40). AKI can be the predisposing factor for sepsis and conversely, sepsis can also cause AKI. The combination of AKI and sepsis is common with high morbidity and risk of death in the ICU and general ward patients (mortality rate of 33.3% and 54.5% respectively (30, 31)) compared to the patients without AKI and sepsis (69). Patients with AKI and sepsis also stay longer in the hospital (mean = 17.4 days, SD = 8.96 days in the ICU and mean = 14.29 days, SD = 5.1 days in the general ward) (32).

Two studies have reported that the incidence and mortality rate of patients with AKI and sepsis in the general wards were high (31, 32). However, findings in the literature could not be generalised across different populations and settings due to the nonuniformity of AKI and sepsis definitions, the inconsistency in the reported patient characteristics, incidence, and outcomes of AKI and sepsis. Thus, a systematic review focusing on patients with AKI and sepsis in general wards was performed to integrate the existing literature and provide the current state of knowledge for patients with AKI and sepsis in general wards.

2.3 Aims

The systematic review aimed to examine and summarise the current evidence of the characteristics, incidence, and outcomes of patients with AKI and sepsis in general wards, including the risk factors and comorbidities of patients with both AKI and sepsis.

2.4 Method

2.4.1. *Search strategy*

A systematic review of studies of patients with AKI and sepsis in general wards was conducted in June 2019. The systematic review followed the PRISMA[a] guidelines (70). Two databases were used for this review: EMBASE and PubMed. The search terms were selected through the following MeSH and keywords for each database: [“acute kidney injury” OR “AKI OR “acute renal failure” OR “ARF”] AND [“sepsis” OR “septic” OR “septic shock”] AND [“hospitali*” OR “ward*” OR “general ward*” OR “non intensive care unit” OR “non ICU” OR “outside intensive care unit” OR “outside ICU”]. The search included studies published in English language and there was no limitation in the publication date.

2.4.2. *Study selection*

All reference details from the two databases searched were downloaded into the reference manager software package, EndNote X8 (EndNote, 2016). The titles and abstracts were screened against the inclusion and exclusion criteria (Table 2.1).

[a] PRISMA emphasises the requirement to have more than one reviewer to review the full set of selected articles, however, due to the time constraint in fulfilling the requirement of the degree of Master of Research, only one reviewer (i.e., the MRes candidate) conducted the systematic review.

Table 2.1 The inclusion and exclusion criteria for patients with AKI and sepsis in general wards

Inclusion criteria	Exclusion criteria
Peer-reviewed papers	Conference abstracts, commentaries, or editorials
Studies for patients with AKI and sepsis	Studies only for AKI or sepsis
Patients admitted to the general ward	Non-general ward setting: the ICU, emergency department, Nephrology ward, Psychiatric ward, etc., and with specific conditions: diabetes, hypertension, post-surgery, etc.
Adults (≥18 years old and over)	Patients <18 years old
Reported the characteristics, incidence and outcomes of patients with both conditions, regardless of AKI or sepsis as the primary condition or the methods used in the study	No measurement of incidence or outcomes of patients with both conditions

In the next step, all titles and abstracts were reviewed based on the inclusion and exclusion criteria. The full texts of all studies after the title and abstract screening were evaluated based on the inclusion and exclusion criteria. Studies were excluded if there was no original research reported. Bibliographies of the included studies were also reviewed for additional studies.

2.4.3. *Data extraction, synthesis, and quality appraisal*

The following information was extracted from each study: first author, year of publication, country of study, study design, and study population. Information regarding the characteristics, incidence, and outcomes of patients with AKI and sepsis in general wards was also extracted from the included studies.

Quality assessment and risk of bias were assessed using the Effective Public Health Practice Project (EPHPP) quantitative checklist (71). This assessment tool was developed in 1999 by Helen Thomas and Dr. Donna Ciliska from the School of Nursing at McMaster University to help researchers, public health practitioners, and decision-makers perform the appraisal or synthesise the research evidence that is relevant to specific clinical questions. The included studies were evaluated according to the following criteria: 1) the selection bias (potential risk of bias in selecting study population), 2) the type of study design, 3) the control of confounders, 4) use of blinding whether the outcome assessor was used and reported, 5) the validity and

reliability of the data collection methods, and 6) the reported withdrawals and drop-outs (see Appendix 3). Each criterion was graded as ‘Strong’, ‘Moderate’ or ‘Weak’. Overall quality assessment will be rated as ‘Strong’ if there are no ‘Weak’ ratings applied, ‘Moderate’ if there is one ‘Weak’ rating applied, and ‘Weak’ if there are two or more ‘Weak’ ratings. This classification structure is shown in Appendix 3.

2.5 Results

The database search strategy resulted in 610 studies. There were 36 duplicate studies, leaving 574 studies for the title and abstract screening. After the title and abstract screening, there were 136 studies which then underwent full-text review. Following title and abstract screening, there were 12 included studies and 3 studies obtained from a bibliographic review. The PRISMA flow diagram (70) for the study selection is shown in Figure 2.1.

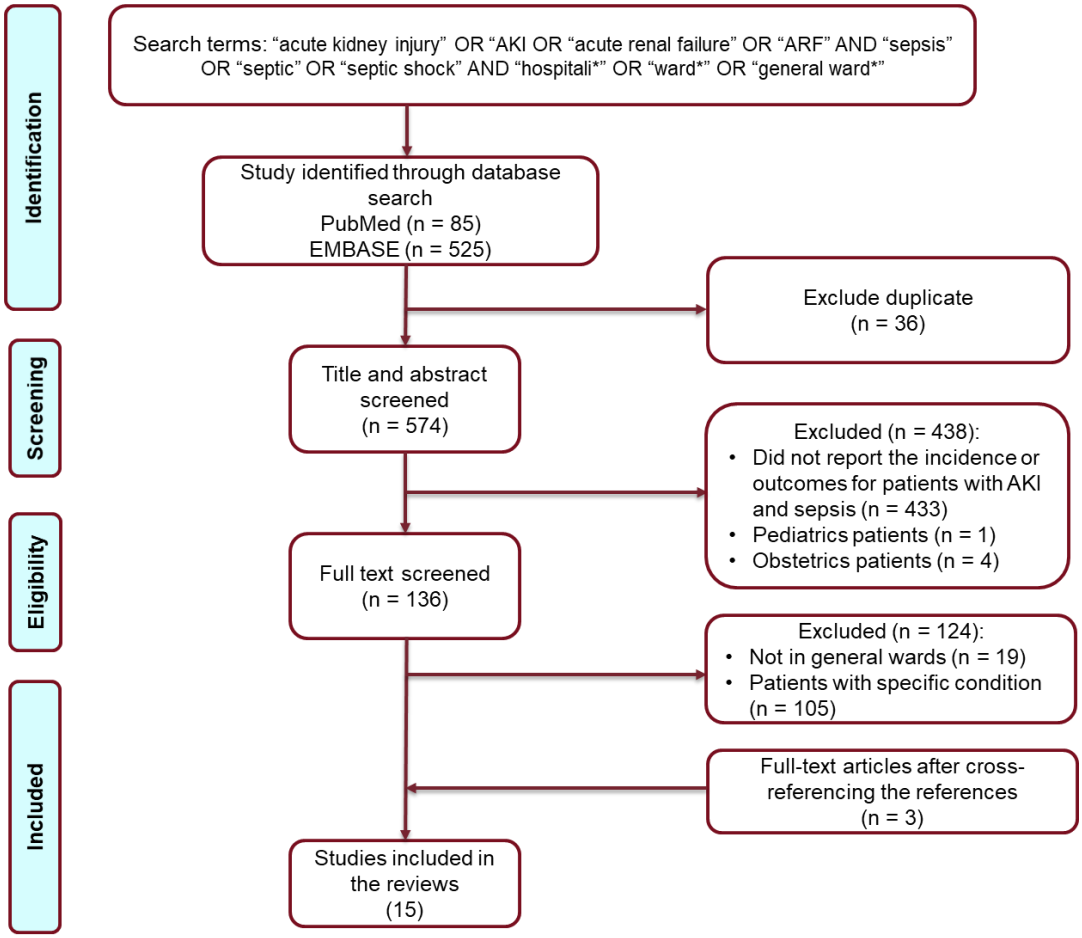


Figure 2.1 PRISMA flow diagram for study selection

2.5.1. *Included studies*

Fifteen studies met the inclusion criteria (Appendix 4). Of the included studies, six studies were from the USA (9, 72-76), two studies were from China (77, 78), two studies were from India (32, 79), one study from the United Kingdom (66), Thailand (80), Jordan (81), Taiwan (31), and Uganda (82) respectively (Figure 2.2). The quality of the included studies was rated as mostly "Moderate" (n = 9) and "Strong" (n = 5), with only one study rated as "Weak" quality. The details of the included studies and their quality assessment are shown in Appendix 3.

Based on the World Bank's classification of countries by income (83), the included studies are grouped into three groups: 1) eight studies from high-income countries: the United States (9, 72-76), the United Kingdom (66), and Taiwan (31); 2) six studies from middle-income countries: China (77, 78), India (32, 79), Jordan (81), and Thailand (80); and 3) one study from low-income country: Uganda (82).

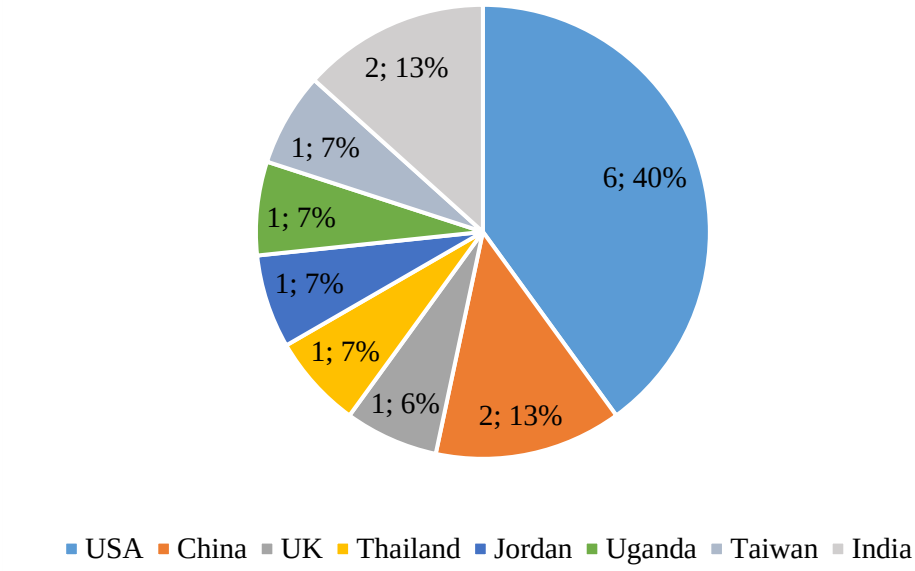


Figure 2.2 Study country for the included studies

Most of the included studies (seven studies) were retrospective cohort studies (9, 31, 72-75, 80). Of these, three studies from the USA used data from the National Inpatient Sample (NIS) as the study population (9, 74, 75), six studies were prospective cohort studies (32, 66, 76, 77, 79, 81), and the other two studies were cross-sectional studies (78, 82).

2.5.2. *Combination of AKI and sepsis definitions*

There were several combinations of definitions used in the selected studies to diagnose AKI and sepsis (Table 2.2), i.e.:

1. AKI guidelines were used in five studies: two studies used AKIN (66, 82), one used RIFLE (32), and two used KDIGO (31, 76),
2. Independent diagnosis based on the changes in patients' serum creatinine (SCr). For example, AKI was identified when there was an increase in SCr level around 25% from the baseline, or if the SCr level is equal or greater than 3.5 mg/dL (used in four studies (77, 79-81)),

3. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes (used in four studies (9, 72, 74, 75)),
4. Combinations of AKI guidelines (AKIN, RIFLE, and KDIGO) and mixed models of creatinine kinetics (used in one study (73)) and,
5. Combinations of KDIGO, independent diagnosis, and The International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) (used in one study (78)).

In contrast to AKI where clinical definitions were used, ICD codes were commonly used to define sepsis (six studies used ICD-9-CM (9, 72-76)), and two studies used ICD-10-CM (66, 78). There was also variation in the guidelines used for the identification of sepsis:

1. *Sepsis-1* guideline (used in three studies (32, 79, 82)),
2. *Sepsis-2* guideline (used in one study (80)) and,
3. Independent diagnosis based on the Systemic Inflammatory Response Syndrome (SIRS) criteria, Sepsis-related Organ Failure Assessment (SOFA) score, or any suspected infections (used in three studies (31, 77, 81)).

This means that the combination of the recorded diagnosis codes (ICD-9-CM and ICD-10-CM) was commonly used to define AKI and sepsis (8 of 15 studies) (Table 2.2).

Table 2.2 The summary of AKI and sepsis definitions in the included studies

AKI definition		**Sepsis definition**			**Sepsis cases identification**	
		Independent definition	Guideline		Administration code	
			Sepsis-1	Sepsis-2	ICD-9-CM	ICD-10-CM
Guideline	AKIN	-	Bagasha (2015)	-	-	Selby (2012)
	RIFLE	-	Singh (2013)	-	-	-
	KDIGO	Pan (2016)	-	-	Heung (2016)	-
Independent Definition		Al-Azzam (2008), Li (2008)	Kohli (2007)	Ruangchan (2016)	-	-
Administration code	ICD-9-CM	-	-	-	Liangos (2006), Waikar (2006), Waikar (2007), Silver (2017),	-
Mixed combinations	KDIGO, RIFLE, AKIN, and model of creatinine kinetics	-	-	-	Zeng (2014)	-
	Independent definition, ICD-10-CM, and KDIGO	-	-	-	-	Yang (2015)

2.5.3. *Characteristics of patients with AKI and sepsis*

Of the fifteen included studies, only two studies reported the characteristics of patients with both AKI and sepsis in general wards (79, 82). A single centre study from India reported that patients with AKI and sepsis were found in 75.4% of patients with age ≥65 and in 59.6% of younger patients (age <65) with AKI (79). These results were reflected in another single centre study from Uganda, which also reported AKI and sepsis in general ward patients over 59 years of age (82).

2.5.4. *Incidence of patients with AKI and sepsis*

The incidence of patients with AKI and sepsis in general wards varied significantly from 0.02% to 32.8%. There was a variation in the different geographic areas reported by Yang et al., who found that the incidence in regional areas was higher compared to metropolitan areas (8% and 5.8% respectively) (78). Another study also found that black American patients with AKI and sepsis had a higher incidence compared to white American patients in the United States (20.3% and 19.5% respectively) (75). Details are provided in Table 2.3.

Table 2.3 The incidence and mortality rate of patients with AKI and sepsis in general wards

Author	Year	Population	Patients characteristics			Incidence AKI and sepsis	In-hospital mortality rate AKI and sepsis	Length of stay (LOS)
			AKI	Sepsis	AKI and sepsis			
Studies involving patients with AKI and sepsis (recorded in any diagnosis field)								
Liangos et al.	2006	29,039,599 hospitalisations	Median age (IQR): 73 (60-82), Male: 51.8%, White: 62.3%, Black: 14.4%	N/A	N/A	0.03% (9,487/29,039,599)	N/A	Median: 7.0 days
Waikar et al.	2006	5,563,381 hospitalisations	1988: median age (IQR): 72 (49-86), Female: 44.2%. 2002: median age (IQR): 72 (45-87), Male: 53.2%	N/A	N/A	N/A	56.3% of 930,023 in 1988-1992; 51.3% of 1,637,899 in 1993-1997; 45.4% of 2,995,459 in 1998-2002	N/A
Kohli et.al	2007	33,301 hospitalisations	Mean age±SD: 43.9 ± 16.9 (18-86 years), Male: 60.2%	N/A	75.4% in elderly patients with AKI (52/69) and 59.6% in young patients with AKI (134/225)	0.6% (186/33,301)	62.9% (117/186)	N/A

Waikar et al.	2007	15,885,742 hospitalisations	White: mean age: 71.7, Male: 53.5%. Black: mean age: 63.3, Male: 50.1%	N/A	N/A	White Americans: 0.4% (63,007/15,885,742), Black Americans: 0.1 % (15,592/15,885,742)	44.4% (27,975/63,007) in White Americans, 41.7% (6,501/76,812) in Black Americans	Median: 7.2-7.4 days
Li et al.	2008	108,744 patients	Mean age±SD: 56.6 ± 18.1 years. 57.8% (185/320) age <60 years. Male: 63%	N/A	N/A	0.02% (25/108,744)	64% (16/25)	Mean±SD: 23.8 ± 20.5 days
Singh et al.	2013	9413 patients	Mean age±SD: 50.13±15.4 years	N/A	N/A	0.1% (10/9413)	N/A	Mean±SD: 14.29 ± 5.1 days
Zeng et al.	2014	31,970 hospitalisations	Median age (IQR): 64 (52-75) years. Male: 50.4%, White: 79.4%	N/A	N/A	12.5% (4,000/31,970)	N/A	Median (IQR): 10 days (6-16 days)
L. Yang et.al	2015	374,286 hospitalisations	11.5% (876/7604) aged 18-39 years, 30.8% (2341/7604) aged 40-59 years, 41% (3120/7604) aged 60-79 years, 16.7% (1267/7604)		N/A	6.4% (483/7604) , 5.8% (328/5662) in academic hospital and 8% (155/1942) in local hospital	25.6% (124/483)	Median (IQR): 18 (10-29) days

			aged ≥80 years. Men: 65.2%					
Heung et al.	2016	104,764 hospitalisations	Mean age±SD: 63.1±10.8 , Male: 94.9%	N/A	N/A	0.2% (183/104,764)	N/A	Mean±SD: 9.2 ± 15.9 days
Silver et al.	2017	29,763,649 hospitalisations	Mean age±SD: 69.0±0.1 years, Male: 52.8%	N/A	N/A	2.1% (612,267/29,763, 649)	N/A	N/A
Studies involving patients with AKI and sepsis that recorded AKI as the primary diagnosis								
Al-Azzam et al.	2008	111 ARF patients	Age <40: 19.8% (22/111) age 40-60: 36.1% (40/111) age >60: 44.1% (49/111), Male: 56.8% (63/111)	N/A	N/A	10.8% (12/111)	N/A	Median: 9.9% : <5 days, 75.7% : 5-14 days and 14.4%: >14 days
Selby et al.	2012	3,930 AKI patients	Median age (IQR): 80 (16) years. Male: 49.5%	N/A	N/A	N/A	41.1% (353/859)	N/A
Pan et al.	2016	201 AKI patients	Mean age: 68, Male:65.2%	N/A	N/A	32.8% (66/201)	30.3% (20/66)	Median: 17 days
Studies involving patients with AKI and sepsis that recorded sepsis as the primary diagnosis								
Bagasha et.al	2015	387 sepsis patients	N/A	Mean age: 37 years, range (18-90)	Age >59 years	The prevalence: 16.3% (63/387)	N/A	Median (IQR): 10 (6-16) days

Ruangchan et al.	2016	723 sepsis patients	N/A	Mean age±SD: 62.9±18.2 years, 63.2% age 60 years older. Male: 50%	N/A	15.1% (109/723)	38.5% (42/109)	Mean ±SD: 8.3 ± 9.4 days

2.5.5. *Patient outcomes*

2.5.5.1 In-hospital mortality rate

The mortality rate of patients with AKI and sepsis in-hospital ranges from 25.6% to 64.0%. The variability in the in-hospital mortality rate of patients with AKI and sepsis related to advanced patient age and ethnic background (66, 75, 77). Selby et al. demonstrated that older patients had worse outcomes, where the median age of patients with AKI and sepsis who did not survive versus those who did was 82 years old and 79 years of age respectively ($p<0.001$) (66). Another study also demonstrated an association of mortality from sepsis and AKI with the advanced age, where approximately 50% of patients who died were older than 80 years of age (77). Mortality among white Americans was higher compared to those for black Americans (44.4% versus 41.7% respectively) (75). The mortality due to AKI and sepsis was also proportional to the severity of AKI. More patients with AKI and sepsis died in AKI stage 3 (31.96%) compared to the mortality of patients with both conditions in AKI stage 1 (16.33%) (66). Despite a high mortality rate in patients with AKI and sepsis in general wards, Waikar et al. reported in 2006 a declining mortality rate from 56.3% in 1988-1992 to 51.3% in 1993-1997, and 45.4% in 1998-2002 (74) (Table 2.3).

2.5.5.2 Length of stay (LOS)

The length of stay for patients with AKI and sepsis in general wards ranges from <5 days to 44 days, with around 75.7% of the patients stayed around 5-14 days in a general ward (81). The LOS of patients with AKI and sepsis was related to the severity of AKI and the mortality rate (72, 73). For instance, Zheng et al. found that stage 3 of AKI patients with sepsis stayed longer compared to patients with stage 1 AKI with sepsis (73). In 2008, Liangos et al. reported that patients with AKI and sepsis stayed longer (2.6 additional days) with lower survival compared to AKI patients without sepsis (72). This finding was consistent with a study by Silver et al., who also reported that the LOS of patients with AKI increased 2.1 days if the patients also had sepsis (9). However, there was a decrease in the proportion of patients admitted at 30 days (30-day LOS) for patients with AKI and sepsis. In 1988-1992, the 30-day LOS was 32.9% and was down to 21.3% in 1998-2002 (74) (Table 2.3).

2.5.6. *Comorbidities that are related to the mortality of patients with AKI or sepsis in general wards*

There were no studies reporting the comorbidities for patients with both AKI and sepsis in general wards. The reported comorbidities were from patients with either AKI or sepsis as the primary diagnosis. For patients with sepsis as the primary diagnosis, only one study reported central nervous system failure as an independent risk factor that increased mortality rate in patients with severe and septic shock (Odds Ratio [OR] 7.3) (80).

For patients with AKI as the primary diagnosis, there were three studies that reported the relationship between comorbid conditions and mortality of patients with AKI (31, 66, 79). The reported comorbidities were cardiovascular disease (especially acute myocardial infarction and congestive cardiac failure), respiratory disease (especially pulmonary disease and respiratory failure), central nervous system disease, diabetes mellitus, peripheral vascular disease, stroke, cancer, and metastatic disease (31, 66, 79). These comorbidities were also found to increase the probability of in-hospital mortality of patients with AKI. It was also reported that liver disease (especially severe liver disease and hepatic failure) had a substantial impact on in-hospital mortality for patients with AKI (2-6 times higher for patients with AKI compared to patients without AKI (OR 2.2-6.1)) (31, 66). The mortality of AKI patients with central nervous system disease, metastatic disease, and respiratory failure was three times higher than patients with similar co-morbidities but without AKI (OR 2.9-3.4) (31, 66, 79). In contrast, it was reported that chronic kidney disease lowered in-hospital mortality around 20% for patients with AKI (31).

2.6 Discussion

2.6.1. *Key findings*

This review found that there is not a substantial amount of evidence on the characteristics and comorbidities of patients with AKI and sepsis in general wards. There were only two studies reported the characteristics of patients with AKI and sepsis, only one study reported the variance of AKI and sepsis incidence based on geographic areas, and none about the comorbidities of patients with both conditions (78, 79, 82). From the available data, it was identified that AKI and sepsis were common in patients admitted to general wards, and these patients have a high mortality rate. The high mortality rate and poor outcomes of patients with AKI and sepsis may also relate to the comorbid conditions at the time of AKI and sepsis diagnosis, but there is no data or limited data available. There was also significant variability in the reported incidence of patients with AKI and sepsis depending on the geographic areas of hospitals (higher incidence in the regional and metropolitan areas) and patient age (more patients with AKI and sepsis in the age group over 60 years old). The reported LOS was also longer in patients with both AKI and sepsis compared to patients without AKI or sepsis. Most included studies in the developed countries used data from the United States and the United Kingdom, and none of the studies were from Australia.

2.6.2. *Relation to previous studies*

2.6.2.1 The incidence of patients with AKI and sepsis

This systematic review found a wide range of incidences reported, many of which were high (0.02% to 32.8%). The in-hospital mortality rates for patients with AKI and sepsis in general wards ranged from 25.6% to 64%. The rate was lower in the ICU (0.7% to 53.9%) than was in general wards (0.02% to 32.8%).

Reasons that could explain the wide variation in the incidence of patients with AKI and sepsis:

1. Variations in the study population and sample size, e.g., all patients in general wards (77), only patients with AKI or sepsis (31), or based on samples from the Veteran Health Administration that has mostly (94.9%) male patients (76).
2. The criteria used to diagnose AKI and sepsis. One previous study reported that around 47.5% of AKI patients in general wards were identified using an independent diagnosis, but were missed using the KDIGO criteria (78). This finding aligned with another study that reported the KDIGO criteria had diagnosed 70% of AKI cases in the ICU, but around 50% of AKI cases were missed when the KDIGO criteria were used to diagnose AKI in surgical and

general wards (78). It has also been reported that the KDIGO criteria identified the highest number of AKI incidence compared to AKIN and RIFLE (73). Misclassification of the disease could also occur because the accuracy of the ICD coding relies on the documentation of the health care professionals and it is well known that AKI is underdiagnosed or under coded in clinical practice (84).

There was one study that reported the variation in the incidence of patients with AKI and sepsis between general wards in regional and metropolitan settings. Yang et al. reported that the incidence rate of patients with AKI and sepsis was higher in regional areas (8%) compared to metropolitan areas (5.8%) in China (78). This finding was similar to the results of a previous study that reported an increased risk of sepsis in regional areas, where low socioeconomic status, poor nutrition, and inadequate housing were related to a high risk of injury and infection (e.g., respiratory, skin, and soft tissue infections) (85). It has been suggested that a higher number of AKI incidence in regional areas of China was due to the high exposure of nephrotoxic drugs (78).

2.6.2.2 The in-hospital mortality rate and length of stay of patients with AKI and sepsis

Our systematic review also found that the in hospital mortality rate of patients with AKI and sepsis in general wards was high (up to 64%). Li et al. reported a low in-hospital survival rate of patients with AKI and sepsis, only 9.6% of patients with AKI and sepsis survived (77). High mortality of patients with AKI and sepsis in general wards could be related to older age, where more patients with AKI and sepsis were from the age group over 60 years (79). Szakmany et al. also reported a higher survival rate in younger patients (1).

The in-hospital mortality rate of patients with AKI and sepsis in general wards was found higher from the systematic review (25.6% to 64%) compared to the mortality rate of patients AKI and sepsis in the ICUs (19.8%-54.4%). This could be caused by, 1) the higher acuity of medical care for patients with AKI and sepsis in the ICUs compared to in the general wards (79), 2) a delay in diagnosing and referring patients to general ward renal specialists (86), 3) late hospital admission (79), and 4) the lack of awareness by medical professionals in recognising AKI and sepsis, especially in general wards (79).

2.6.2.3 The relationship between characteristics and comorbidities of patients with AKI or sepsis

This systematic review identified that AKI and sepsis were mostly found in patients over 59 years or elderly (79, 82). Kohli at al. reported that the outcomes of patients with AKI were associated

with the occurrence of certain diseases related to ageing (79). The findings were similar to the result of a study by Funk et al. who also reported the increased risk of kidney damage in the elderly patients who received contrast media (mean age±SD 77±7 years for patients with AKI, and mean age±SD 73±8 years for patients without AKI) (59). A recent Australian study also reported a high mortality rate in older patients with sepsis in general wards (87).

There is likely to be an interaction between premorbid conditions, health status, and patient characteristics with higher susceptibility to develop AKI or sepsis (46). For instance, AKI and sepsis are more common in older patients, patients with one or more comorbidities (e.g., diabetes mellitus, chronic kidney disease), patients with a specific condition, such as immune dysregulation (e.g., inflammatory diseases, Human Immunodeficiency Virus (HIV)), and risks of infections due to medical treatment (e.g., haemodialysis catheter, mechanical ventilation) (46).

There was no available information from the literature about comorbidities related to patients with both AKI and sepsis. The reported comorbidities were only for patients with AKI or sepsis. There were several patient groups with AKI or sepsis who had a high risk of mortality. The high-risk groups were patients with central nervous system failure, liver disease, respiratory disease, cardiovascular disease, metastatic disease, and cancer. A study by Hering and Winklewski reported that changes in the metabolic and circulatory system in patients with central nervous system failure led to kidney damage due to hypoperfusion and ischemia in the kidney, and also metabolic imbalance could aggravate sepsis (88). The pathological changes in the liver, lung, and myocardium in the heart exacerbated the cross organ talk injury in AKI (pre-renal and distant organ injury) and enhanced damage to other organs due to the contribution of released endotoxins in sepsis (66, 79). Similarly, the irreversible multi-organ damage in patients with metastatic disease and cancer increased the likelihood of multi-organ failure in the presence of AKI or sepsis (66).

In contrast, Pan et al. reported that chronic kidney disease could reduce the mortality of AKI patients because most patients were managed by a nephrologist (31). This potentially means that the prognosis of patients with chronic kidney disease could be improved with an early diagnosis of AKI or a timely intervention of a nephrologist (31).

Of the fifteen included studies, there were four studies that reported the association between the pre-existing conditions (comorbidities) and mortality for AKI patients. One paper reported the association of comorbidities and mortality in severe sepsis or septic shock patients. There was no

study reported about the comorbidities of patients with both AKI and sepsis. This means that the comorbidities and the relationship between age, mortality, and comorbidities of patients with both AKI and sepsis in general wards remain unclear.

2.6.2.4 Limitations

Despite extensive searching, this systematic review might have missed some relevant studies due to the variety in AKI and sepsis definitions and study populations. For example, studies of patients with AKI (ARF) and sepsis (septic/shock) that used in-hospital, follow-up, patient discharge data, and did not specifically describe a general ward population may not have been included in this systematic review. Meta-analysis was not performed due to the heterogeneity of the study design, methodology in diagnosing and managing patients with AKI and sepsis in the selected studies. In addition, this systematic review only included studies in English, which means related findings from studies about AKI and sepsis in general wards in different languages are missed.

To minimise the number of missing studies, the search for systematic review: 1) used broad search terms to include general ward populations and various definitions of AKI and sepsis in the literature, 2) did not have any restrictions on publication year, and 3) included any relevant studies from cross-referencing. As there was only one reviewer involved in this systematic review, two research librarians were also consulted in designing the search strategy and assisted with the database searches to reduce bias in selecting studies.

2.7 Conclusion

This systematic review investigated the general hospital population and presented the current evidence and details of the characteristics, incidence, and outcomes of patients with both AKI and sepsis in general wards. The findings show that the incidence and mortality of patients with AKI and sepsis in general wards are high. However, there was limited available information about the characteristics, incidence, and outcomes of patients with both conditions in general wards, especially in Australia. Further investigation of the characteristics, incidence, comorbid conditions, length of stay, and the relationship between associated factors in the Australian population will help better understand patients with both AKI and sepsis. Additional data from various institutions and ICUs will help describe a more accurate incidence rate of patients with both AKI and sepsis and its resulting outcomes, thus providing health providers greater information to improve outcomes of patients with AKI and sepsis.

CHAPTER 3. RETROSPECTIVE OBSERVATIONAL COHORT STUDY

3.1 Overview of Chapter 3

Chapter 3 presents the methods used and findings of a retrospective observational cohort study examining the characteristics, incidence, outcomes, and variation over time of general ward patients with AKI and sepsis in four Australian hospitals.

3.2 Methods

3.2.1. *Design and setting*

A retrospective observational cohort study was conducted using a linked dataset containing information extracted from Patient Admission Systems (PAS) and Laboratory Information Systems (LIS) from four hospitals in the South-Eastern Sydney/Illawarra regions of New South Wales, Australia (84) to examine the characteristics, incidence, and outcomes of patients with AKI and sepsis (i.e., the second aim of this thesis). This multicentre study included data from hospitals A, B, C (metropolitan hospitals) and hospital D (inner regional hospital) over five years (between January 2009 and December 2013) and investigated the variation of incidence and outcomes of patients with AKI and sepsis across different hospitals (i.e., the third aim of this thesis). In Australia, the health care system provides a comprehensive range of services from preventative health, general, urgent, and chronic care and is funded in partnership by the federal and state governments (89). All hospitals involved in the study are tertiary referral centres with an emergency department and ICU. However, AKI patients diagnosed in ICU were not included in the data.

3.2.2. *Study population and data collection*

The study included all hospitalised patients aged 18 and over. Patients who were not tested for serum/plasma creatinine test during the study period or already receiving dialysis or in the ICU were excluded (84). De-identified data from PAS and LIS from the previous work of our research group (for further details see Campbell et al. (84)) were used in this study. The linked data files

included information about in-hospital patients, such as patient characteristics (age and gender), diagnosis codes, date of hospital admission and discharge, length of stay (LOS), and hospital geographic area (metropolitan or regional). The diagnosis codes contained the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM) codes in relation to the diagnosis of the comorbidities of in-hospital patients.

3.2.3. *Diagnoses defined in the data*

AKI diagnosis and staging of AKI were defined using the Kidney Disease: Improving Global Outcomes Work Group (KDIGO) algorithm. Stage 1 of AKI was defined as an increase of serum creatinine 1.5-1.9 times from the baseline (37) within 7 days, or an increase of serum creatinine ≥ 26.52 μmol/L within 48 hours; stage 2 of AKI was defined as an increase of serum creatinine 2.0-2.9 times from the baseline; and stage 3 of AKI was defined as an increase of serum creatinine ≥ 353.6 μmol/L or 3.0 times from the baseline (11). Sepsis diagnosis and other comorbidities were defined according to the sepsis-related ICD-10-AM diagnosis codes (Appendix 5). The incidence of AKI and sepsis is defined as any cases of AKI diagnosis by KDIGO (based on serum/plasma creatinine test) and sepsis diagnosis by the ICD codes during the study period regardless of whether it was a primary or secondary diagnosis.

3.2.4. *Outcomes*

The primary outcome of this study was the trend of the incidence rate of patients with AKI and sepsis in general wards over five years period. The secondary outcomes were the characteristics, comorbidities, and length of stay of patients with AKI and sepsis in general wards.

3.2.5. *Statistical analysis*

In a situation where a patient had multiple hospitalisations during the study period, each hospitalisation was treated as an independent case. Thus, the number of admissions was used to calculate the incidence and outcomes (length of stay) of AKI and sepsis. Meanwhile, the patient characteristics, such as age and gender, were examined using the information from the first admission.

The comorbidities and variation of the number of hospitalised patients (the number of admissions) and the outcomes of patients with AKI and sepsis were also examined for each hospital over the 5-year study period. For categorical variables, values were presented as numbers (frequencies) and percentages. For continuous variables, means and standard deviations were calculated for the normal distribution, while median and interquartile range (IQR) were calculated for skewed distribution. The Chi-square test or Fisher's exact test was used to compare categorical variables and the Student t-test or Mann-Whitney test to compare continuous variables of patients with and without AKI and sepsis depending on whether the data were parametric or non-parametric. All p-values were two-tailed, and a p-value <0.05 was deemed statistically significant. All analyses were conducted using IBM SPSS Statistics for Windows (version 25.0, released 2017). The reporting of this study follows the STROBE (Strengthening the reporting of observational studies in epidemiology) statement (90) (details in Appendix 12).

3.2.6. *Ethical approval*

Ethics approval was obtained from the South-Eastern Sydney Health District Human Research Ethics Committee [16/041 (HREC/16/POWH/412)] (see Appendix 1 and 2).

3.3 Results

3.3.1. *Patient characteristics*

In the 5-year study period (2009-2013), there were 370,969 admissions from 192,133 patients in four hospitals in New South Wales, Australia. Of these 192,133 patients, 121,583 patients (63.3%) had only a single admission to the hospital, while 70,550 patients (36.7%) had two or more admissions.

Characteristics were presented using the first admission record for each patient. Based on the first admission record, the median age of patients with AKI and sepsis was 13 years older than patients without AKI and sepsis (72 [IQR: 60-82] vs. 59 [IQR: 39-75], p<0.001) (Table 3.1). There were more male patients identified with AKI and sepsis than female patients (58.0% vs. 42.0%, p<0.001), as shown in Table 3.1.

Table 3.1 The characteristics of patients with and without AKI and sepsis in the first admission

Patient characteristics	All hospitalised patients	Without AKI and sepsis	With AKI and sepsis
Number of patients	192,133	190,107*	2,026
Median age [IQR]	61 [40-76]	59 [39-75]	72 [60-82]
Range age	18-111	18-111	18-103
Male (%)	94,546 (49.2%)	84,479 (48.8%)	1,176 (58.0%)
Age groups (years)			
18-45	58,919 (30.7%)	62,355 (32.8%)	103 (5.1%)
46-60	36,722 (19.1%)	37,071 (19.5%)	363 (17.9%)
61-75	46,688 (24.3%)	44,865 (23.6%)	606 (29.9%)
>75	58,919 (30.7%)	45,626 (24%)	954 (47.1%)

* included a number of patients (53,069 patients from 82,079 admissions) who could not be assessed for their AKI status due to no creatinine test were ordered during their hospitalisation (no AKI status or unknown status). In view of this, we assume most of them would not have kidney issues.

Of 2,026 patients with AKI and sepsis, 1,500 patients (74.0%) were over 60 years old and only 526 (26.0%) patients were above 20 and below 60 years old. The percentage of patients with AKI and sepsis increased with age and 47.1% of AKI and sepsis patients were over 75 years old.

3.3.2. *Incidence of AKI, sepsis, and AKI and sepsis*

Of 370,969 admissions over the 5-year study period, AKI diagnosis was detected in 12.4% (46,101/370,969) of hospital admissions. Sepsis was identified in 3.4% (12,456/370,696) of admissions, while AKI and sepsis in 1.6% (6,057/370,969) of all hospital admissions (Figure 3.1) (details in Appendix 6).

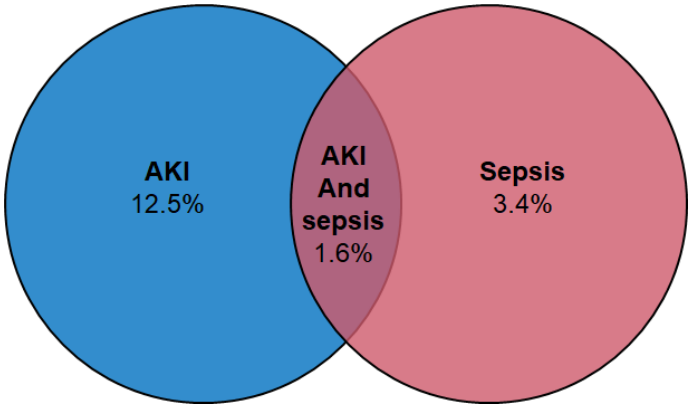


Figure 3.1 The incidence of AKI, sepsis, and AKI and sepsis of all hospital admissions (2009-2013)

The incidence of sepsis was found in around 9.7% of 33,246 AKI stage 1 hospitalisations, 21.3% of 6,185 of AKI stage 2 hospitalisations, and 22.5% of 6,670 of AKI stage 3 hospitalisations (Figure 3.2). The incidence of AKI with sepsis was significantly higher in patients with stage 2 and 3 AKI compared to patients with stage 1 AKI (21.3% and 22.5% vs. 9.7%, p<0.001).

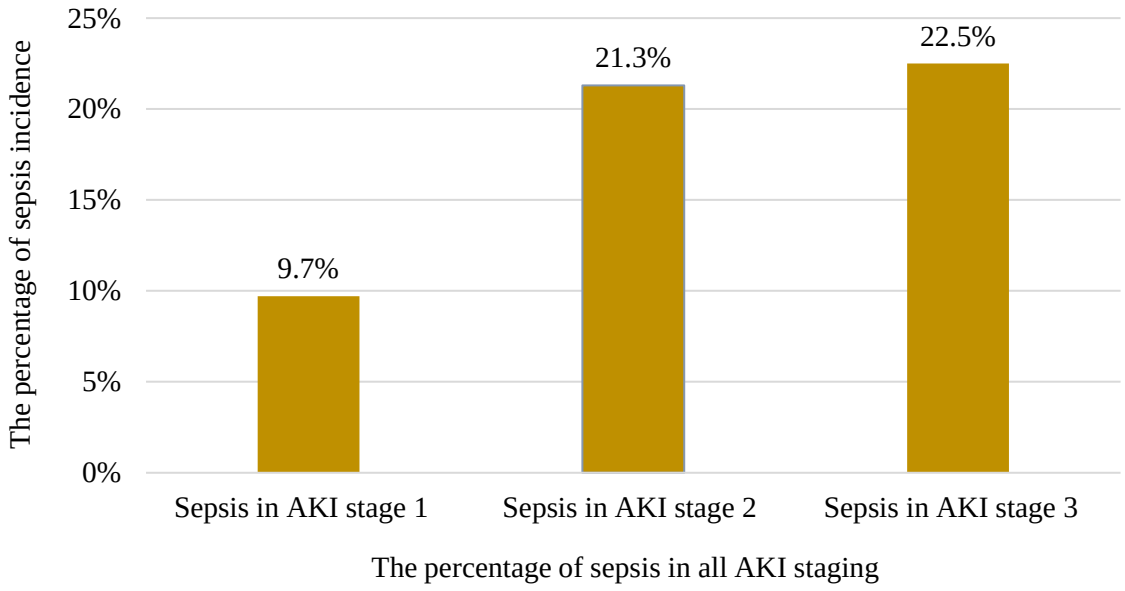


Figure 3.2 The incidence of sepsis in all AKI staging

3.3.3. *Comorbidities and outcomes of hospitalisations with AKI and sepsis compared to hospitalisations without AKI and sepsis*

3.3.3.1 Comorbidities

The incidence of AKI and sepsis was significantly higher (7-8 times higher) in hospitalisations within specific comorbidities (such as in chronic kidney disease, renal disease, and congestive heart failure) compared to admissions without AKI and sepsis ($p<0.001$). This indicates that hospitalised patients with AKI and sepsis were more likely to have selected comorbidities (Table 3.2) compared to patients who were hospitalised without AKI and sepsis.

Table 3.2 Comparison of hospital admissions with and without AKI and sepsis

Characteristics	**All admissions**	**Without AKI and sepsis**	**With AKI and sepsis**	**p-value** *
Total number of admissions (hospitalisations)	370,969	318,469	6,057	
LOS (median) days	3.1	2.5	16.9	<0.001 †
IQR	1-7.2	0.8-6.0	8.0-35.6	
Number of admissions (median [IQR])	1 [1-3]	1 [1-3]	2 [1-4]	<0.001 †
Range of number admissions (times)	1-86	1-85	1-54	
Comorbidities	N (% of all admissions)	N (% of all admissions)	N (% of all admissions)	N (% of all admissions)
Chronic kidney disease	29,134 (7.9)	14,427 (4.5)	2,127 (35.1)	<0.001 ‡
Renal disease	23,818 (6.4)	11,284 (3.5)	1,687 (27.9)	<0.001 ‡
Congestive heart failure	18,557 (5.0)	11,181 (3.5)	1,211 (20.0)	<0.001 ‡
Diabetes	16,832 (4.5)	13,665 (4.3)	418 (6.9)	<0.001 ‡
Cerebral vascular disease	15,125 (4.1)	12,242 (3.8)	416 (6.9)	<0.001 ‡
Acute myocardial infarction	13,718 (3.7)	9,644 (3.0)	568 (9.4)	<0.001 ‡
Diabetes complications	13,707 (3.7)	7,443 (2.3)	988 (16.3)	<0.001 ‡
Peripheral vascular disease	2,421 (0.7)	1,654 (0.5)	111 (1.8)	<0.001 ‡

Note: IQR = Interquartile range; Statistics: p-value: * = <0.001 is considered significant; † = Mann-Whitney U test; ‡ = Chi-square test.

Among 6,057 patients with AKI and sepsis, in relation to age, some pre-existing diseases were more common in older patients (age >60 years old) compared to younger patients (age 18-60 years old) ($p<0.001$). In contrast, the peripheral vascular disease was more common in younger patients (18-60 years old) than in older patients (> 60 years old) (Table 3.3).

Table 3.3 Comorbidities that are related to age for AKI and sepsis

Comorbidities	**Age 18-60 years (N=1,345, 22.2%) N (col %)**	**Age >60 years (N=4,712, 77.8%) N (col %)**
Acute myocardial infarction	55 (4.1%)	513 (10.9%)
Cerebral vascular accident	73 (5.4%)	343 (7.3%)
Chronic kidney disease	379 (28.2%)	1,748 (37.1%)
Congestive heart failure	140 (10.4%)	1,071 (22.7%)
Diabetes	81 (6.0%)	337 (7.2%)
Diabetes complications	156 (11.6%)	832 (17.7%)
Peripheral vascular disease	25 (1.9%)	86 (1.8%)
Renal disease	269 (20.0%)	1,418 (30.1%)

3.3.3.2 Admissions and length of stay

The median number of admissions with AKI and sepsis was two times higher than admissions without AKI and sepsis (2 [IQR: 1-4] versus 1 [IQR: 1-3] respectively, $p<0.001$). The length of stay (LOS) of hospitalisations for patients with AKI and sepsis was seven times longer compared to patients without AKI and sepsis (median 16.9 [IQR: 8.0-35.6] days versus 2.5 [IQR: 0.8-6.0] days respectively, $p<0.001$) (Table 3.2). The shortest LOS for AKI and sepsis hospitalisations were in the age group >75 years (Figure 3.3).

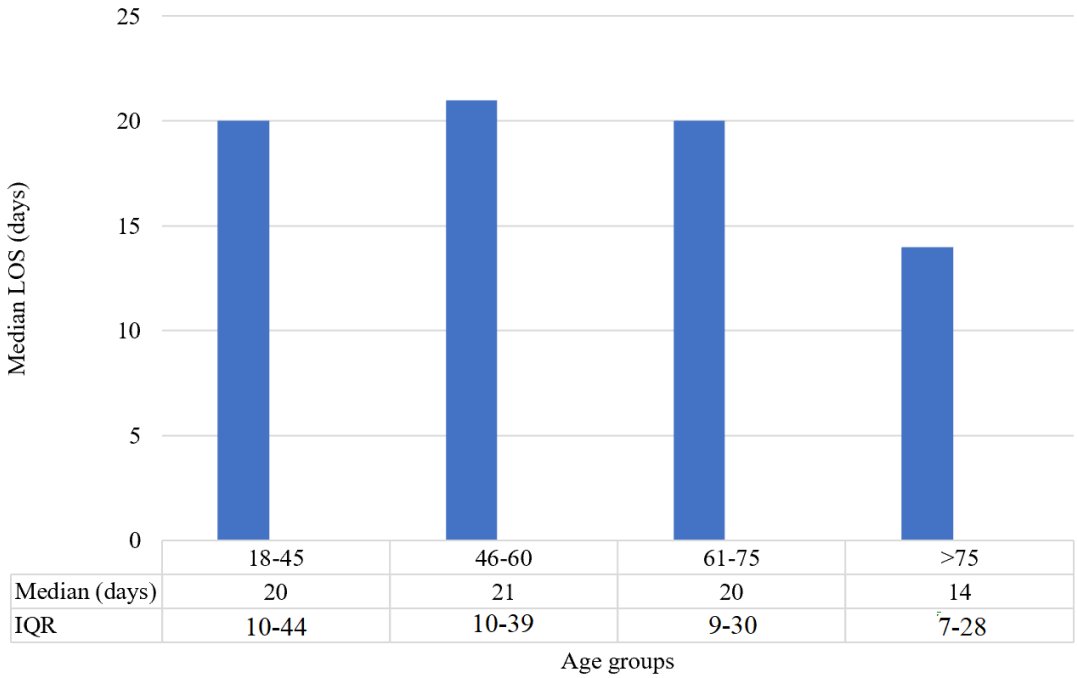


Figure 3.3 The variation of LOS of AKI and sepsis hospitalisation among age groups

The length of hospital stay of patients with AKI and sepsis was affected by the associated comorbidities. The longest median hospital stay was for AKI and sepsis admissions with peripheral vascular disease (34 [IQR: 15-74]), followed by cerebral vascular disease (31 [IQR: 14-60]), heart disease (acute myocardial infarction and congestive heart failure (20 [IQR: 9-41]), with diabetes complication (18 [IQR: 9-36]), and without diabetes complication (19 [IQR: 10-37]) (Table 3.4).

Table 3.4 The LOS of AKI and sepsis hospitalisations for selected comorbidities

Comorbidities	**Median (IQR) length of stay (in days)**
Peripheral vascular disease	34 (15-74)
Cerebral vascular disease	31 (14-60)
Acute myocardial infraction	20 (9-41)
Congestive heart failure	20 (10-40)
Diabetes	19 (10-37)
Diabetes with complication	18 (9-36)
Chronic kidney disease	17 (8-33)
Renal disease	16 (9-36)

IQR = Interquartile range

The LOS of AKI and sepsis hospitalised patients among age groups also varied with selected comorbidities (Figure 3.4). The longest LOS was found in the age group 18-45 years with

peripheral vascular disease (118 [IQR: 32-130]), cerebral vascular disease (61 [IQR: 15-84]), diabetes (39 [IQR: 11-77]), and diabetes with complications (27 [IQR: 11-46]) (details are presented in Appendix 7).

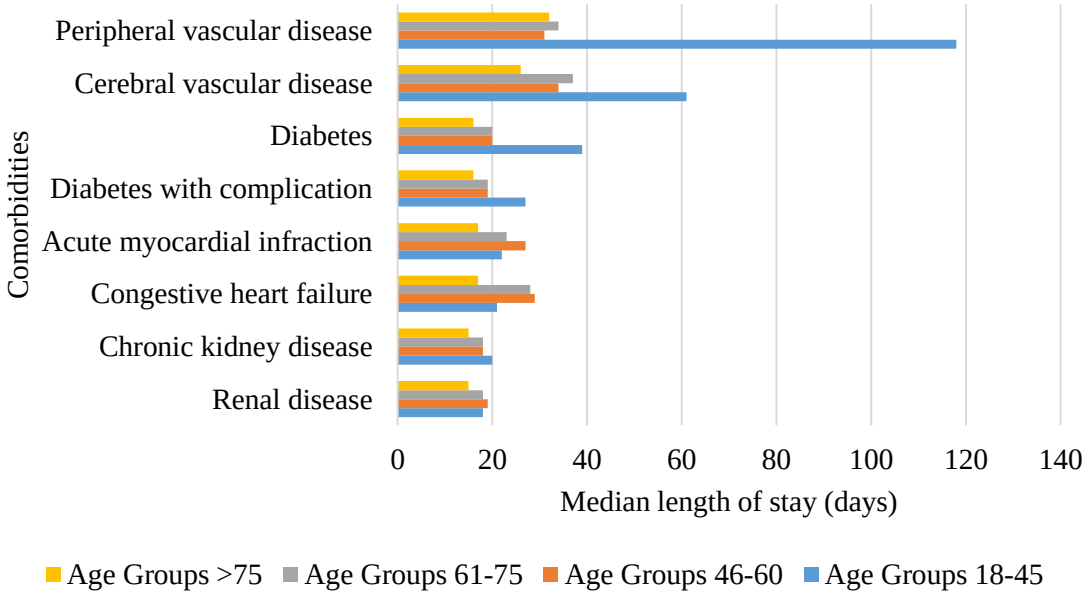


Figure 3.4 The LOS of AKI and sepsis hospitalisations in specific age groups with selected comorbidities

3.3.4. *Variation of AKI and sepsis in four hospitals from 2009-2013*

3.3.4.1 Patient characteristics

The characteristics of patients with AKI and sepsis from the four hospitals during the study period based on the first admission records are summarised in Table 3.5. The majority of patients with AKI and sepsis were from metropolitan hospitals (811 of 2,026 in hospital A, 629 of 2,026 in hospital B, 435 of 2,026 in hospital C) and only 7% (151/2,026) in the regional hospital (hospital D). Data from across all hospitals showed that the number of patients with AKI and sepsis increased with age. The oldest patients were in the regional hospital (76 [IQR: 63-83]), where most of the patients (50.3%) were above 75 years of age.

Table 3.5 Summary of patient characteristics with AKI and sepsis from the four hospitals

Characteristics	Hospital				Total
	A	B	C	D	
Number of patients	811	629	435	151	2,026
Age (median [IQR])	72 [59-83]	71 [58-80]	75 [62-82]	76 [63-83]	72 [60-82]
Age group (col %)					
18-45	86 (10.6)	83 (13.2)	22 (5.1)	9 (6.0)	200 (9.9)
46-60	130 (16)	97 (15.4)	78 (17.9)	21 (13.9)	326 (16.1)
61-75	248 (30.6)	212 (33.7)	130 (29.9)	45 (29.8)	635 (31.3)
>75	347 (42.8)	237 (37.7)	205 (47.1)	76 (50.3)	865 (42.7)
Female (col %)	347 (42.8)	249 (39.6)	189 (43.4)	65 (43.0)	850 (42)
Male (col %)	464 (57.2)	380 (60.4)	246 (56.6)	86 (57.0)	1,176 (58)

IQR = Interquartile range

3.3.4.2 Variation of AKI and sepsis admissions

Of the 6,057 AKI and sepsis hospitalisations, there were more male patients with AKI and sepsis than female patients identified in the four hospitals (54.8%-58.3% and 41.7%-45.8% respectively) (Figure 3.5). The percentage of admissions for male patients with AKI and sepsis tended to increase from 2009 to 2013, while there was a decrease for female patients (Figure 3.5).

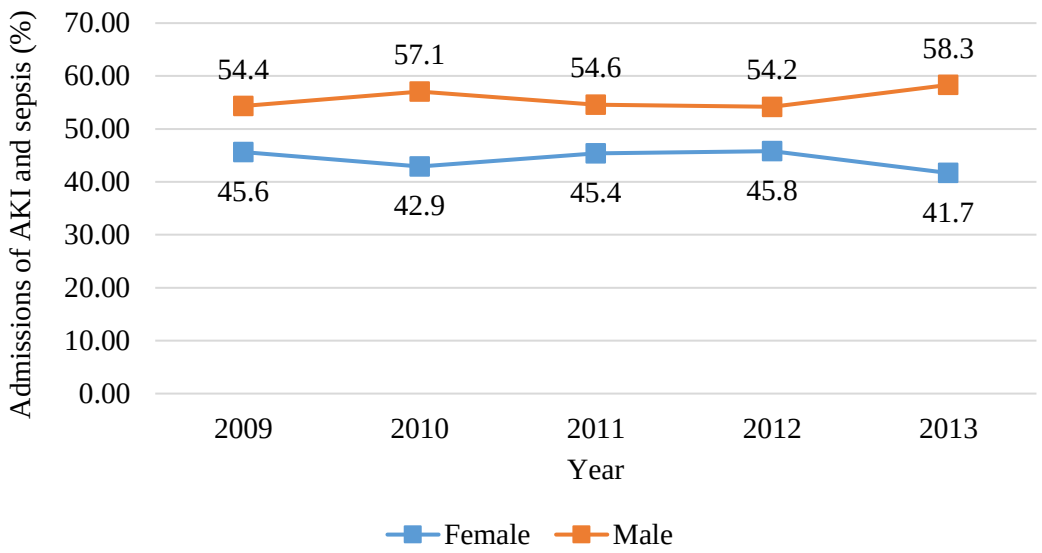
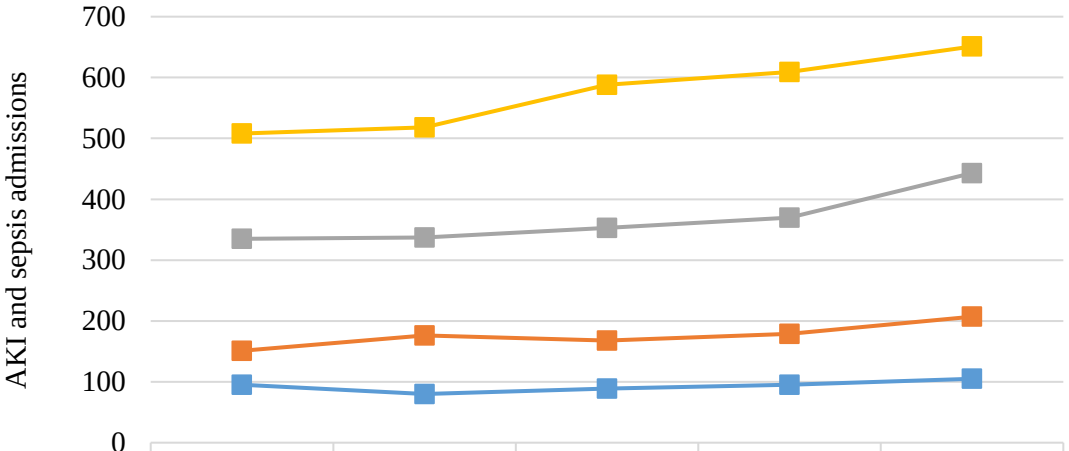


Figure 3.5 The number of hospital admissions based on gender from the four hospitals (2009-2013)

The number of AKI and sepsis hospitalisations among the age groups in all hospitals increased between January 2009 to December 2013, especially for the age groups 61-75 and >75 years (Figure 3.6). However, the increase in AKI and sepsis hospitalisation could be due to the increasing number of hospitalisations in all hospitals (Appendix 8).



	2009	2010	2011	2012	2013
18-45	95	80	89	95	105
46-60	151	176	168	179	207
61-75	335	337	353	370	443
>75	508	518	588	609	651

Figure 3.6 Variation in the number of AKI and sepsis admission for different age groups in all hospitals from 2009 to 2013

3.3.4.3 Variation in the incidence of AKI and sepsis over a five-year period in the four hospitals

In general, there was little variation (1.62%-1.76%) in the incidence of patients with AKI and sepsis from January 2009 to December 2013 for all four hospitals (details are shown in Appendix 6). During the study period, it was identified that there was a higher number of admissions for AKI and sepsis in 2009 compared to 2013 (1,089 admissions vs. 1,406 admissions). The increase in the number of hospital admissions was followed by an increase in the incidence of AKI and sepsis from 1.62% (1,089/67,300) in 2009 to 1.76% (1,406/80,0890) in 2013 (Figure 3.7).

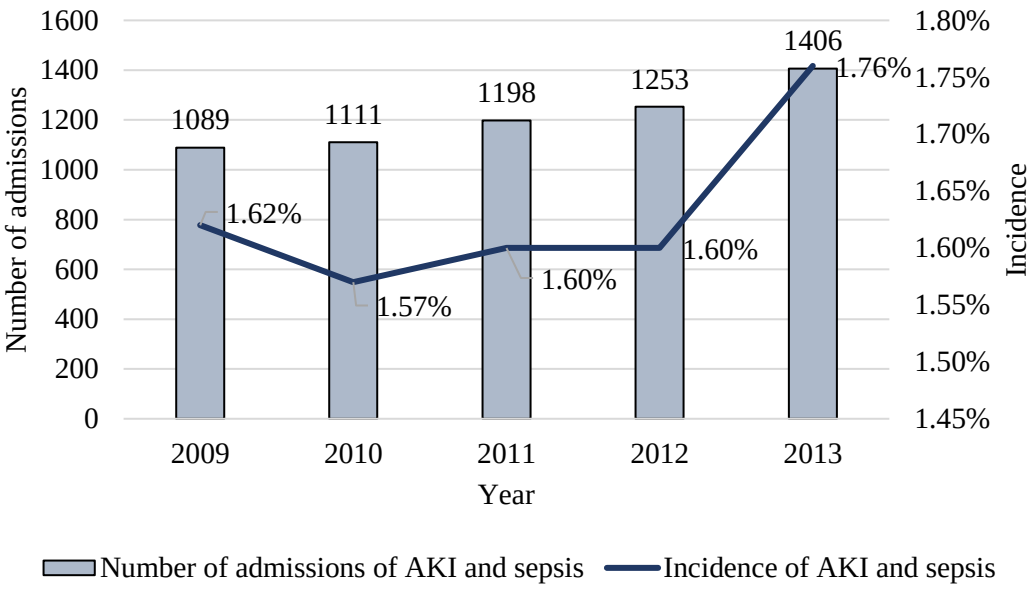
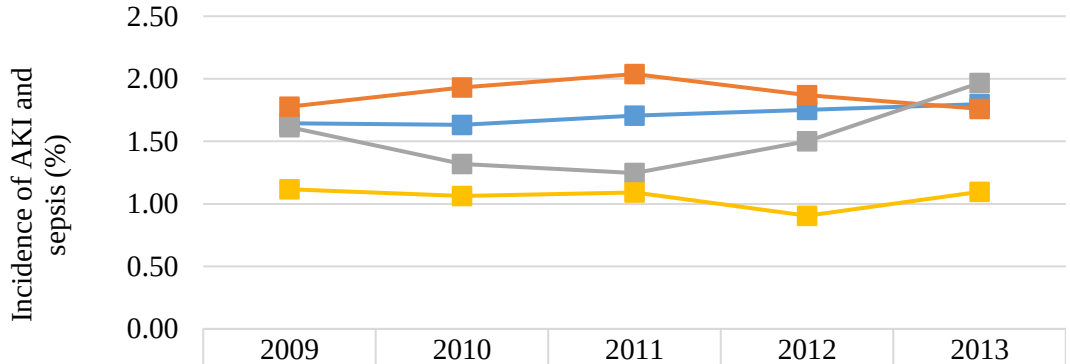


Figure 3.7 Incidence of AKI and sepsis admissions from the four hospitals between 2009 and 2013

The variation of AKI and sepsis incidence over five years in each hospital is shown in Figure 3.8 (details are provided in Appendix 8). During the study period, the lowest AKI and sepsis incidence was in the regional hospital (hospital D) compared to the metropolitan hospitals (hospitals A, B, and C) (0.90% - 1.12% vs. 1.25% - 2.04%). In general, the incidence of AKI and sepsis patients varied over time and the increase was small. In hospital C, this involved an increase in the incidence of AKI and sepsis from 1.61% (278/17,238) in 2009 to 1.93% (469/23,854) in 2013. There was a slight decrease in the AKI and sepsis incidence in hospital B in 2013 (Figure 3.8).

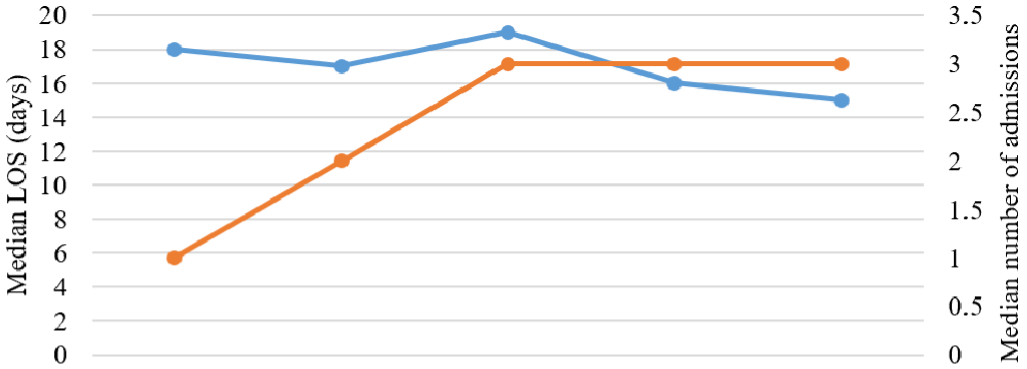


	2009	2010	2011	2012	2013
Hospital A	1.64	1.63	1.71	1.75	1.80
Hospital B	1.78	1.93	2.04	1.87	1.76
Hospital C	1.61	1.32	1.25	1.50	1.97
Hospital D	1.12	1.06	1.09	0.90	1.10

Figure 3.8 The variation of AKI and sepsis incidence in each hospital from 2009-2013

3.3.4.4 Variation of outcomes in four hospitals from 2009 to 2013

The median number of times AKI and sepsis patients were hospitalised also increased from 1 (IQR: 1-2) admissions in 2009 to 3 (IQR: 2-6) admissions in 2013. However, the duration of stay for AKI and sepsis patients in the four hospitals has decreased from 18 days in 2009 to 15 days (Figure 3.9).



	2009	2010	2011	2012	2013
LOS (median (IQR)) days	18.0 (7.7-35.2)	17.1 (8.3-36.5)	18.6 (8.2-35.8)	16.3 (8.3-31.8)	15.2 (7.7-30.0)
Number of admissions (median (IQR))	1 (1-2)	2 (1-4)	3 (1-4)	3 (1-5)	3 (2-6)

Figure 3.9 The LOS and number of admissions (hospitalisations) of AKI and sepsis patients in all hospitals from 2009 to 2013

The variation in the length of stay (LOS) between each hospital over five years is shown in Figure 3.10 (see more details in Appendix 9). The median LOS for AKI and sepsis admissions decreased in the three metropolitan hospitals (hospitals A, B, and C) from 16-21 days in 2009 to 15-17 days in 2013. In contrast, there was a slight increase in the median LOS in the rural hospital (hospital D) from 8 days in 2009 to 10 days in 2013. The decrease in LOS of AKI and sepsis patients was also present in all age groups (Figure 3.11).

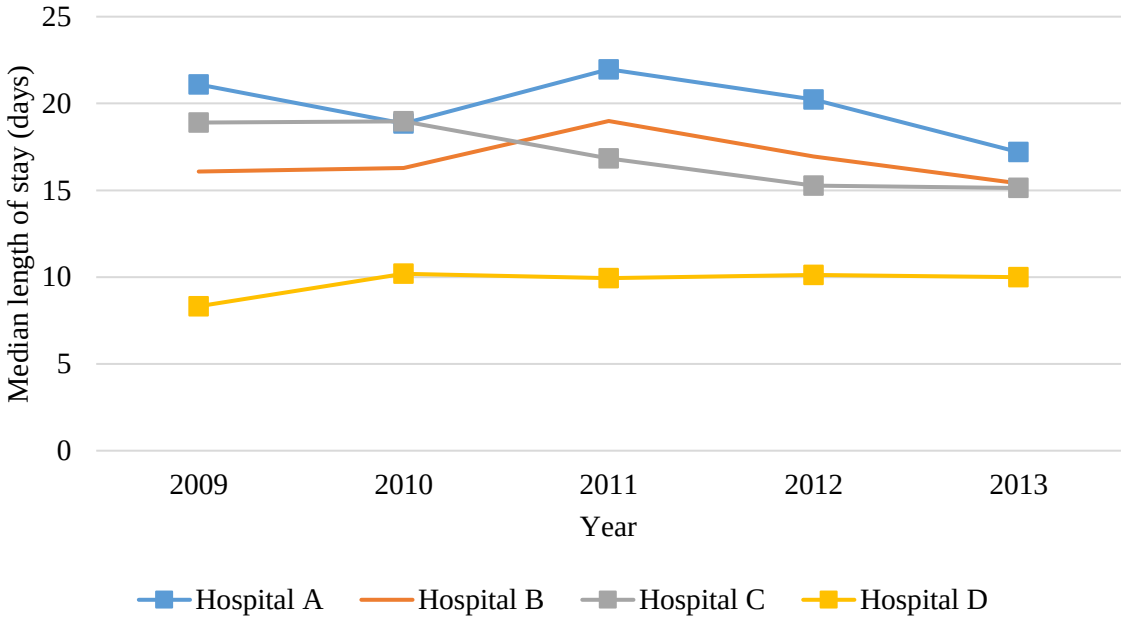


Figure 3.10 The median LOS for patients with AKI and sepsis per hospital from 2009-2013

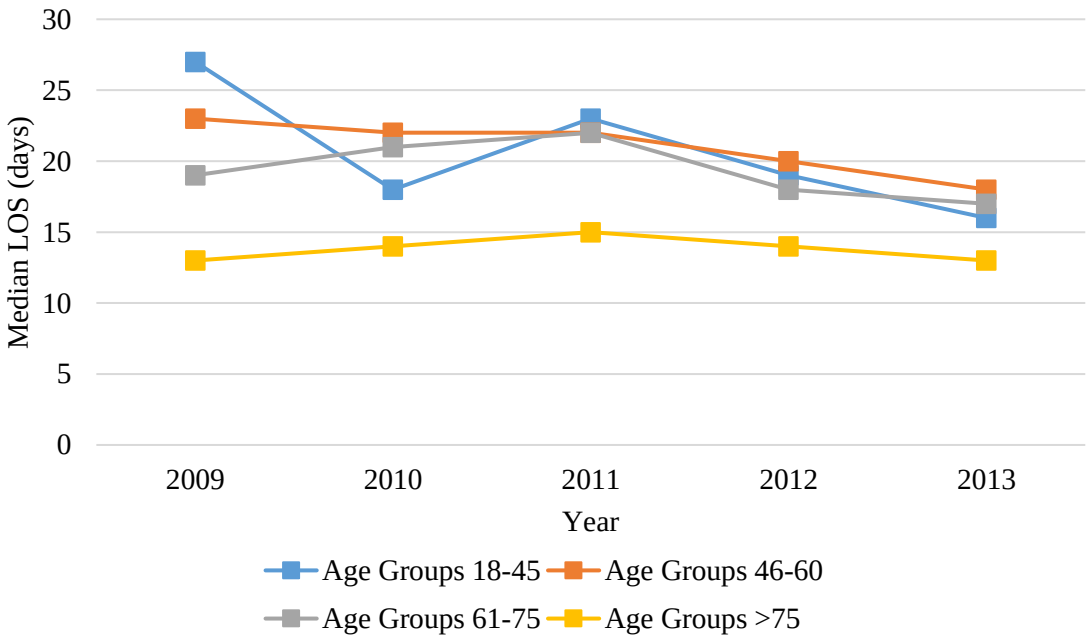


Figure 3.11 The median length of stay (LOS) between age groups from 2009 to 2013

During the study period, the percentage of sepsis incidence was slightly increased in all AKI staging, from 8.6% of 6,580 AKI stage 1, 23.6% of 1,274 AKI stage 2, and 21.6% of 1,294 AKI stage 3 hospitalisations in 2009 to 12.3% of 6,506 AKI stage 1, 23.6% of 1,185 AKI stage 2, and 23.5% of 1,384 AKI stage 3 hospitalisations in 2013. (Figure 3.12). The incidence of sepsis was high in patients with stage 2 and 3 AKI across four hospitals, with the highest incidence was in patients with stage 3 AKI (19.8%-25.6%), with the lowest incidence was in patients with stage 1 AKI (9.0%-10.1%) (Figure 3.13).

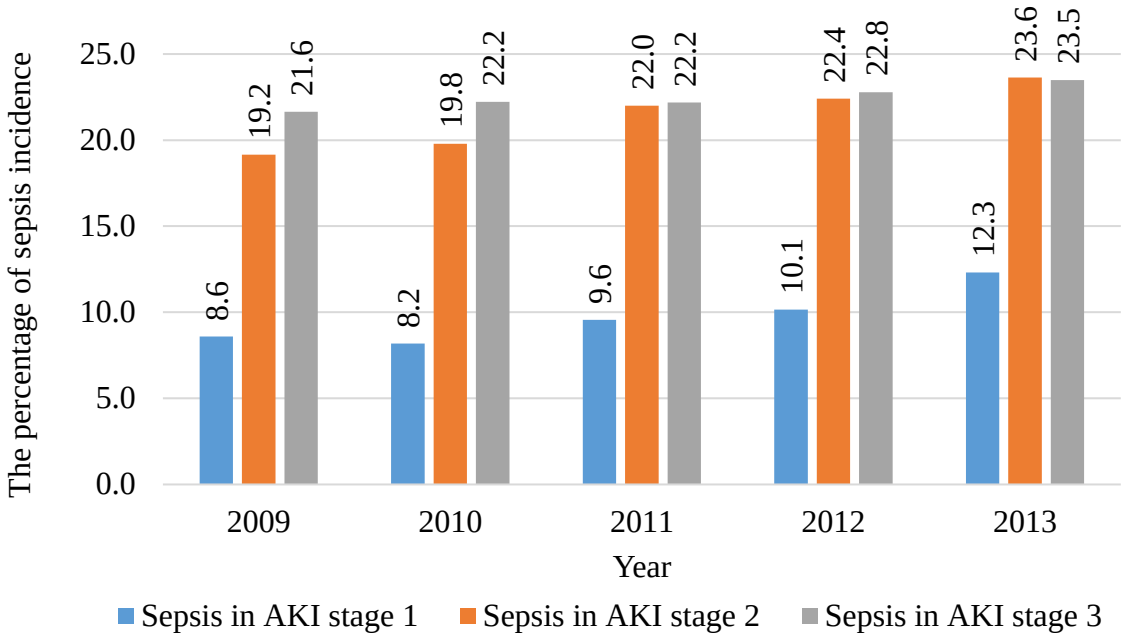


Figure 3.12 The incidence of sepsis in all staging AKI from 2009-2013

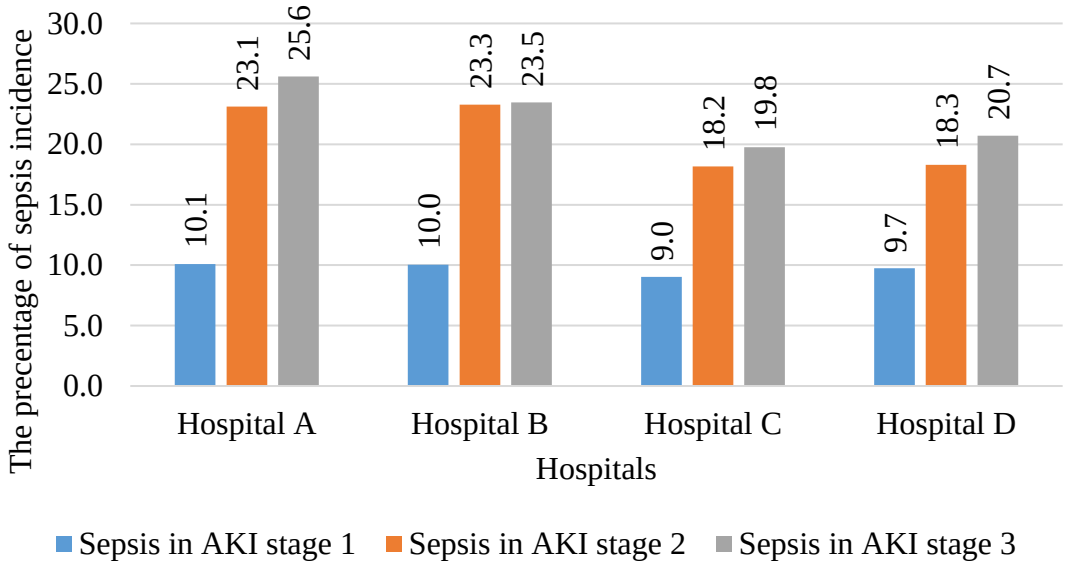


Figure 3.13 The incidence of sepsis in all staging AKI in the four hospitals

It was also identified that the percentage of all AKI stages from 2009 to 2013 decreased (Figure 3.14). In AKI stage 1, the percentage was down from 9.8% (6,580/67,300) in 2009 to 8.1% (6,506/80,089) in 2013, AKI stage 2 from 1.9% (1,274/67,300) in 2009 to 1.5% (1,185/80,089) in 2013, and AKI stages 3 from 1.9% (1,294/67,300) in 2009 to 1.7% (1,384/80,089) in 2013 (details in Appendix 10). However, there was an increase in the percentage of sepsis hospitalisations (Figure 3.15). The percentage of sepsis hospitalisations increased from 3.0% (2,038/67,300) in 2009 to 4.1% (3,308/80,089) in 2013 (details in Appendix 10).

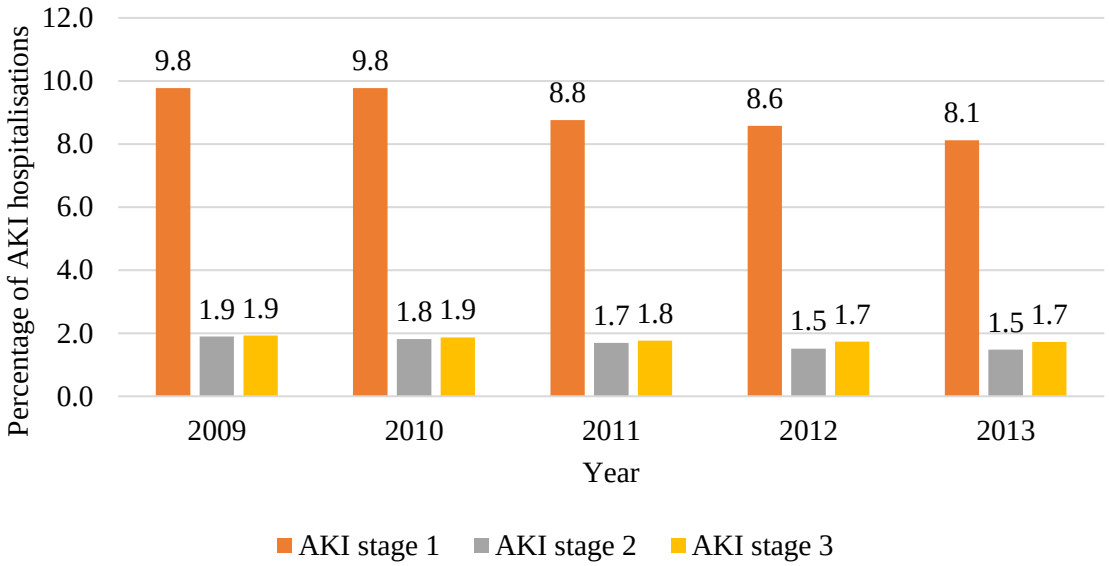


Figure 3.14 The incidence of AKI stages from 2009 to 2013

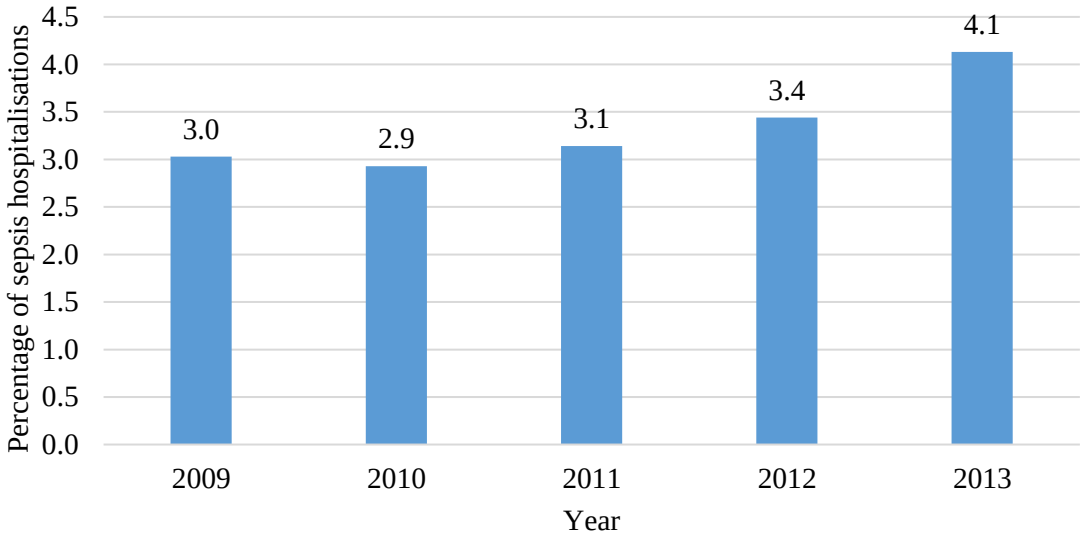


Figure 3.15 The incidence of sepsis from 2009 to 2013

The highest incidence of AKI stage 1 was found in the metropolitan hospitals with 9.9% (11,938/120,006) in hospital A, 9.1% (9,143/100,267) in hospital B, and 8.9% (9,330/105,393) in hospital C. Of 45,303 hospitalisations in the regional hospital (hospital D), hospital D has the lowest incidence for all AKI staging (6.3% for AKI stage 1, 1.3% for AKI stage 2, and 0.9% for AKI stage 3) (Figure 3.16). The incidence of sepsis was similar between hospitals, 3.7% (4,429/120,006) in hospital A, 3.5% (3,507/100,267) in hospital B, 3.1% (3,308/105,393) in hospital C, and 2.6% (1,159/45,303) in hospital D (Figure 3.17). Details are provided in Appendix 11 and 12.

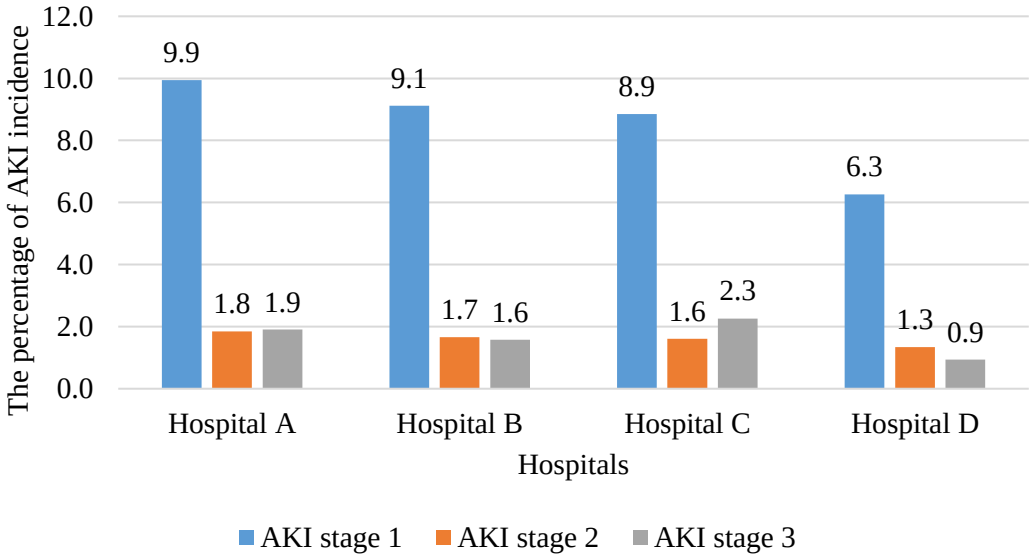


Figure 3.16 The incidence of AKI stage 1, 2, and 3 in the four hospitals

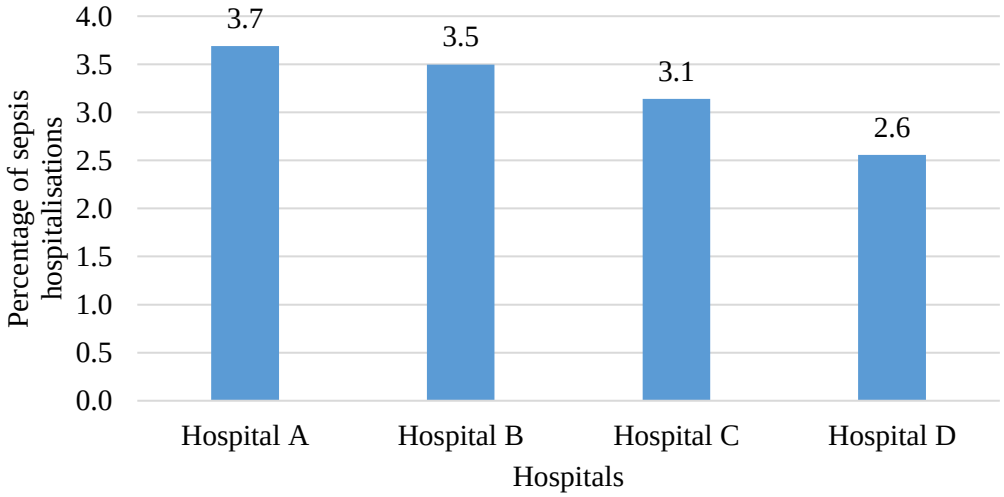


Figure 3.17 The incidence of sepsis in the four hospitals

3.4 Discussion

3.4.1. *The characteristics, incidence, and outcomes*

In this multicentre study, AKI and sepsis was detected in 1.6% of hospitalisations across the four metropolitan and regional hospitals between January 2009 and December 2013. Patients with AKI and sepsis were mostly males (58%), elderly >75 years old (47.1%) with median age 72 (IQR: 60-82) and were commonly found in hospitalisations with AKI stages 2 and 3 (Table 3.1, Figure 3.3). Our findings showed that the median age of patients with AKI and sepsis were similar to the findings in two studies from India (79) and Uganda (82) (see Chapter 2). Those studies reported that in general wards, patients with AKI and sepsis were older (>59 years old), or 75.4% of patients were above 60 years old (79, 82). Our finding concorded with a multicentre study from 57 ICUs in Australia and New Zealand, which also reported the mean age±SD of patients with AKI and sepsis was 66.7±15.5 (4).

During the study period, the incidence of patients with AKI and sepsis increased with age (Table 3.1) and was shown by a high incidence of AKI and sepsis in the elderly (age >60 years old). The high number of AKI and sepsis cases in older groups could be due to more comorbidities. Patients with either chronic kidney disease, renal disease, congestive heart failure, or diabetes with complications had a higher incidence of AKI and sepsis than patients without AKI and sepsis (Table 3.2). This suggests that certain characteristics, for instance, older age (above 60 years), male, and accompanied with specific comorbidities, would increase the possibility of AKI and sepsis admissions in the general ward.

We found that patients with AKI and sepsis stayed almost seven times longer than patients without AKI and sepsis (median: 16.9 days vs. 2.5 days, $p < 0.001$) (Table 3.2). The majority of AKI and sepsis patients with selected comorbidities have longer LOS. Especially in the age group 18-45 years, patients stayed around 39 days to 118 days in the hospital if accompanied by peripheral vascular disease, cerebral vascular disease, and diabetes. (details are provided in Appendix 7). The prolonged stay of patients with AKI and sepsis in general wards was likely due to the chronic diseases (e.g., peripheral vascular disease, cerebral vascular disease, and diabetes) found in the patients with AKI and sepsis, which may cause the patients to stay longer in the medical ward (4, 91, 92). This suggests that the cost burden of patients with AKI and sepsis in general wards could be higher compared to patients without AKI and sepsis, not only due to a longer LOS, but also the treatments to the accompanying diseases (91, 93).

However, it was identified that the LOS in the age group >75 years was shorter compared to the age groups <75 years old (14 days vs. 20-21 days) (Figure 3.3). This finding could be related to the poor outcomes of AKI and sepsis in elderly patients (low survival rates in patients with AKI and sepsis over 75 compared to younger age patients (19)) who had more comorbidities (such as renal disease, heart disease, and diabetes) that were commonly found in stage 2 and 3 AKI than in the younger age groups.

3.4.2. *Variation of AKI and sepsis during the study period across different hospitals*

Our findings found that the incidence of AKI and sepsis was slightly increased from 2009 to 2013 (Figure 3.7, Figure 3.8, and Appendix 6). The increase of the incidence of AKI and sepsis could be due to the increase in the incidence of sepsis in all staging of AKI (Figure 3.12 and 3.15). We also observed that the incidence of sepsis was higher in stage 2 and 3 AKI compared to stage 1 AKI, where 1 in 5 patients with AKI stage 2 or 3 had sepsis (Figure 3.12 and 3.13). This finding was similar to other previous studies that reported the incidence of sepsis associated with the greater severity of AKI (4, 52). It was predicted that the deterioration in the kidney function increased the susceptibility of sepsis development, and once sepsis developed in AKI patients, the morbidity and mortality of patients with AKI and sepsis also increased (52). This means that it is important for clinicians to monitor the AKI progression from an early stage to reduce poor outcomes (52).

We also noted that the increase of AKI and sepsis incidence was followed by the increasing number of AKI and sepsis admissions (three times higher in 2013 than in 2009), especially in people over 60 years old (Figure 3.6). This finding supports the notion in previous studies that also reported the growth of AKI or sepsis was related to the increase of the number of patients who were susceptible to both diseases such as older age (>60 years) (94, 95). It was suggested that ageing increased the risk of AKI and sepsis (94, 95). This was due to the functional and structural changes that reduced the kidney's function and the body's response to infection (94, 95). Another reported factor that had contributed to the growth of AKI and sepsis was the increase of the number of patients with specific comorbidities such as chronic kidney disease, diabetes, and congestive heart failure. This concordance with our finding, which found the number of admissions for patients over 60 years old who have more comorbidities increased by around 30% from 2009 to 2013 (Table 3.3 and Figure 3.6).

Another interesting finding from this research was the incidence of AKI and sepsis in metropolitan hospitals was slightly higher compared to a regional hospital in New South Wales, Australia (1.7% vs. 1.05%). It was predicted that there was a tendency in developed countries that patients (especially age <60 years old) with sepsis in a rural area would seek care in a larger hospital in a metropolitan area (96). The shortest LOS for patients with AKI and sepsis across the four hospitals was in the regional hospital. This could be due to the limited bed availability in the rural hospitals that increased patients' turnover (a shorter LOS) and led to more transfer to a larger hospital (97, 98).

Compared to the reported incidence of AKI and sepsis (around 6.4%-30.3%) in developing countries (31, 78, 81, 99) (see Chapter 2), the incidence of AKI and sepsis in the cohort study from the four hospitals in Australia was considered low (1.6%). The low incidence of AKI and sepsis was also similar to the findings from two studies that reported 2.1% incidence rate in general wards in the USA (9, 75). The advanced health care systems and supports from the government in the developed countries in raising awareness and early identification of AKI and sepsis, especially in high-risk populations, could be the factors that prevented the development of AKI and sepsis (9, 75, 100). In contrast, the high incidence of AKI and sepsis in the developing countries could be due to socioeconomic factors (inadequate housing, less accessible of sanitation and safe drinking water supply) and health status of the population (poor nutrition, comorbidities such as diabetes or tuberculosis) (32, 79, 101, 102). These factors could increase the susceptibility to infectious diseases from bacteria, viruses, or parasites (as predisposing factors of AKI and sepsis) (32, 79, 101, 102).

3.5 Limitations

There are several limitations in this study:

1. This study only focuses on patients who had serum creatinine results because AKI cases were identified based on the creatinine results. However, the majority of in-hospital patients (83.7%) had a laboratory test and serum creatinine is commonly included in the laboratory test set for in-hospital patients (103).
2. The analysis in the retrospective observational cohort study is primarily descriptive. There are many different factors that could impact the outcomes (the LOS associated with AKI and sepsis patients), that need to be adjusted and measured by comprehensive inferential statistics. However, the research provides new baseline information on patients with AKI and sepsis in general wards.

3. Due to the multicentre design and the retrospective nature of this study, the decision-making process in coding for AKI or sepsis using the ICD-10-AM system could be different among the four hospitals. This means that there was a possibility of error in diagnosing, classifying, and coding the information.
4. The use of ICD-10-AM codes to identify medical conditions for identification of sepsis and the comorbidities related to AKI and sepsis may also affect the accuracy of data. AKI diagnosis (based on the KDIGO) has been used in many studies, such as in (31, 73, 76). Sepsis patients were identified based on the ICD-10-AM codes, which were previously used in another Australian study (see (104)). However, there is a possibility that some patients with sepsis were not recorded as such by the ICD-10-AM recording process.
5. There was no available information on the temporal order of AKI and sepsis injury (sepsis before AKI, AKI before sepsis, or simultaneous exposure). This means there was a possibility that there were some patients in our study who did not have two conditions (AKI and sepsis) concurrently at the same time due to long hospital stay. Unfortunately, these patients could not be identified by our dataset.
6. Finally, mortality, transfer, and readmissions data were unavailable for this project. Thus, the complications caused whether by AKI or sepsis and the implications of AKI and sepsis to the study population could not be evaluated.

3.6 Conclusion

In summary, this study found that patients with AKI and sepsis were mostly older patients (age ≥60 years, median age 72 [IQR: 60-82]), more common in male (55.8%), had higher morbidity, a longer LOS, and multiple admissions, compared to patients without AKI and sepsis ($p<0.001$). Over the 5-year study period, the variation of AKI and sepsis incidence in four hospitals in New South Wales, Australia was ranging from 1.62% to 1.76%, with the incidence in the three metropolitan hospitals (1.25%- 2.04%) was higher than in the regional hospital (0.9% - 1.12%). It was also identified that the AKI and sepsis incidence increased with the severity of AKI (especially in stage 2 and 3 AKI).

CHAPTER 4. DISCUSSIONS AND CONCLUSIONS: PATIENTS WITH AKI AND SEPSIS IN GENERAL WARDS

Chapter 4 summarises the findings from the systematic review and cohort study presented in Chapters 2 and 3 respectively to address the research aims defined in Chapter 1. This chapter also discusses the contributions and implications of the study, followed by a discussion of the overall strengths and limitations of the study as well as identifying some future directions. This is followed by a conclusion to the research presented in this thesis.

4.1 Discussion of key findings for aim 1: the reported incidence and outcomes of patients with AKI and sepsis in general wards

A systematic review was performed to identify, examine, and summarise the reported characteristics, incidence, and outcomes of patients with AKI and sepsis in general wards (see Chapter 2). The results from the systematic review provide updates of the current status and knowledge gap in the literature about patients with AKI and sepsis in general wards. As reported in the systematic review, AKI and sepsis in general wards account for up to one-third of hospitalisations and are associated with high morbidity and mortality. There were various definitions used to define AKI and sepsis. This resulted in: 1) a huge range of reported incidence and mortality rates, and 2) difficulties in comparing the epidemiology of patients with AKI and sepsis. Furthermore, patients with AKI and sepsis in the general ward population were understudied as evidenced by inadequate reporting of 1) the characteristics of patients with AKI and sepsis, 2) the relation between the variation in the incidence rate and the geographic areas of the studied population, and 3) other comorbidities associated with AKI and sepsis. This emphasises the need to investigate patients with AKI and sepsis in general wards, which was conducted in this MRes research.

4.2 Discussion of key findings for aims 2 and 3: the characteristics, incidence, outcomes, and variation over time (from 2009 to 2013) of general ward patients with AKI and sepsis in Australia

A retrospective observational cohort study was conducted to investigate the incidence and main outcomes of patients with AKI and sepsis in general wards in four hospitals in Australia (three metropolitan hospitals and one regional hospital). This study found different characteristics and outcomes between patients with AKI and sepsis and patients without AKI and sepsis, different incidence of AKI and sepsis in metropolitan and regional hospitals, the relation between the comorbidities associated with AKI and sepsis and the duration of stay in hospital, and the variation of outcomes in four hospitals over the 5-year study period.

Patients with AKI and sepsis in general wards were older, had more admissions, a longer stay in a hospital, and had more comorbidities (e.g., chronic kidney disease, congestive heart failure, or diabetes) compared to patients without AKI and sepsis. AKI and sepsis patients with the above-mentioned chronic diseases had LOS two times or even four times longer than patients without AKI and sepsis. Previous studies have also reported that patients with AKI and sepsis in the ICU setting were also older, generally sicker due to more comorbidities and had longer LOS compared to patients without AKI and sepsis (4, 28, 58, 105). This means that patients with AKI and sepsis in both settings had a poorer prognosis than patients without AKI and sepsis.

Our finding also shows a strong association between patients with AKI and sepsis and chronic kidney disease, congestive heart failure, or diabetes. This finding aligns with previous studies (13, 106-114). Previous studies also reported that AKI and sepsis caused multiple organ damage to the kidney itself and distant organ (110, 111, 113-118). This was due to inflammation from AKI that could: 1) cause distant organ injury in the liver, heart, brain, and lung, and 2) reduce blood perfusion that could diminish cardiac function and might have superimposed effect in renal ischemia (especially in patients with diabetes) (113-115). Furthermore, sepsis could also trigger molecular inflammation pathway through cytokines or radicals that 1) induced AKI especially in patients who already have kidney impairment (such as in chronic kidney disease), 2) caused an injury in the endothelial, or atherosclerosis due to activation of the platelet that can have a harmful effect on the cardiac function (110, 111, 116-118).

Our findings suggest that it is a good idea for future multi-specialist team care, (e.g., a collaboration team consists of a nephrologist, endocrinologist, and cardiologist) for management

or treatment of patients with AKI and sepsis in general wards (19, 114). The involvement of multi-specialist team care, together with critical care outreach services, will be beneficial in facilitating transfer patients from general wards to ICU or vice versa in a timely manner to support fast treatment in the ICU or recovery in general wards (119). This multi-specialist team care should also be followed by a long-term follow up to reduce readmission after patients have been discharged (19, 114). A previous study reported nearly one-third of the patients with AKI and sepsis were more likely to be readmitted to the hospital within 30-90 days after discharge due to their chronic comorbidities (120). Therefore, the involvement of clinicians in monitoring patients with AKI and sepsis after discharge is essential to identify any risk factors that related to the readmission and to reduce or prevent other factors that could increase the risk of readmissions such as infections and nephrotoxic agents (121-123). Based on the Australian Commission on Safety and Quality in Health Care report, the readmission status (30-day readmissions) could a quality metric measurement used to quantify and monitor the effectiveness of healthcare delivery in hospitals after patients are discharged (124). There were also some studies suggested that follow up for outpatient with AKI or sepsis could reduce AKI or sepsis complications (125-127).

It was also identified from our study that a higher incidence of AKI and sepsis in metropolitan hospitals compared to the regional hospital. The lower incidence of AKI and sepsis in the regional hospital could be due to a number of patients with AKI and sepsis who lived near to the major city would prefer to go to bigger hospitals in metropolitan instead (96). However, previous studies reported that the incidence of AKI or sepsis was identified high in the outer regional areas (the remote and very remote areas), especially in the Indigenous population who lived in both areas (13, 128, 129). The high proportion of AKI and sepsis could be caused by the socioeconomic factors that might relate to poor health status and a high rate of chronic kidney disease, which is related to AKI and sepsis (13, 128).

During the study period, there was a small increase in the incidence of AKI and sepsis (only around 14%) compared to the incidence in 2009. The increase in AKI and sepsis incidence could be caused by an increase in sepsis incidence (from 3.0% in 2009 to 4.1% in 2013 in our findings). The findings also concord with a previous Australian study that reported the incidence of sepsis increased from 7.2% in 2000 to 11.1% in 2012 (130). Similarly, the study by Bashaw et al. (4) also estimates that the number of patients with septic AKI in the ICU is likely to increase over time. This is probably due to an ageing population, the presence of comorbidities, increased awareness in sepsis recognition, and increased use of sepsis ICD code (131).

It was also identified from our study that there was a reduction in the LOS of patients with both AKI and sepsis. A study in the US reported a similar result where there was a reduction in the hospital stay (around five days) and a decrease in the mortality rate (around 12.4%) for patients with sepsis over the years (132, 133). In addition, it was also identified that there was an improvement in the outcomes for patients with AKI (lower number of mortality rate and a reduction around 23% in the hospital stay) (134, 135). In other words, this suggests that the outcomes (lower morbidity and mortality) of AKI and sepsis patients have improved over the years.

4.3 Implications of the study

This research project, to the best of our knowledge, is the first study to investigate patients with both AKI and sepsis in general wards in Australia. Other related studies in Australia for AKI and sepsis have focused either on patients with AKI only (13, 84, 136), patients with sepsis only (137-139), or only considered patients with both AKI and sepsis in the ICU setting (4, 50, 140). This project advances knowledge by increasing our understanding of the characteristics, incidence, and outcomes of patients with both AKI and sepsis in general wards; and highlights limited knowledge about patients with both conditions for future research directions.

This study has identified several significant differences in the incidence and outcomes of patients with both AKI and sepsis between metropolitan and rural hospitals in New South Wales, Australia. The findings suggest that there is a need for better early detection methods and management to ensure patients with both AKI and sepsis in rural areas (older patients with longer hospital stays) will be able to receive appropriate care during their hospital stay (141).

This study is unique as it has used linked data extracted databases of the four studied hospitals: Patient Admission System (PAS) and Laboratory Information Systems (LIS). Together with laboratory-based and clinical decision support systems, this study could promote and facilitate early detection and management of patients with AKI and sepsis (84, 142, 143). Therefore, this study could help health professionals design better targeted and more cost-effective care and management for patients with both AKI and sepsis, especially in general wards.

Finally, the dissemination of the results of this study would be enhanced by the engagement with consumer representatives. Translating this work into practice will require active involvement of

patients and health providers to increase patients' safety and also the quality of patient-centred care services in Australia.

4.4 Limitations

There are several limitations in this study:

1. Due to the study settings and practical constraints in time and data access, the findings from this research project may not cover all demographics information (such as socioeconomic, ethnicity, income status, education, employment status) or other related outcomes (e.g., mortality, readmission, discharge status, etc.) about patients with AKI and sepsis in general wards. More comprehensive hospital data could help examine the financial cost and burden of patients with AKI and sepsis in the community.
2. The nature of the retrospective study may introduce selection bias and information bias. The selection bias was because the study population was from hospitalised patients who were sicker, older, and thus have worse outcomes than the community dwellers. The information bias was because of the incomplete data or inconsistency in recording the data for all patients during the study period. The bias could affect the accuracy and consistency of the measurement of risk factors and outcomes in this study. Because the five-year study was relatively short, it was therefore possible to obtain a consistent diagnosis for the outcome of patients with AKI and sepsis in general wards.
3. The findings from this research project may not capture all cases of AKI and sepsis, and may not be representative of general wards in Australia or of the Australian population. There was only one regional hospital in the included study. There is a need to include study populations from more regional and metropolitan areas in New South Wales and other states in Australia to explore the differences in patients with AKI and sepsis in metropolitan and regional hospitals.

4.5 Strengths

This study has several strengths:

1. Sample size

   This study used a large number of samples (370,969 hospitalisations in Australia). This means the study was able to extract more information about AKI and sepsis incidence, which could then be stratified by the characteristics of the study population (age and gender), the number of admissions, LOS, comorbidities, in each hospital from January 2009 to December 2013.

2. Sample population

   The data used in the cohort study were from four hospitals in both metropolitan and regional areas; hence, the analysis captured an accurate estimation of AKI and sepsis incidences, especially in New South Wales, Australia. As first AKI and sepsis study in Australian general wards, the data and analysis in this study enrich the understanding of hospitalised patients with AKI and sepsis in the general ward setting in Australia.
3. Using a linked data

   The use of linked data from two databases from the four hospitals and laboratories gives richer and more accurate information about AKI and sepsis patients instead of using single or several disparate information sources.

4.6 Conclusions

What is already known about this topic:

1. AKI and sepsis is common in hospitalised patients especially, in the ICU setting.
2. There was variation in the incidence and outcomes of patients with AKI and sepsis between the ICU and the general ward population
3. There was also variation in the definitions and guidelines of AKI and sepsis across studies, which made the comparison of incidence and outcomes difficult to perform.
4. Previous studies on patients with AKI and sepsis focussed on critically ill patients in the ICU setting.

What this thesis contributes:

1. The systematic review in this research project confirms that the available data about patients with AKI and sepsis in general wards were limited, especially for the Australian population.
2. The retrospective observational cohort study presents the characteristics of patients with AKI and sepsis in the Australian general ward setting. The findings show that the incidence of AKI and sepsis is low in the Australian general ward population. There was a little variation in the incidence of AKI and sepsis in the Australian general wards and with poor outcomes (more comorbidities and with longer LOS). An increase in the incidence of patients with AKI and sepsis in general wards was identified between 2009 to 2013.

Given the poor outcomes of patients with AKI and sepsis, future studies on data from various hospitals in Australia (e.g., to explore more differences between regional and metropolitan hospitals) are needed to improve our understandings of patient outcomes, mortality, and

readmission patterns. It is also important to conduct studies on various population groups (e.g., Australian remote and very remote areas, the Indigenous Australians population, etc.) to know the real burden of AKI and sepsis to the health system in Australia. An exploration for the reasons of heterogeneity in the results for patients with AKI and sepsis in general wards is also needed, e.g., whether the AKI and sepsis cases were identified and managed on general wards or identified in general wards but then transferred to the ICUs. Finally, future research on developing better tools, guidelines, and protocol for early identification (such as an electronic alert or identification tool for high-risk patients in general wards (104, 144)), monitoring, and management of patients with AKI and sepsis (especially for hospitals in rural areas) will help improve the outcomes and survival of patients with AKI and sepsis; hence, reducing the economic burden of AKI and sepsis on the society.

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Appendix 1 & 2 of this thesis have been removed as they may contain sensitive/confidential content

Appendix 3. The quality appraisal check

	Selection bias	Type of study design	Controlled confounders	Blinding	Data collection methods	Withdrawals and drop-outs	Quality assessment
Liangos et al. (2006)	2	2	2	2	1	2	STRONG
Waikar et al. (2006)	2	2	2	3	1	2	MODERATE
Kohli et.al (2007)	1	2	2	2	1	3	MODERATE
Waikar et al. (2007)	3	2	1	2	1	2	MODERATE
Al-Azzam et al. (2008)	2	2	2	3	2	3	WEAK
Li et al. (2008)	2	2	1	2	2	3	MODERATE
Selby et al. (2012)	1	2	3	2	2	1	MODERATE
Singh et al. (2013)	2	2	2	1	2	3	MODERATE
Zeng et al. (2014)	2	2	1	2	2	2	STRONG
Bagasha et.al (2015)	2	2	1	2	2	1	STRONG
L. Yang et.al (2015)	2	2	2	1	2	1	STRONG
Ruangchan et al. (2016)	2	2	2	2	2	3	MODERATE
Heung et al. (2016)	2	2	1	2	2	1	STRONG
Pan et al. (2016)	1	2	1	1	2	3	MODERATE
Silver et al. (2017)	2	2	2	2	2	3	MODERATE

Abbreviation: 1 = Strong; 2 = Moderate; 3 = Weak

Appendix 4. Summary of the selected studies included in the systematic review

Author	Year	Location	Method	Study period	Population	Patients characteristics of AKI and sepsis	The incidence rate of			AKI and sepsis outcomes		
							AKI	Sepsis	AKI and sepsis	Mortality rate	Length of Stay (LOS)	Others
Liangos et al. (72)	2006	USA	Retrospective cohort study, National Hospital Discharge Survey database	2001	29,039,599 hospitalisation	N/A	1.92% (558,032/29,039,559)	N/A	0.03% (9,487/29,039,599)	N/A	N/A	N/A
Waikar et al. (74)	2006	USA	Retrospective cohort study, National Inpatient Sample (NIS)	1998-2002	19.48% (1,083,745 patients discharges with ARF)	N/A	1998: 0.4% (61 per 100,000), 2002: 2.1% (288 per 100,000)	N/A	N/A	N/A	N/A	N/A
Kohli et.al (79)	2007	India	Prospective study, single centre	July 2004 - June 2005	33,301 hospitalised patients	75.4% in eldery patients with AKI (52/69) and 59.6% in young patients with AKI (134/225)	0.88% (294/33,301) or 6.6/1000 hospitalisation	N/A	0.6% (186/33,301)	N/A	N/A	186/294 (63.26%) with sepsis, 52/69 (75.4%) eldery and 134/225 (59.6%) young. 69/186 (37.1%) survivors, 117/186 (62.9%)

												nonsurvivors.
Waikar et al. (75)	2007	USA	Retrospective cohort study, The Nationwide Inpatient Sample	2000-2003	15,885,742 hospitalisation	N/A	White: 2.03% (323,116/15,885,742), black: 0.4% (76,812/15,885,742)	N/A	White: 0.4% (63,007/15,885,742), black: 0.1 % (15,592/15,885,742)	White: 44.4% (27,975/63,007) black: 41.7% (6,501/76,812)	White: 7.2, black 7.4	19.5% white ARF patients with sepsis, 20.3% black ARF patients with sepsis
Al-Azzam et al. (81)	2008	Jordan	Cohort study	Des 2005-April 2006	111 patients with diagnose of ARF	N/A	N/A	N/A	10.8% (12/111)	N/A	9.9% (11/111) : <5 days, 75.7% (84/111): 5-14 days and 14.4% (16/111): >14 days	10.8% (12/111) ARF due to sepsis
Li et al. (77)	2008	China	Prospective cohort study, Single centre	Des 2003-Des 2006	108,744 patients admitted to hospital	N/A	0.294% (320/108,744)	N/A	0.02% (25/108.744)	64% (16/25) but only 9.6% (21/218) who survived	23.8 (± 20.5) days	7.8% (25/320) ARF due to sepsis
Selby et al. (66)	2012	UK	Prospective study, single centre	Oct 2010-Oct 2011	3,930 AKI patients	N/A	62% (2437/3,930) stage 1, 20.6% (811/3,390) stage 2,	N/A	N/A	41.1% (353/859)	N/A	N/A

							(82)17.4% (682/3,930) stage 3					
Singh et al. (32)	2013	India	Prospective cohort study	December 2009-April 2011	9413 patients in medical ward, 10532 in surgical ward, and 1504 in ICU	N/A	0.54% (51) medical, 0.72% (76) surgical, and 2.2% (34) ICU	N/A	0.1% (10/9413) in medical, 0.3% (26/10,532) in surgical, and 0.8% (12/1504) in ICU	N/A	N/A	N/A
Zeng et al. (73)	2014	USA	Retrospective cohort study, Single centre	Jan 2010-Des 2010	25,859 patients, with total 31,970 hospitalisation.	N/A	18.3% (5848/31,970)	N/A	12.5% (4,000/31,970)	N/A	6-16 days	8.7% (2,736/31,970)
Bagasha et.al (82)	2015	Uganda	Prospective Cross-sectional observational study, single centre	Jan - April 2013	387 general ward patients.	age >59 years (p=0.023)	16% (63/387)	N/A	The prevalence: 16.3%	N/A	N/A	63 patients sepsis related AKI, age >59 years (p=0.023)
L. Yang et.al (78)	2015	China	Cross-sectional survey, Multi centre	Jan - July 2013	374,286 patients	N/A	42% (3195/7604) , 40% inacademic hospital (2266/5662) , 47.8% in local hospital (929/1942)	N/A	6.4% (483/7604) , 5.8% (328/5662) in academic hospital and 8% (155/1942) in local hospital	25.6% (124/483)	18 days (10-29)	6.4% (483/7604) with sepsis, 5.8% in academic hospital (328/5662) and 8% in local hospital (155/1942)

Ruangchan et al. (80)	2016	Thailand	Retrospective cohort study, Single centre	Des 2013-May 2014	723 patients sepsis	N/A	N/A	N/A	15.1% (109/723)	38.5% (42/109)	8.3±9.4 days	47.8% (109/228) severe sepsis or septic shock patients with ARF
Heung et al. (76)	2016	USA	Prospective cohort study, National data sample the Veteran Health Administration hospitalisation	Oct 2010-Sept 2012	104,764 follow up	N/A	16.3% (17,049/104,764)	N/A	0.2% (183/104,764)	N/A	9.2±15.9	1.1% (183/17,049) AKI patients with sepsis
Pan et al. (31)	2016	Taiwan	Retrospective cohort study	September - November 2014	201 AKI patiens	N/A	64.18% (129) of 201	N/A	32.8% (66/201)	30.3% (20/66)	N/A	N/A
Silver et al. (9)	2017	USA	Retrospective cohort study, National Inpatient sample	2012 National Inpatient sample	29,763,649 hospitalisations	N/A	10.2% (3,031,026/29,763,649)	5.30 %	2.1% (612,267/29,763,649)	N/A	N/A	20.2% from 3,031,026 AKI patients with Sepsis. Prevalence sepsis 5.3% (1,577,242/29,763,649)

Appendix 5. ID-10-AM codes used in this study

Condition	ICD-10-AM code
Acute myocardial infarction	I21, I22, I252
Congestive heart failure	I50
Peripheral vascular disease	I71, I790, I739, R02, Z958, Z959
Cerebral vascular disease	I60, I61, I62, I63, I65, I66, G450, G451, G452, G458, G459, G46, I64, G454, I670, I671, I672, I674, I675, I676, I677 I678, I679, I681, I682, I688, I69
Diabetes	E109, E119, E139, E149, E101, E111, E131, E141, E105, E115, E135, E145
Diabetes complications	E102, E112, E132, E142 E103, E113, E133, E143 E104, E114, E134, E144
Chronic kidney disease / Renal disease	E10.2, E11.2, E13.2, E14.2, I12, I13, I15.0, I15.1, N00 – N08, N11, N12, N14, N15, N16, N18, N19, N25 – N28, N39.1, N39.2, Q60 – Q63, T82.4, T86.1, Z49.0, Z94.0, Z99.2
Acute kidney injury	N00, N10, N17, E10.29, E11.29, E13.29, E14.29, O90.4, O08.4, N99.0
Sepsis	A01.0, A02.1, A19, A24.1, A32.7, A39.4, A40.0, A40.1, A40.2, A40.3, A40.8, A40.9, A41.0, A41.1, A41.2, A41.3, A41.4, A41.50, A41.51, A41.51, A41.52, A41.58, A41.8, A41.9, A42.7, A43.0, A48.1, A48.3, A54.8, A78, B37.7, B38.7, B39.3, B40.7, B41.7, B42.7, B44.7, B45.7, B46.4, R57.2, R65.0, R65.1, T81.42

Appendix 6. The summary of admissions characteristics of AKI and sepsis in four hospitals from 2009 to 2013

Admissions Characteristics	**Study period**					
	2009	**2010**	**2011**	**2012**	**2013**	**Total**
	(N= 67,300)	**(N= 70,561)**	**(N= 74,856)**	**(N= 78,163)**	**(N= 80,089)**	**(N= 370,969)**
Number of admissions	1,089 (1.62%)	1,111 (1.57%)	1,198 (1.60%)	1,253 (1.60%)	1,406 (1.76%)	6,057 (1.63%)
Age (Median (IQR))	74 (62-83)	73 (61-83)	75 (63-84)	75 (62-83)	74 (62-83)	74 (62-83)
Range (years)	18-99	18-103	18-102	19-101	18-99	18-103
Age group						
18-45	95 (8.7%)	80 (7.2%)	89 (7.4%)	95 (7.6%)	105 (7.5%)	464 (7.7%)
46-60	151 (13.9%)	176 (15.8%)	168 (14%)	179 (14.3%)	207 (14.7%)	881 (14.5%)
61-75	335 (30.8%)	337 (30.3%)	353 (29.5%)	370 (29.5%)	443 (31.5%)	1838 (30.3%)
>75	508 (46.6%)	518 (46.6%)	588 (49.1%)	609 (48.6%)	651 (46.3%)	2874 (47.4%)
Gender						
Female	497 (45.6%)	477 (42.9%)	544 (45.4%)	574 (45.8%)	586 (41.7%)	2678 (44.2%)
Male	592 (54.4%)	634 (57.1%)	654 (54.6%)	679 (54.2%)	820 (58.3%)	3379 (55.8%)
LOS (median (IQR) days	17.97	17.07	18.62	16.26	15.24	16.88
	(7.73-35.18)	(8.28-36.47)	(8.24-35.78)	(8.25-31.74)	(7.72-29.99)	(8.02-33.58)
Number of admission (median (IQR))	1 (1-2)	2 (1-4)	3 (1-4)	3 (1-5)	3 (2-6)	2 (1-4)
Range of number admissions (times)	1-20	1-21	1-22	1-23	1-24	1-25

Appendix 7. The variation of LOS based on age groups and comorbidities of AKI and sepsis

Comorbidities	Age Groups 18-45	Age Groups 46-60	Age Groups 61-75	Age Groups >75
	Median (IQR) length of stay in days			
Renal disease	18 (9-43)	19 (9-35)	18 (9-39)	15 (2-29)
Chronic kidney disease	20 (9-49)	18 (9-36)	18 (9-38)	15 (7-29)
Congestive heart failure	21 (16-36)	29 (12-56)	28 (14-52)	17 (9-32)
Acute myocardial infraction	22 (14-63)	27 (12-51)	23 (11-54)	17 (8-36)
Diabetes with complication	27 (11-46)	19 (9-41)	19 (9-38)	16 (8-30)
Diabetes	39 (11-77)	20 (11-41)	20 (12-37)	16 (7-36)
Cerebral vascular disease	61 (15-84)	34 (16-80)	37 (20-62)	26 (10-49)
Peripheral vascular disease	118 (32-130)	31 (17-48)	34 (14-66)	32 (13-72)

Appendix 8. Summary of admissions in each hospital from 2009 to 2013

All admissions in four hospitals

	2009	2010	2011	2012	2013	Total
Hospital A	19,896	19,427	19,755	19,762	21,427	100,267
Hospital B	22,285	23,102	23,901	25,031	25,687	120,006
Hospital C	17,238	19,652	21,667	22,982	23,854	105,393
Hospital D	7,881	8,380	9,533	10,388	9,121	45,303
						370,969

AKI and sepsis admissions

	2009	2010	2011	2012	2013	Total
Hospital A	327	317	337	346	385	1712
Hospital B	396	446	487	468	452	2249
Hospital C	278	259	270	345	469	1621
Hospital D	88	89	104	94	100	475
						6057

Appendix 9. The variation of length of stay from AKI and sepsis admissions in each hospital from 2009-2013

LOS (median (IQR)) days	**2009**	**2010**	**2011**	**2012**	**2013**
Hospital A (IQR)	21.09 (8.51-48.56)	18.85 (8.31-44.26)	21.97 (9.64-45.36)	20.23 (8.75-40.86)	17.2 (7.48-34.32)
Hospital B (IQR)	16.08 (7.39-32.94)	16.28 (8.02-37.86)	18.99 (8.85-35.35)	16.94 (8.73-35.34)	15.4 (7.97-30.96)
Hospital C (IQR)	18.9 (10.18-3.47)	18.97 (10.65-2.27)	16.84 (7.76-31.78)	15.26 (8.47-26.23)	15.13 (8.04-27.7)
Hospital D (IQR)	8.32 (4.02-21.64)	10.19 (3.23-21.07)	9.93 (5.47-23.16)	10.12 (4.95-23.23)	9.99 (4.31-23.87)

LOS= Length of stay

Appendix 10. The summary of AKI staging and sepsis incidence in from 2009 to 2013

AKI and sepsis	2009 N=67,300 Col(%)	2010 N=70,561 Col(%)	2011 N=74,856 Col(%)	2012 N=78,163 Col(%)	2013 N=80,089 Col(%)
AKI stage 1	6,580 (9.8%)	6,899 (9.8%)	6,559 (8.8%)	6,702 (8.6%)	6,506 (8.1%)
AKI stage 2	1,274 (1.9%)	1,279 (1.8%)	1,264 (1.7%)	1,183 (1.5%)	1,185 (1.5%)
AKI stage 3	1,294 (1.9%)	1,319 (1.9%)	1,321 (1.8%)	1,352 (1.7%)	1,384 (1.7%)
Sepsis	2,038 (3.03%)	2,069 (2.93%)	2,352 (3.14%)	2,689 (3.44%)	3,308 (4.13%)

Appendix 11. The summary of AKI staging and sepsis incidence in four hospitals

AKI and sepsis	Hospital A N=120,006 Col (%)	Hospital B N=100,267 Col (%)	Hospital C N=105,393 Col (%)	Hospital D N=45,303 Col (%)
AKI stage 1	11,938 (9.9%)	9,143 (9.1%)	9,330 (8.9%)	2,835 (6.3%)
AKI stage 2	2,212 (1.8%)	1,670 (1.7%)	1,696 (1.6%)	607 (1.3%)
AKI stage 3	2,285 (1.9%	1,577 (1.6%)	2,383 (2.3%)	425 (0.9%)
Sepsis	4,429 (3.7%)	3,507 (3.5%)	3,308 (3.1%)	1,159 (2.6%)

Appendix 12. STROBE checklist of the observational cohort study

	Item No	Recommendation	Thesis page reference
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	30
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7-8
Objectives	3	State specific objectives, including any prespecified hypotheses	31
Methods			
Study design	4	Present key elements of study design early in the paper	30
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	30-31
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	30-31
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	N/A
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	N/A
Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	N/A

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	31-32
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	31-32
		(*b*) Describe any methods used to examine subgroups and interactions	30-31
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	31-32
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	32-33
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	32-33, 38-39
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	Report numbers of outcome events or summary measures over time	32-46
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	35
		(*b*) Report category boundaries when continuous variables were categorized	N/A

		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	35-46
Discussion			
Key results	18	Summarise key results with reference to study objectives	47-49
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	49-50
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	49-50
Generalisability	21	Discuss the generalisability (external validity) of the study results	31,50
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N/A