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Infections in Patients with Chronic Kidney Disease: Patterns, Outcomes and the Role of Vitamin D for Future Prevention

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Infections in Patients with Chronic Kidney Disease: Patterns, Outcomes and the Role of Vitamin D for Future Prevention

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To Shaoping Huang, Chengxi Su, my parents Zhiwei Su, Aihong Shi,
my parents-in-law Xiquan Huang, Xiuqiong Huang
and my family

“When I let go of what I am, I become what I might be.”

– Lao Tzu

“以其终不自为大，故能成其大”

- 老子

PREFACE

Life is a journey during which we face ups and downs, twists and turns. However, your mind leads you to where you want to go.

In my childhood, I suffered from recurrent tonsillitis. This granted me multiple opportunities to contact medical doctors and to try traditional Chinese medicine (TCM) as a treatment of infections without antibiotics. Curiosity about why humans get sick and how disease is managed drove me to apply to medical school at the entrance examination for higher education in China, 2004.

I majored in integrated TCM and Western medicine, having had the opportunity to learn western medicine in Southern Medical University and acquire knowledge of TCM in Guangzhou university of Chinese Medicine. Both are located in Guangzhou city and are top medical universities in their fields in China. Western medicine and TCM are grounded on different philosophies and explain human physiology and pathology in different ways. One might expect that these differences might drive a medical student mad when he/she tries to understand both at the same time. However, they are actually well- integrated in clinical practice in China. The safety and efficacy of TCM has always been challenged by the Western world, owing to lack of knowledge. Is the current integration of TCM and Western medicine is good or bad? Can different perspectives improve medical care? It has always been my dream to broaden my knowledge, develop critical thinking and innovate healthcare.

Thanks to the support of the China Scholarship Council and Guangdong Provincial Hospital of Chinese Medicine, the second affiliated hospital, Guangzhou University of Chinese Medicine, I was able to develop my critical thinking and pursue my PhD from 2015 at Karolinska Institutet, a world famous medical university.

As a medical doctor specialized in Nephrology, I struggled to find a research topic to fit my background as well as my main supervisor Professor Cecilia Stålsby Lundborg's research area - antibiotic resistance. I was also uncertain about the source of data and whether TCM would be suitable to investigate in my PhD study.

Luckily, I found a way with the support of Professor Cecilia, co-supervisor Professor Juan Jesus Carrero, Professor Xusheng Liu and Professor Bengt Lindholm. Chronic kidney disease (CKD) is becoming more prevalent than before as the society is ageing. As a progressive disease occurring in more than 10% of the adult population, CKD is an emerging public health problem. Hospital data of daily practice reveals that the two main reasons for patients with CKD being admitted to hospital are cardiovascular disease (CVD) and infections. Previous research interest has focused on CVD in patients with CKD. Not enough attention has been paid to the infections in this population. Higher rates of infections in patients with kidney disease and greater use of antibiotics are putting this

population at risk of antibiotic resistance. Furthermore, these patients can potentially transmit resistant pathogens to patients in other sections of the healthcare facilities.

I hope my thesis will contribute to the understanding of factors linked to the poor outcomes of infections in patients with CKD, and highlight the importance of future infection prevention for this vulnerable population as well as for public health in general.

Now, I am at the end of my PhD study and I believe that this is just the beginning of another journey. I hope that the methods and critical thinking I learnt during my PhD study will assist the future evaluation of TCM, improve integrated medical care and promote better health for all.

ABSTRACT

Background: Chronic kidney disease (CKD) is increasingly recognized as a global public health problem. Patients with CKD are at high risk of infections. Frequent episodes of infections with greater use of antibiotics might put this population at risk of infections caused by resistant organisms. Thus, infection issues in patients with CKD could be related to another public health problem - antibiotic resistance.

Aim: To investigate the antibiotic resistant patterns of pathogens responsible for infections, ascertain short-term and long-term patient outcomes during and after hospitalizations with infections and explore the role of vitamin D for infection prevention in patients with CKD.

Methods: The thesis consists of two observational studies (**Paper I & II**), one cohort study (**Paper III**) and one systematic review and meta-analysis (**Paper IV**). **Paper I, II & III** explored the association between kidney function (defined as estimated glomerular filtration rate, eGFR) and various outcomes. These outcomes included microbial pattern (**Paper I**), prevalence of infections with multi-drug resistant organisms (MDROs) in the first positive microbial cultures (**Paper I**), intensive care unit admission (**Paper II**), length of hospital stay (**Paper II**), medical expense (**Paper II**), and mortality (**Paper II & III**). These were assessed in patients hospitalized with infections, using electronic medical records from four hospitals from 2012 to 2015 in China. **Paper IV** obtained data from existing literature to explore the association of infections with vitamin D status or use of vitamin D in patients treated with long-term dialysis.

Results: In adult patients hospitalized with infections, the proportion of Gram-negative bacteria decreased while the proportion of Gram-positive bacteria increased across eGFR strata. Compared with the reference eGFR, lower eGFR was associated with: higher odds of infections by MDROs (19% and 41% higher in those with eGFR between 30-59 ml/min/1.73 m^2 and eGFR <30 ml/min/1.73 m^2, respectively) (**Paper I**); more than two-fold higher adjusted odds of ICU admission, longer median length of hospital stay ($P< 0.001$), inferred 20.0% higher costs in those with eGFR< 60 ml/min/1.73 m^2 ($P< 0.001$) (**Paper II**); progressively increased risks of cardiovascular mortality (subdistribution hazard ratio [SHR] 2.15 for eGFR 30-59 mL/min/1.73m^2; SHR 3.19 for eGFR<30 mL/min/1.73m^2) (**Paper III**). In the systematic review of vitamin D and infections in patients treated with long-term dialysis, the risk of composite infections was 39% lower in those with high/normal levels of 25-hydroxy vitamin D than that in those with low levels. Compared to those who did not use vitamin D, the pooled adjusted risk of composite infection was 41% lower in those who used vitamin D (**Paper IV**).

Conclusions: CKD patients hospitalized with infections have a higher risk of infections by MDROs, poorer in-hospital outcomes resulting in higher medical costs and increased risk of cardiovascular mortality in the long-run. Use of vitamin D to achieve high/normal serum levels of 25(OH)-vitamin D might help lowering the risk of infections in maintenance

dialysis patients. Further research is needed to investigate the potential role of vitamin D therapy in infection prevention among non-dialysis dependent CKD patients.

LIST OF SCIENTIFIC PAPERS

The thesis is based on the following papers. They are referred to in the text by their Roman numerals (I-IV). Published papers are reproduced with permission from the publishers.

I. **Guobin Su**, Hong Xu, Emilia Riggi, Zhiren He, Liming Lu, Bengt Lindholm, Gaetano Marrone, Zehuai Wen, Xusheng Liu, David W Johnson, Juan Jesus Carrero, Cecilia Stålsby Lundborg. Association of Kidney Function with Infections by Multidrug-Resistant Organisms: An Electronic Medical Record Analysis. Scientific Reports 2018, 8(1):13372.

II. **Guobin Su**, Hong Xu, Gaetano Marrone, Bengt Lindholm, Zehuai Wen, Xusheng Liu, Juan Jesus Carrero, Cecilia Stålsby Lundborg. Chronic kidney disease is associated with poorer in-hospital outcomes in patients hospitalized with infections: Electronic record analysis from China. Scientific Reports 2017, 7(1):11530.

III. **Guobin Su**, Yanjun Xu, Xiaojun Xu, Hong Xu, Liming Lu, Gaetano Marrone, Bengt Lindholm, Zehuai Wen, Xusheng Liu, David W Johnson, Juan Jesus Carrero, Cecilia Stålsby Lundborg. Association between reduced renal function and cardiovascular mortality in patients hospitalized with infection: A multi-center cohort study. European Journal of Internal Medicine 2018, 57:32-38

IV. **Guobin Su**, Zhuangzhu Liu, Xindong Qin, Hong Xu, Xusheng Liu, Zehuai Wen, Bengt Lindholm, Juan Jesus Carrero, David W Johnson, Nele Brusselaers, Cecilia Stålsby Lundborg. Vitamin D deficiency and treatment versus risk of infection in end-stage renal disease patients under dialysis: A systematic review and meta-analysis. Nephrology Dialysis Transplantation 2019, 34(1):146-156

OTHER PAPERS NOT INCLUDED IN THE THESIS

1. Chuan Zou, Lihong Yang, Yuchi Wu, **Guobin Su**, Shuhui Chen, Xinfeng Guo, Xiuqing Wu, Xusheng Liu, Qizhan Lin. Auricular acupressure on specific points for hemodialysis patients with insomnia: a pilot randomized controlled trial. PLOS ONE 2015, 10(4):e122724.
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CONTENTS

LIST OF ABBREVIATIONS

AVF	Arteriovenous Fistulas
AOR	Adjusted Odds Ratio
CAIRHs	Community-Acquired Infection-Related Hospitalizations
CBM	China Biology Medicine disc
CDC	Center for Disease Control and Prevention
CI	Confidence Interval
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration Formula
CLSI	Clinical and Laboratory Standards Institute
CNKI	Chinese National Knowledge Infrastructure
CVD	Cardiovascular Disease
DRGs	Diagnosis-Related Group-based case-mix funding system
ECDC	European Centre for Disease Prevention and Control
eGFR	Estimated Glomerular Filtration Rate
EMR	Electronic Medical Record
ESBL	Extended Spectrum Beta-Lactamase
ESKD	End-Stage Kidney Disease
FFS	Fee-For-Service
GDHCM	Guangdong Provincial Hospital of Chinese Medicine
GFR	Glomerular Filtration Rate
HAIRHs	Healthcare-Associated Infection-Related Hospitalizations
IBM	International Business Machines Corporation
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
IRHs	Infection-Related Hospitalizations
HD	Hemodialysis
HR	Hazard Ratio
KDIGO	Kidney Disease Improving Global Outcomes
LOHS	Length of Hospital Stay

MDROs	Multidrug-resistant Organisms
MDR-GNB	Multidrug-Resistant Gram-Negative Bacteria
MOOSE	Meta-analysis of Observational Studies in Epidemiology
MRSA	Methicillin-Resistant Staphylococcus Aureus
NAP	National Action Plan
NDD-CKD	Non-Dialysis Dependent Chronic Kidney Disease
NHANES	National Health and Nutrition Examination Survey
NOS	Newcastle-Ottawa Scale
OR	Odds Ratio
PD	Peritoneal Dialysis
PRC	People's Republic of China
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
RR	Relative Risk
RRT	Renal replacement therapy
SCR	Serum Creatinine
S-PICO	Study design, Population, Intervention, Comparison and Outcomes
UEBMI	Urban Employees Basic Medical Insurance
UIRHs	Undefined Infection-Related Hospitalizations
UK	United Kingdom
URBMI	Urban Resident Basic Medical Insurance
US	United States
VDRAs	Vitamin D Receptor Activators
VRE	Vancomycin-Resistant Enterococci
25(OH)D	25-hydroxy vitamin D
$1,25(OH)_2D$	1,25-dihydroxy vitamin D

1 BACKGROUND

1.1 CHRONIC KIDNEY DISEASE (CKD): A PUBLIC HEALTH PROBLEM

1.1.1 The definition of CKD

Chronic kidney disease (CKD) is increasingly recognized as a global public health problem due to its high prevalence, high rate of complications, high health care costs and poor outcomes. More than 850 million people worldwide have some forms of CKD – this is roughly double the number of people who live with diabetes and 20 times more than those with cancer (1, 2).

According to the Kidney Disease Improving Global Outcomes (KDIGO) initiative, an individual is classified as having CKD if abnormalities of kidney structure or function persist for more than three months (3). KDIGO provides a classification of severity, defining numerous stages of CKD based on glomerular filtration rate (GFR) and the extent of albuminuria (Figure 1). Although the KDIGO criteria emphasize the importance of both GFR and albuminuria in describing the risk of progressing to adverse outcomes, data for albuminuria are not always available in clinical practice for various reasons, such as under-recognition of its importance. GFR is the best available indicator of overall kidney function, and represents the total amount of fluid filtered through all of the functioning nephrons per unit of time (4). When CKD is defined solely by GFR, we refer to a GFR of less than 60 mL/min per 1.73 m^2 (5).

Patients with CKD are at increased risk of numerous complications such as anemia, metabolic acidosis (reduced acid excretion by the kidneys) and CVD, which together increase the complexity of patient management. If complications are not well controlled, patients with CKD may progress rapidly to end-stage kidney disease (ESKD), which usually requires renal replacement therapy (RRT), either kidney transplantation or dialysis (hemodialysis or peritoneal dialysis), to support their life.

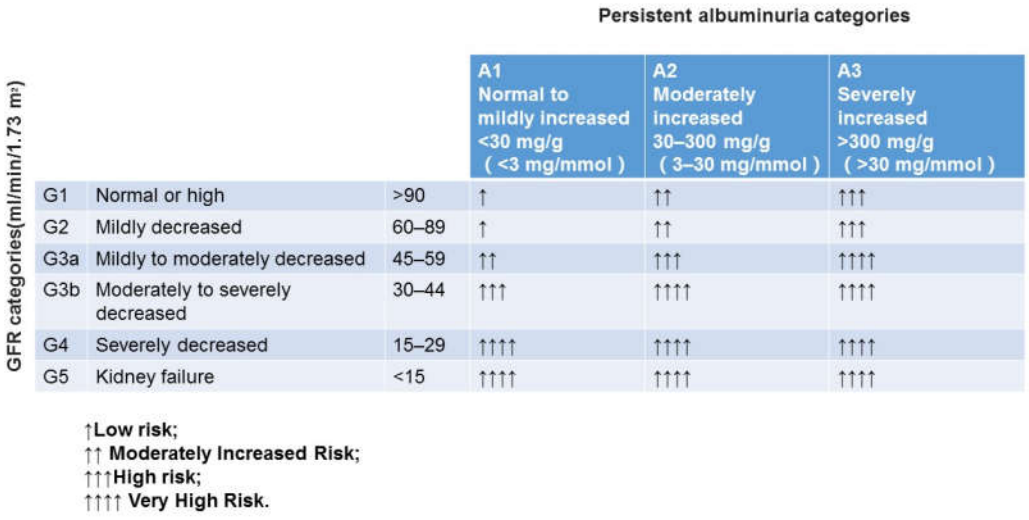


Figure 1. The Kidney Disease Improving Global Outcomes (KDIGO) classification of chronic kidney disease (CKD). CKD is defined as abnormalities of kidney structure or function, present for more than 3 months. KDIGO recommend that CKD is classified into different risk groups based on cause, glomerular filtration rate (GFR) category, and albuminuria category, which define the risk of progressing to adverse outcomes (such as progression to end-stage kidney disease, cardiovascular disease, hospitalization, acute kidney injury or death).

1.1.2 Prevalence and causes of CKD

The prevalence of CKD is rising worldwide, with the fastest growth occurring in low- and middle-income countries (1). The global mean CKD prevalence of stages G1-G5 is 13.4% (95% CI, 11.7-15.1%) (6). A recent study enrolling 12 low- and middle-income countries in six regions of the world, found a higher prevalence of 14.3% (95% CI, 14.0% to 14.5%) in general populations and 36.1% (95% CI, 34.7% to 37.6%) in high-risk populations (7). In terms of CKD stages 3–5, the global prevalence was 10.6% (9.2-12.2%). It varies substantially across countries, with values reported as low as 5.8% in Australia (8), 6% in Sweden (9) and 6.9% in the United States (US) (10). Notably, most prevalence data are based on GFR only and do not consider albuminuria (11). This means that the actual prevalence of CKD is probably higher. As the global population ages, the prevalence of stages 3–5 CKD in adults more than 65 years old is projected to exceed 28% in 2030 (12).

When patients with CKD progress to ESKD, they require RRT, either kidney transplantation or dialysis. It was estimated that 2.6 million people received RRT worldwide in 2010, whereas the number of patients needing RRT ranged between 4.9 and 9.7 million (13). The global prevalence of ESKD is 280 per million people undergoing dialysis, compared with 65

per million people who have a functioning kidney transplant (5). Worldwide use of RRT will more than double to 5.4 million people by 2030, with the most growth in Asia (1.0 million to a projected 2.2 million) and with the most rapid relative increase projected for Latin America (13).

The causes of CKD vary globally. The main causes are diabetes and hypertension in all high- and middle-income countries, but also in many low-income countries (5). CKD from glomerulonephritis and unknown causes are, on the other hand, more common in Asia and sub-Saharan Africa (5).

1.1.3 Personal health and social economic burden of CKD

1.1.3.1 Mortality

According to the 2015 Global Burden of Disease study, the number of deaths attributed to CKD increased by 36.9% from 1990 to 2005 and continued to rise by 18.4% from 2005 to 2015. CKD was ranked the 17th leading global cause of life lost in 2015 (14). Both myocardial infarction and cardiovascular death increase as GFR declines and the albuminuria increases (15, 16). Cardiovascular mortality is estimated to be 57% higher in people with a GFR less than 60 mL/min per 1.73 m² and 63% higher in people with microalbuminuria (17, 18). The five-year survival of people with ESKD on dialysis is between 13% and 60% lower than people in the general population of similar ages (19).

1.1.3.2 Cardiovascular complications

The risk of having a non-fatal myocardial infarction is increased by 33% in patients with GFR < 60 mL/min per 1.73 m² and by 48% in those with microalbuminuria (15, 16). Similarly, stroke risk increases by 7% for every 10 mL/min per 1.73 m² decreases in GFR and by 10% for every 25 mg/mmol increases in the albumin-creatinine ratio (20).

1.1.3.3 Quality of life

A consistent reduction in health-related quality of life has been shown among patients with reductions in GFR, including those on RRT (21, 22). A recent Korean population-based study reported a 2% reduction in health-related quality of life for stage 2 and stage 3a CKD, a 5% reduction for stage 3b, and a 7% reduction for stage 4 or 5, compared with stage 1 (23).

1.1.3.4 Medical cost and health-care services

The treatment of CKD and ESKD imposes substantial societal costs. Costs for CKD are not limited to RRT, but also include non-renal health-care costs (such as cardiovascular events, etc.), costs not related to health care (such as loss of productivity due to unemployment, etc.) and costs for patients with CKD who are not yet receiving RRT (such as costs of health technology, diagnostics, and medication, etc.) (24).

RRT is the only available life-prolonging treatment for ESKD. The medical costs associated with the treatment of ESKD are disproportionate to the size of the population. In the US, the number of patients with ESKD accounts for only a small fraction (0.5%) of the US population, but health care expenditure for adults receiving dialysis and/or kidney transplantation exceed $47 billion US dollars per year or 7% of the total Medicare budget (25).

In brief, CKD is a public health problem which deserves increased global attention due to its high prevalence, high mortality, and high level of comorbidities, associated poor quality of life, and large consumption of health-care resources.

1.2 INFECTIONS IN PATIENTS WITH CKD: A FORGOTTEN ISSUE

Although great progress has been made in improving the management of patients with CKD over the past few decades, mortality and morbidity rates remain high compared with age- and sex-matched individuals (24). This is predominantly due to cardiovascular disease (CVD) and infections (26). A great deal of attention has been paid to CVD, but the same cannot be said for infections (27).

1.2.1 Higher risk of infections in patients with CKD

Studies that associate infections with reduced kidney function are accumulating (28). All point estimates and most confidence intervals suggest a strong and graded association of infections incidence with CKD severity. An increased risk of infections associated with reduced estimated glomerular filtration rate (eGFR) has also been observed in outpatient settings. A cohort study among elderly diabetics identified in primary care in the United Kingdom (UK) showed that patients with decreased kidney function had increased incidence of lower respiratory tract infections and sepsis (29, 30). A similar association has also been observed in the health care ambulatory services in Sweden, which further confirmed this association across all types of infections (31).

Not only are the risks higher of mild or moderate infections in outpatient settings, but this association persists when it comes to severe infections that require hospitalizations. Higher risk of infection-related hospitalizations (IRHs) has been observed in those with reduced eGFR from studies in Taiwan (32), Hong Kong (33), Canada (34, 35), and the United States (US) (36-38). There was a graded increase of infection risk at mildly to moderately reduced eGFR. This pattern was observed for all-cause infections, as well as type-specific infections, such as pneumonia. Compared to those with eGFR of 60-104 ml/min/1.73 m^2, the risk of hospitalization with pneumonia was 3.23 times higher in those with eGFR of 45 to 59 mL/min/1.73 m^2, 9.67 for eGFR of 30 to 44 mL/min/1.73 m^2, and 15.04 for eGFR less than 30 mL/min/1.73 m^2 (34). Data from the 2016 United States Renal Data System showed that the incidence of hospitalization for infections was 614 per 1000 person-years in individuals aged 65 years or older with any stage of CKD, which was nearly 3 times higher than the incidence of 214 per 1000 person-years in those without CKD (39). Although cardiovascular disease is still the leading cause of hospitalization (23%), infections accounts for 21% of all-cause hospitalization, almost identical to cardiovascular disease (39). Thus, it is important to recognize infections as a leading cause of hospitalization among individuals with CKD.

1.2.2 Potential mechanisms for higher risk of infection in patients with CKD

The underlying mechanisms for higher risk of infections in patients with CKD are multifactorial, including patient characteristics, compromised immune system, etc.

Many characteristics intrinsic to CKD predispose to infections, including advanced age (40, 41), coexisting illnesses (such as diabetes and cardiovascular disease) (42, 43), complications (anemia, malnutrition, hypoalbuminaemia) (44), immunosuppressive therapy for kidney disease and increased exposure to infectious agents from frequent healthcare use (26).

A compromised immune function is another contributor to the higher risk of infections in this population (45). A number of factors may contribute to the impaired immune system in CKD, including uremic toxin retention, inflammation, oxidative stress, and mineral-bone disorder. Uremic toxins, such as indoxyl sulfate, p-cresyl sulfate and trimethylamine-N-oxide, are metabolites of tryptophan, tyrosine and trimethylamine (46, 47). These toxins are elevated in patients with CKD, which can impair both leucocyte and endothelial function. Two small studies of hemodialysis patients suggested that increased p-cresol sulfate levels were associated with increased risk of infections (48, 49). When it comes to inflammation, a number of inflammatory cytokines such as tumor necrosis factor-alpha, interleukin-6, and C-reactive protein) increase along with the loss of kidney function (50). Previous

epidemiological studies have shown that these inflammatory markers were associated with an increased risk of infections (51, 52). Oxidative stress was increased and antioxidant capacity was decreased among patients with CKD (53), leading to impaired immune response (54). Some studies suggested that bone and mineral disorders, such as vitamin D deficiency (55, 56), and lower fibroblast growth factor 23 (57), also contributed to the increased risk of infections in these patients. It is well-known that there is a high prevalence of vitamin D deficiency [both the major circulating metabolite, 25-hydroxyvitamin D, (25(OH)D), and activated vitamin D (1, 25-dihydroxy vitamin D)] among patients with CKD, due to dietary restrictions and deficient renal 1α-hydroxylase activity (58). Vitamin D may protect against pathogens given that 25(OH)D supports the induction of antimicrobial peptides in response to both viral and bacterial stimuli (59). Moreover, vitamin D metabolites have been reported to induce innate antimicrobial effects, including induction of autophagy, and synthesis of both reactive nitrogen intermediates and reactive oxygen intermediates (60). Some observational studies associated higher level of 25(OH)D with a lower risk of infections in patients with ESKD (55, 56).

In addition to the above mentioned potential mechanisms, RRT *per se* predisposes patients with ESKD to infections. For example, repeated needle punctures of arteriovenous fistulas (AVF) /grafts or dialysis catheters (peritoneal or vascular) are potential risk factors for infections as they disrupt the protective cutaneous barrier. Medical devices such as mechanical ventilation, central venous catheter, and urinary catheter are frequently used for CKD patients and are important sources of infections. Kidney transplant patients require life-long immunosuppressive medication (26), which also predisposes them to infections.

1.2.3 Treatment challenges related to infection caused by antibiotic-resistant bacteria in patients with CKD

High risk of infections and greater use of antibiotics could contribute to a higher prevalence of infections caused by antibiotic-resistant bacteria in patients with CKD. Infections with resistant bacteria introduces treatment challenges in patients with CKD since resistance to first-line antibiotics requires the use of second and third line antibiotics with potential nephrotoxicity (61).

High prevalence of colonization and infections with multi-drug resistant organisms (MDROs), defined as non-susceptibility to at least one agent in three or more antibiotic classes, such as *methicillin-resistant Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE), have been observed in the dialysis population (62, 63).

1.3 STRATEGIES THAT MIGHT REDUCE THE RISK OF INFECTIONS IN PATIENTS WITH CKD

Given the risks and poor outcomes associated with infections in patients with CKD and ESKD, strategies to prevent infections are of utmost importance. Vaccination (64) whenever possible could be one option to reduce the risk of infections in patients with CKD.

In the 2013 KDIGO guideline, annual vaccination with influenza vaccine was recommended for all adults with CKD unless contraindicated. Pneumococcal vaccination was recommended for all adults with eGFR < 30 ml/min/1.73 m^2 and those at high risk of pneumococcal infections, such as individuals with nephrotic syndrome, diabetes, or those on immunosuppressive drugs. In addition, revaccination was recommended for adults with CKD after 5 years of receiving pneumococcal vaccination (3). However, patients with advanced CKD and ESKD seem to have reduced responsiveness to vaccination; they develop lower levels of antibody titers and have a more rapid loss of antibody titers, compared to healthy individuals (65, 66). These means that patients with CKD might not benefit from vaccinations in the same way as the general population. A few studies suggested that a high-dose or adjuvant influenza vaccine might have better effectiveness than a regular vaccine in the elderly (67). However, the evidence is controversial in patients with ESKD, not only for influenza vaccination (68-70) but also for pneumococcal vaccination (71, 72). Limited data of vaccination is available in patients with non-dialysis dependent CKD. Both of the available studies were conducted almost twenty years ago and showed that patients with non-dialysis dependent CKD had antibody response after pneumococcal vaccination but that antibody levels declined rapidly within six months (73, 74). Future studies are needed to assess the effectiveness of influenza/pneumococcal vaccination and to determine the optimal dose, frequency, and delivery strategy in a broader range of individuals with CKD.

Health-care associated infections (HAIs) are more common in patients with CKD. Standard prevention strategies, such as good hand hygiene, prompt removal of devices (such as central venous catheter, and urinary catheter, etc.) and maximal barrier precautions during treatment procedures, are critical for minimizing the risk of HAIs, especially in those with CKD (75).

1.4 PROFILE OF CHINA

1.4.1 Country demographics

The People's Republic of China (PRC) is located in East Asia. The country is bounded by the Yellow Sea and the East China Sea to the east; Vietnam, Laos, India, Bhutan and Nepal to the

south; Pakistan to the southwest; and Afghanistan, Tajikistan, Kyrgyzstan and Kazakhstan to the west; Mongolia, Russia and North Korea to the north. With a population of around 1.404 billion in 2017 according to World Population Prospects from the United Nations, China is the world's most populous country. Covering approximately 9,600,000 square kilometers, it is the third largest country by total area (76).

1.4.2 Patients with CKD in China

The occurrence of CKD in adults in China is similar to that in other low or middle-income countries, with a cross-sectional survey of a nationally representative sample finding a prevalence of 10.8% (10.2% - 11.3%) (77). The number of patients with CKD in China is therefore estimated to be around 120 million, the highest total for a single country (78).

Diabetes is becoming the leading cause of CKD in China (79). Furthermore, China is confronting the increased threat of ESKD. Data on RRT among 3 million urban insured employees in Nanjing, revealed that from 2005 to 2014, the prevalence of patients undergoing RRT increased and, importantly, the urban population doubled (80).

1.4.3 Healthcare system reform in China

The National Health Commission of PRC oversees the health services system and the health needs of the Chinese population. All major medical facilities are run by the government, but some private health services have emerged in recent years.

During the period from 1949 to the early 1980s, the Chinese government owned, funded, and ran all hospitals. Physicians were employees of the state. There was no health insurance since health services were nearly free of charge at that time (81).

After economic reforms in around 1980, China reduced the role of government in all economic and social sectors, including health care. The government continued to own hospitals but exerted little control over the behavior of health care organizations, which acted like for-profit entities (82). Physicians working for hospitals received a large number of bonuses for increasing hospital profits. However, this market reform resulted in public anger, lack of access to health care for those unable to pay the increased medical cost, distrust toward health care institutions and professionals and even in physical attacks on physicians (82).

To address the discontent with health care, in 2003 the government of China took the step of introducing a health insurance scheme covering in-hospital expenses for rural residents. A profound health care reform was then announced in 2009, with the goal of providing

affordable and equitable basic health care for all by 2020. The reform is ongoing and anchored in five interdependent areas: Expanding coverage to insure more than 90% of the population, establishing a national essential medicines system to meet all citizen's primary needs for medicine, piloting public hospital reforms, improving the primary care delivery system to provide basic health care and managing referrals to specialist care and hospitals, making public health services available and equal for all (83).

1.4.3.1 Insurance and payment system in China

During the 2009 healthcare reform, China introduced insurance systems for urban residents (Urban Employees Basic Medical Insurance, UEBMI, and Urban Resident Basic Medical Insurance, URBMI), farmers (New Rural Cooperative Medical Service) and those living in poverty in both urban and rural areas (Medical Assistance Program), to achieve universal coverage (84). By 2012, a government-subsidized insurance system provided 95% of the population with modest but comprehensive health coverage, with funding sourced from tax and premiums (82).

Local government financing is allocated at the provincial level every year, based on the the number of hospital beds. However, government allocations cover less than 10% of funding for most public hospitals (85). The major proportion (more than 90%) of funds for public hospitals comes from fees for medical services and medicines.

The fee-for-service (FFS) payment system was once the prevailing method of payment in Chinese public hospitals, which reimburses hospitals retrospectively based on clinic visits, examinations and treatment programs. Under the FFS payment system, improper incentives are largely responsible for the rising costs of health care. For public hospitals to obtain their funds, physicians were encouraged to prescribe expensive or profitable medications, which were not always beneficial to patients. This behavior drove the rising medical costs (86).

Along with limited financial resources, the rapid increase in health care costs prompted the decision to move away from a retrospective FFS payment model to a prospective payment system – Diagnosis-related group (DRGs)-based case-mix funding system (or so-called single disease reimbursement payment) (87). Ideally, DRGs are "diagnosis-related" groups of patients that are homogenous in terms of clinical significance and resource consumption. Therefore, individuals with the same DRG classification are medically and economically similar. Under a DRG-based case-mix payment system, hospitals receive a fixed rate for each admission according to a patient's DRG category. The pre-defined fee for treating patients in a single DRG category sets a limit on the overall expenses for individual patients regardless

of the actual cost of caring for the individual. If the actual medical expenses exceed the pre-defined fee, the excess is borne by the hospital. Ideally, hospitals should increase the efficiency and quantity of medical services and contain costs to make a profit (87).

1.4.3.1 Antibiotic resistance and policy in China

Antibiotic resistance and overuse of antibiotics have become a public health crisis in China. China has the world's most rapid growth rate of resistance with high resistance rates of the most common bacteria (88). Methicillin-resistant *S. aureus*, Extended Spectrum Beta-Lactamase (ESBL)-producing *Enterobacteriaceae* and carbapenem-resistant *Acinetobacter baumannii* account for more than 50% of microbial isolates (89). Several factors are involved, including misuse and overuse of antibiotics among humans as well as in livestock (90). The total antibiotic usage in China in 2013 was approximately 162,000 tons, including human use (48%) and use in animals (52%) (91), which was almost half of the antibiotic usage worldwide. As a last resort treatment of bacterial infections, colistin is not yet available for hospital use in China. However, mcr-1-containing plasmid-mediated colistin-resistant *Enterobacteriaceae* has been identified in clinical samples and animals in China (92, 93). This indicates that antibiotics use in agriculture in China is one of the driving forces of antibiotic resistance. Overall, these data suggest that China is one of the world's leading countries with serious problems in terms of antibiotic misuse and antibiotic resistance.

To cope with the problem of antibiotic resistance, the government of China introduced an essential medicines programme for public health-care institutions in 2009 to reduce irrational drug use (eg, over-prescription of antibiotics) (83). In 2010, the Health Ministry of China separated doctors' pay from prescription drug sales. Since 2012, China has run a national campaign in hospitals to promote the rational use of antibiotics. Drugs with the highest resistance rates can be prescribed only by specialists (83). Those who violate the rules can lose prescription rights or their medical license (94). In 2016, the Chinese Government announced a national action plan (NAP) to combat antimicrobial resistance. The China NAP highlights four key strategies: 1) Coordination of 15 ministries involved in the regulation of antibacterial agents and antimicrobial resistance control at a national level; 2) Implementation of a "one-health concept" integrating agriculture, health, and environmental protection departments; 3) Substantial financial investment for improvement of facilities, surveillance, and research; and 4) Promotion of international collaborations (95).

1.5 THESIS RATIONALE AND KNOWLEDGE GAP

In patients with CKD, susceptibility to infections results in the more frequent use of antibiotics (106) and more hospitalizations (29, 31, 35), which also increases their exposure to microbes, including MDROs (107). The focus has been placed mainly on dialysis patients in previous studies (67, 68, 108, 109). However, it is unclear whether infections caused by MDROs are more common in patients with non-dialysis dependent CKD (NDD-CKD) than those in the non-CKD population; this needs to be confirmed. The higher infection risk among CKD patients might also contribute to the emergence and spread of MDROs. This might place the global population at risk of infections caused by resistant bacteria.

There has been little exploration on whether in-hospital outcomes (admission rates, lengths of stay, mortality during admission) or economic burden differ between these patients. This has implications for how medical resources are allocated at a societal level, especially in the context of the DRGs in China: Payment/reimbursement to the hospital from government is the same if patients are admitted for the same cause, regardless of comorbidities (85).

Infections might also be associated with an increased risk of cardiovascular events (96-98). Previous studies have shown that infections leads to increased risk of cardiovascular events and cardiovascular mortality in dialysis patients (43, 99). It is unclear whether, and to what extent, reduced kidney function predisposes to higher cardiovascular-related mortality in the context of infections. Knowledge of the relationship between kidney function and cause-specific mortality in the context of infections may help to better inform and tailor treatment and prevention strategies.

When it comes to infection preventive strategies, vitamin D seems to have promising potential. In the general population, studies show that a higher level of 25(OH)D and the use of vitamin D supplements are associated with a lower risk of infections (100, 101). However, observational studies have shown conflicting results in dialysis patients (55, 56, 102-107). We therefore found it useful to undertake a systematic review and meta-analysis on the association between serum concentrations/use of vitamin D and infection risk in this population.

2 AIM AND OBJECTIVES

2.1 OVERALL AIM

To investigate the antibiotic resistant patterns of pathogens responsible for the infections, ascertain short-and long-term outcomes during and after hospitalizations with infections and explore the role of vitamin D for infection prevention in patients with CKD.

2.2 SPECIFIC OBJECTIVES

1) To describe microbial patterns of infections and explore the association between kidney function at admission and the risk of infections by multi-drug resistant organisms in patients hospitalized with infections (**Study I**).
2) To compare the short-term outcomes (in-hospital mortality, the rate of intensive care admission, length of hospital stay and medical expense) of infection-related hospitalizations between patients with and without CKD (**Study II**).
3) To characterize the cause of death and explore the association between kidney function at admission and long-term cause-specific mortality in patients hospitalized with infections (**Study III**).
4) To explore the association between circulating vitamin D concentrations and risk of infections in CKD patients treated with chronic dialysis and to explore whether the use of vitamin D supplements or vitamin D receptor activators affects these outcomes (**Study IV**).

To fulfill the aim and objectives, this thesis contains four studies (Figure 2).

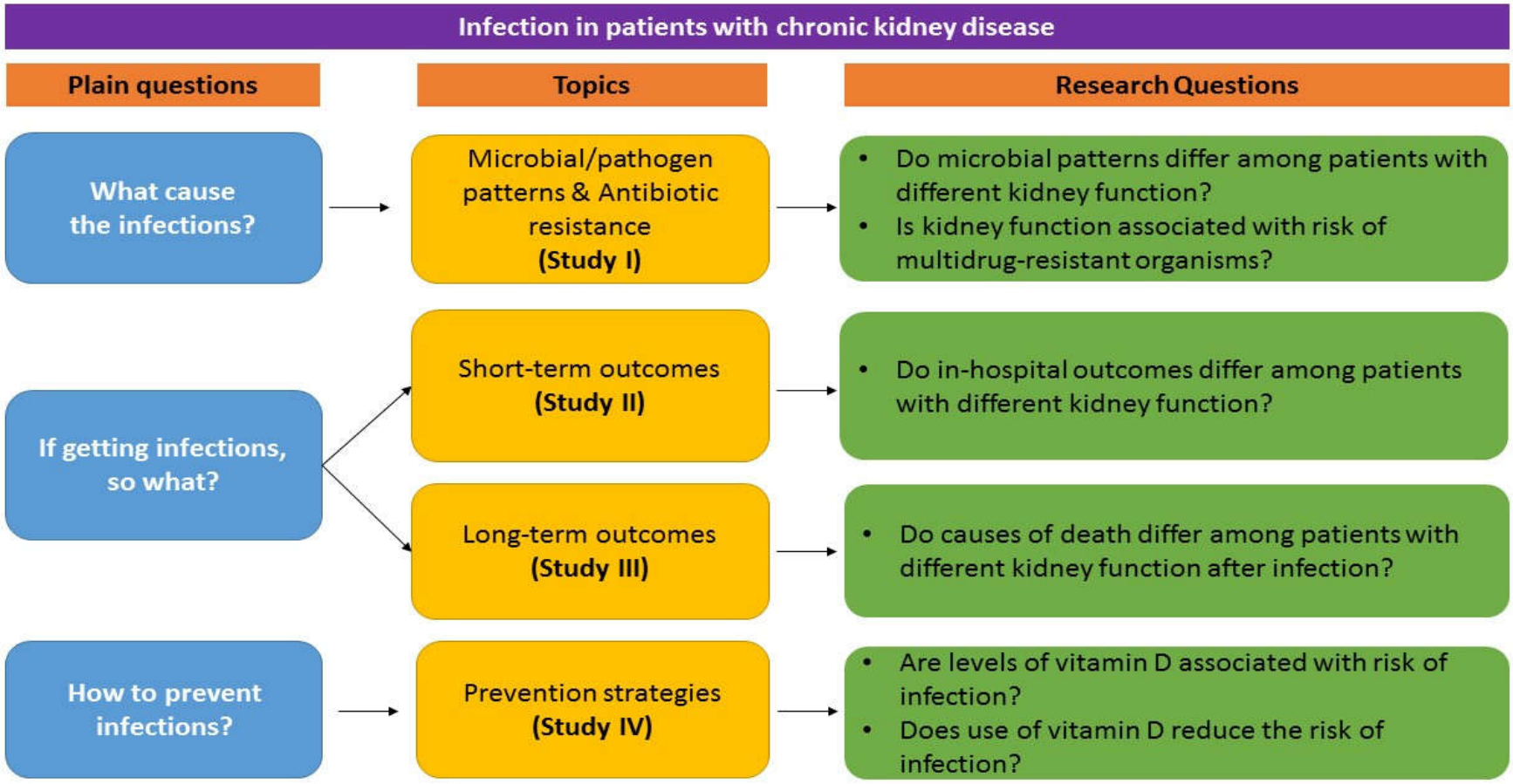


Figure 2. Study framework

3 METHODS

3.1 OVERVIEW OF THE STUDY DESIGN

The study I and II were observational studies based on data collected from the electronic health records in Guangdong provincial hospital of Chinese medicine (GDHCM), Guangzhou city, China. **Study III** was a cohort study using data from the electronic health records from GDHCM and linked with data from the death registry at the Center for Disease Control and Prevention, China. **Study IV** was a systematic review and meta-analysis of existing literature (**Table 1.**).

Table 1. Overview of paper's topics and methods

Topics	Study design	Study population	Exposure/comparison	Outcomes	Data analysis
Microbial pattern & Antibiotic resistance **(Study I)**	Observational study	20,642 adult patients from 4 hospitals in China from 2012-2015, who were (1) hospitalized with a discharge diagnosis of infection, (2) had a serum creatinine measurement at admission, (3) not on dialysis or kidney transplantation. and (4) had a positive microbial culture result in which the type of sample matched the type of infection.	Estimated glomerular filtration rate (eGFR, ml/min/1.73m^2) • 60-104 (Reference) • vs. 30-59 • vs. <30	Multidrug-resistant organism	The multivariable logistic regression model
Short-term outcomes **(Study II)**	Observational study	6,283 adult patients from 4 hospitals in China from 2012-2015, who were (1) hospitalized with a discharge diagnosis of infection, (2) had a serum creatinine measurement 1-12 months at outpatient visits before index hospitalization, (3) not on dialysis or kidney transplantation.	eGRF (ml/min/1.73m^2) • ≥60 (Reference) • vs. <60	• In-hospital mortality • Intensive care unit admission • Length of hospital stay • Medical costs	Mixed-effects logistic regression model and generalized linear model
Long-term outcomes **(Study III)**	Cohort study	40,524 adult patients from 4 hospitals in China from 2012-2015, who were (1) hospitalized with a discharge diagnosis of infection, (2) had a serum creatinine measurement at admission, (3) not on dialysis or kidney transplantation.	eGRF (ml/min/1.73m^2) • ≥60 (Reference) • vs. 30-59 • vs. <30	• All-cause mortality • Cardiovascular mortality	Multivariable Cox regression and competing risk analyses
Prevention strategies **(Study IV)**	Systematic review and meta-analysis	Literature until Dec 2017 who reported (1) patients in long-term dialysis, (2) either had records of levels of serum 25-hydroxy vitamin D or use of vitamin D, (3) had infections as outcomes.	• Serum of 25(OH)VitD High vs. Low • Nutritional vitamin D or vitamin D receptor activator Use vs. non-use	Infection-related outcomes • Infections • Infection-related hospitalization • Infection-related mortality	Random-effects meta-analysis Meta-regression

3.2 STUDY SETTINGS (STUDY I, II, III)

Data used in **Studies I, II and III** were from GDHCM, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine. GDHCH is located in Guangzhou city.

Guangzhou is the capital city of the Guangdong province, located in the southern part of China, 120 km north-northwest of Hong Kong and 145 km north of Macau. It has a population of 13,501,100 residents as of 2015 (108). As the third largest city in China in terms of total economic volume, Guangzhou serves as one of the major transportation hubs and one of the leading commercial and manufacturing cities in mainland China.

GDHCM is one of the oldest and the largest hospitals of Chinese medicine. It has four branches located in different districts of Guangzhou city and serves as one of the main referral centers for these districts. GDHCM provides both modern medicine and Chinese medicine such as Chinese herbal medicine, acupuncture and medicinal massage to patients, according to patients' parallel diagnosis of modern medicine and Chinese medicine. It has over 70,000 inpatients and seven million outpatient visits per year and is one of the leading hospitals in terms of outpatient visits in mainland China. The four hospital branches share the same electronic medical record (EMR) database, developed by International Business Machines Corporation (IBM), which includes all inpatient and outpatient medical records as well as costs invoiced.

Figure 3. Study location

3.3 STUDY POPULATION (STUDIES I, II, III)

3.3.1 The study population (Definitions common to Studies I, II, III)

Patients were eligible for inclusion in our studies if they were adults (≥18 years), had at least one discharge diagnosis of infection according to the *International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM)* **(Appendix Table S1)** (109), between August 2012 and December 2015, regardless of diagnosis order. We excluded those patients who had been undergoing renal replacement therapy (RRT - kidney transplantation or dialysis) before the date of admission. Since the exact infection date was unknown, the date of admission was used as the proxy date for an infection.

A number of discharge diagnoses were not considered as acute infections in **Studies I, II, III**: those commonly found only in infants or children, pregnancy-related infections, delivery-related infections, ear infections, eye infections, thyroiditis, pituitary gland infections, oral/mouth infections, pancreatitis, chronic infections such as chronic hepatitis B and C, HIV (human immunodeficiency virus) infections, cholecystitis associated with cholelithiasis/choledocholithiasis, parasitic or protozoal diseases, sexually transmitted infections, and device-dialysis related infections.

The selected infections were classified broadly into mutually exclusive categories: 1) Respiratory tract infection, including pneumonia; 2) Genitourinary infections, including urinary tract infections; 3) Bloodstream infections or sepsis; 4) Abdominal infections; 5) Skin and soft tissue infections; 6) Cardiovascular infections; 7) Musculoskeletal infections; 8) Nervous system infections; 9) Other infections of interest.

3.3.2 Additional inclusion criteria for Study I

In **Study I**, we only included those who had 1) serum creatinine measurement available at admission; 2) a positive microbial culture result in which the type of sample aligned with the type of infections (**Appendix Table S2**). Only the first admission record was used for patients with multiple hospital admissions. In case of multiple infection diagnoses during the same hospitalization, only one infection diagnosis was used and only if the type of first positive culture matched the discharge diagnosis of infections. For example, the first positive midstream urine culture should match to urinary tract

infections; Bacteraemia/sepsis was valid if it had a positive culture of any type. Thus, each hospitalization had a unique culture-confirmed infection diagnosis.

3.3.3 Additional inclusion criteria for Study II

In **Study II**, we only included those with at least one serum creatinine measurement at outpatient visits between one and twelve months prior to hospitalization with infections. In case of multiple outpatient serum creatinine, we chose the eGFR value closest in time to the hospitalization (1-12 months before) as a proxy for kidney function. Since we included only those with serum creatinine at the outpatient visit, no one was lost to follow-up at the time of discharge from GDHCM.

3.3.4 Additional inclusion criteria for Study III

In **Study III**, we only included those who had at least one serum creatinine measurement available at admission. All patients were followed until their death. Data were censored on 31 August 2016 if patients were still alive. Only the first admission record was used in patients with multiple hospital admissions.

3.4 EXPOSURE: ESTIMATED KIDNEY FUNCTION

We used the eGFR as an indicator of kidney function in **Studies I**, **II and III**. eGFR was estimated by age, sex, serum creatinine concentration and race, according to the established Kidney Disease Improving Global Outcome initiative, and calculated by the CKD-EPI (CKD Epidemiology Collaboration) formula (110). Serum creatinine concentration was assessed by the enzymatic method. The same standardized procedure was used in all laboratories in the different branches of GDHCM. The standard and quality of the laboratory in GDHCM were certified by the International Organization for Standardization, ISO 15189.

3.4.1 Categories of eGFR at admission (Studies I, III)

We estimated eGFR using the serum creatinine at admission. In clinical practice, eGFR at the time of admission provides an important indicator of kidney function to help inform clinical decision-making, although it does not differentiate between acute and chronic kidney dysfunction. In **Study I,** four categories of eGFR were studied: eGFR≥105, 60-104, 30-59, and <30 ml/min/1.73 m^2, with eGFR of 60-104 ml/min/1.73

m^2 serving as the reference group as this range showed the lowest risk of infections and eGFR≥105 ml/min/1.73 m^2 might indicate malnutrition (34).

In **Study III** patients were divided into three categories of eGFR: ≥ 60, 30-59 and < 30 mL/min/1.73m^2. eGFR ≥ 60 served as the reference group since this group was observed to have the lowest risk of death in previous studies (111, 112).

3.4.2 Categories of eGFR at outpatient visits (Study II)

In **Study II**, we first identified patients hospitalized with infections and traced them back to find those with a serum creatinine value at outpatient visits. In case of more than one value, we chose the eGFR value closest in time to the hospitalization (1-12 months prior to the hospitalization) as a proxy for kidney function. The reason for this was to have an estimation of renal function from serum creatinine tests not influenced by the acute nature of the hospitalization. CKD was defined as eGFR <60 ml/min per 1.73 m^2, while non-CKD was defined as eGFR ≥ 60 ml/min per 1.73 m^2.

3.5 OUTCOMES

3.5.1 Multidrug-resistant organisms (MDROs) (Study I)

According to the international expert proposal initiative by the CDC and European Centre for Disease Prevention and Control (ECDC), MDROs mainly focused on five bacteria, including *Enterococcus spp.*, *Enterobacteriaceae* (other than *Salmonella* and *Shigella*), *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Acinetobacter spp.*, and acquires non-susceptibility to at least one agent in three or more antimicrobial categories. Non-susceptibility refers to either a resistant, intermediate or non-susceptible result obtained from in vitro antimicrobial susceptibility testing (113). The first positive culture was used to avoid the influence of the initial antimicrobial therapy on culture result and different culture results during the same hospitalization.

According to Clinical and Laboratory Standards Institute (CLSI) procedures (114, 115), a number of procedures were applied to identify bacteria, including sampling, culture, microbiological tests based on Gram staining, microscopic observation of bacterial morphotypes, characteristics in culture medium and various specific biochemical reactions. Antibiotic susceptibility testing and antibiotics panel used for susceptibility

testing were also performed according to CLSI procedures, CLSI guidelines and local prescription pattern (114). Susceptibility analysis system (MicroScan® WalkAway® 96 Plus; Beckman Coulter, Brea, CA) was used to determine the minimum inhibitory concentrations (MICs). The antibiotic susceptibility was interpreted using the CLSI MIC breakpoints at the time the test was conducted (114). The standard and quality of the laboratory in GDHCM are certified by the International Organization for Standardization, ISO 15189.

3.5.2 In-hospital outcomes (Study II)

In-hospital outcomes included in-hospital mortality, admission to an intensive care unit (ICU), the length of hospital stay (LOSH) and medical costs. All the data mentioned above were extracted from the EMR of GDHCM. Medical costs during a hospitalization were extracted from the billing system in GDHCM. Total medical costs included investigation-related costs (considering laboratory, imaging, pathology and consumable items), ward-related costs (considering all other cost incurred while in the ward), cost of non-surgical therapies (acupuncture, physiotherapy, injection, etc.), costs of surgical therapies (including anesthesia and related materials) and medicine costs.

3.5.3 Cause-specific mortality (Study III)

Mortality data was linked with the death registry from the CDC in Guangdong province, China. Cause of death was classified into five broad categories using *ICD-10-CM*: cardiovascular disease, acute infections, cancer, chronic kidney disease and other cause of death. The death registry in CDC had comprehensive records of deaths in Guangdong province, including time of death and cause of death. The cause of death in the registry of the CDC database was determined by the attending physician, medical examiner or other certifiers. The codes of death used in the analysis were adapted from the previous studies (116, 117) and are listed in **Appendix Table S3.**

3.6 COVARIATES

Age (categorized as 18–44, 45–59, 60-74 and ≥ 75 years old), sex and comorbidities were extracted from the EMR database of GDHCM. Comorbidities were ascertained from the discharge diagnosis according to the classification of Charlson comorbidities index using an established *ICD-10* algorithm (118), including congestive heart failure,

myocardial infarction, cerebrovascular disease, peripheral vascular disease, dementia, chronic pulmonary disease, peptic ulcer disease, rheumatologic disease, hemiplegia or paraplegia, liver disease, diabetes, and cancer/malignancy. According to the GDHCM policy, discharge diagnosis was required to include all the comorbid conditions from patients' medical history.

Infection-related hospitalizations were sub-classified as community-acquired infection-related hospitalizations (CAIRHs), health care-associated infection-related hospitalizations (HAIRHs) and undefined infection-related hospitalizations (UIRHs). CAIRHs were defined as those with infection diagnosis at admission. HAIRHs were defined as those with onset of infections after 48 hours after admission (119) and confirmed by health care-associated infection report in the database which was audited by infection professionals in GDHCM. UIRHs were those who did not fulfill any of the above criteria.

3.7 SYSTEMATIC REVIEW METHODOLOGY (STUDY IV)

The systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (120) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) (121). The protocol was registered with the PROSPERO International Prospective Register of Systematic Reviews (http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018084779).

3.7.1 Inclusion and Exclusion Criteria

The inclusion criteria were presented according to the Study design, Population, Intervention, Comparison and Outcomes (S-PICO) model as follow: 1) Intervention studies (randomized controlled trials or non-randomized intervention studies) or case-controlled studies or cohort studies; and 2) end-stage kidney disease patients (age ≥ 18 years old) undergoing hemodialysis or peritoneal dialysis; and either 3) Available data for different concentrations of serum 25-hydroxy vitamin D [25(OH)D, the major circulating vitamin D metabolite]; or (4) For drug use studies, at least one group receiving either a vitamin D receptor activator (VDRA) (Paricalcitol, Doxercalciferol, Calcitriol, Alfacalcidol, Maxacalcitol, Falecalcitriol) or nutritional vitamin D

(D2/ergocalciferol and/or D3/ cholecalciferol) supplements, whilst the other groups received placebo or no treatment; & 5) Available data for outcomes of interest: Infection-related mortality, risk of infection-related hospitalization, or risk of any infections. We excluded editorials, reviews, case reports and case series articles. Since the aim of this analysis was to compare outcomes for patients with high/normal versus low serum 25(OH)D levels, we excluded studies where original individual data were not accessible to permit categorization of serum 25(OH)D levels.

3.7.2 Information sources and search strategies

The search was conducted using four English-language databases [Cochrane Central Register of Controlled Trials, Pubmed, (**Appendix Table S4**), EMBASE (Elsevier), Web of Science] and three Chinese databases [Chinese National Knowledge Infrastructure (CNKI), China Biology Medicine disc (CBM), Wanfang Data Knowledge Service Platform (WanFang)], from inception until Dec 31, 2017. We also kept track of the other resources such as conference proceedings in order to identify "grey literature". The search strategy was adapted from the published Cochrane review [12] keeping the key terms: 'vitamin D', and 'dialysis' and 'infection'.

3.7.3 Data extraction

We used predefined forms to extract data from the included studies, including study design, region, participants, concentration or level used as a cut-off to define vitamin D deficiency, intervention details (types of vitamin D, dose, frequency, duration, modes of administration if applicable), comparison, outcomes, results and follow-up period. For each study, relative risks (RR) were extracted including incidence rate ratios, odds ratios (OR) and hazard ratios (HR), as well as risk assessments based on the most fully adjusted models. If RR was not available in the studies, the numbers or incidences of the outcomes were extracted to calculate the RRs.

3.7.4 Risk of bias assessment of included studies

The risk of bias of each included randomized control trials was assessed using the Cochrane Collaboration's tool. For cohort and case-controlled studies, the Newcastle-Ottawa Scale (NOS) tool was used (122). In the case of any disagreement, a third author also assessed the study.

3.8 DATA ANALYSIS

Numerical variables were summarized as mean with standard deviation, or median with interquartile range, as appropriate. Categorical variables were summarized using proportions. Differences in baseline characteristics and the proportion between or among groups were compared using the Mann-Whitney U test, analysis of variance, chi-square test, Fisher´s exact test, or Wilcoxon rank-sum test, as appropriate. All the data extracted from electronic medical records databases in **Studies I and II** were complete, with no missing data and loss to follow-up. In **Study III**, we assumed an absence record in the death registry to indicate that the patients were alive and considered censored on 31 August 2016. A P-value < 0.05 was considered significant. All statistical analyses were performed using STATA version 14.2 (StataCorp, College Station, TX, USA).

3.8.1 Statistics in Study I

For the odds ratio (OR) of MDROs, we used multivariable logistic regression adjusted for age group (18-44; 45-59; 60-74; ≥75 years), sex, and Charlson comorbidity index (excluding the renal disease score).

3.8.2 Statistics in Study II

For ORs of death and ICU admission during hospitalization in patients with different kidney function, we used a mixed-effects logistic regression model to set multiple hospitalizations within a patient as a cluster and patients as a random effect.

For the length of hospital stay and estimation of total medical cost, we used generalized linear regression models. For this analysis, we did not adjust for the cluster effect within patients since we considered any hospital stay as an independent statistical unit. Given the inflation rate changes over time, we compared medical expenses between those with and without CKD adjusted for inflation rate based on costs in 2012.

3.8.3 Statistics in Study III

We used multinomial logistic regression marginal prediction to estimate the age- & sex-adjusted cause-specific death proportions. Cox regression models were adjusted for age groups, sex, and Charlson comorbidities index (excluding renal score), presented at different time points after admission (7 days after admission, 28 days after admission, 90 days after admission and 365 days after admission). The association of kidney

function and cardiovascular-related death was examined by a competing risk analysis (Fine and Gray proportional subdistribution hazards models) (123).

3.8.4 Statistics in Study IV

For each outcome measure of interest, random-effects meta-analysis was used to pool relative risks (RRs) for the dichotomous composite outcome (infection-related mortality, infection-related hospitalizations and any non-hospitalized-fatal infections) in order to determine the effect of different levels of 25(OH)D (high/normal vs. low), or according to use of vitamin D versus placebo/no use.

We performed additional empirical Bayes meta-regression models in studies addressing the use of vitamin D as the exposure. These included types of administration (oral or intravenous) and study sample size (<500 or ≥500 participants) and types of dialysis therapy (HD or PD). The presence of small study effects and publication bias was evaluated by Egger regression asymmetry analysis (124).

3.9 ETHICAL PERMISSION

The ethics board committee of GDHCM provided ethical approval for **Studies I, II and III** (B2016-194-01). Informed consent was not needed since the studies involved analysis of anonymized existing data and records. The study was carried out in accordance with the Declaration of Helsinki, International Ethical Guideline for Biomedical Research Involving Human Subjects. **Study IV** was a systematic review and meta-analysis. Since all the data were extracted from the published literature, an ethical permit was not required.

4 MAIN FINDINGS

The main findings derived from **Studies I-IV** are summarized and presented below. The section is divided into three main sub-sections: Microbial patterns (**Study I**), outcomes (**Study II & Study III)** in non-dialysis patients hospitalized with infections and the role of vitamin D in infection risk in those under chronic dialysis (**Study IV**).

4.1 MICROBIAL PATTERN OF INFECTIONS IN PATIENTS WITH DIFFERENT KIDNEY FUNCTION (STUDY I)

4.1.1 Microbial pattern

Among 7,228 first positive microbial cultures, Gram-negative (G-) bacteria were the predominant detected bacteria, followed by Gram-positive (G+) bacteria, *Mycoplasmataceae* and fungi. Compared to patients with eGFR 60-104 ml/min/1.73m^2 (reference group), the proportion of G- bacteria decreased (from 68% to 63%) across decreasing eGFR strata, while the proportion of G+ increased (from 14% to 18%) (**Figure 4**).

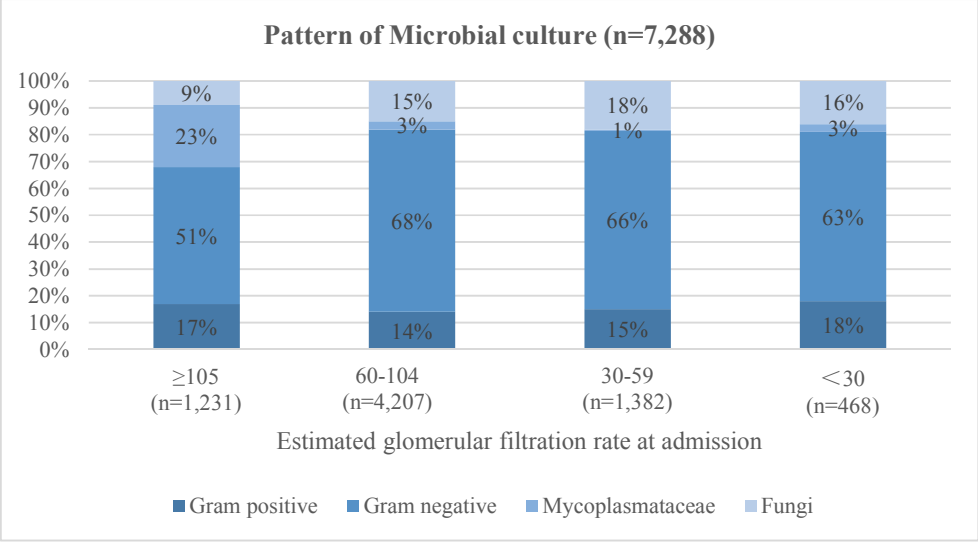


Figure 4. The pattern of the first positive microbial culture by different eGFR categories in 7,228 patients hospitalized with infections in four hospitals of Guangzhou, China

4.1.2 MDROs pattern

In 2,565 MDROs, it was observed that different eGFR categories had different positive culture patterns. G+ MDROs increased while G- MDROs decreased from the group of eGFR between 60-104 ml/min/1.73m^2 (**Figure 5**).

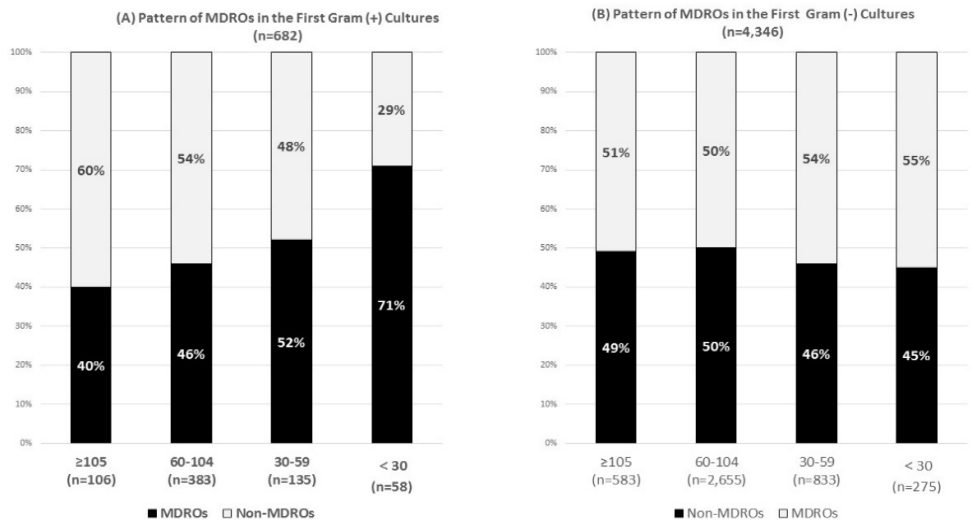


Figure 5. The pattern of gram positive and gram negative multi-drug resistant organisms (MDROs) by different eGFR categories

4.1.3 The odds ratio of MDROs

The crude proportions of MDROs in the first positive cultures were 49.2%, 49.9%, 53.5% and 58.0% in patients with eGFR ≥105, 60-104, 30-59 and <30 ml/min/1.73m^2, respectively.

The results of multivariable logistic regression models show that the odds of MDROs increased as eGFR category decreased. Compared to eGFR 60-104 ml/min/1.73m^2 (reference), the odds of infections by MDROs was 19% and 41% higher in those with eGFR between 30-60 ml/min/1.73 m^2 [Adjusted odds ratio (AOR): 1.19, 95% Confidence interval (CI):1.02-1.38, *P*=0.02] and eGFR <30 ml/min/1.73 m^2 (AOR: 1.41, 95% CI:1.12-1.78, *P*< 0.01), respectively. The trends persisted in subgroup analysis across sex, age group, single pneumonia, single urinary tract infections, sepsis, health-care-associated infections, community-acquired infections and in patients with or without diabetes, although they did not reach statistical significance (**Figure 6**).

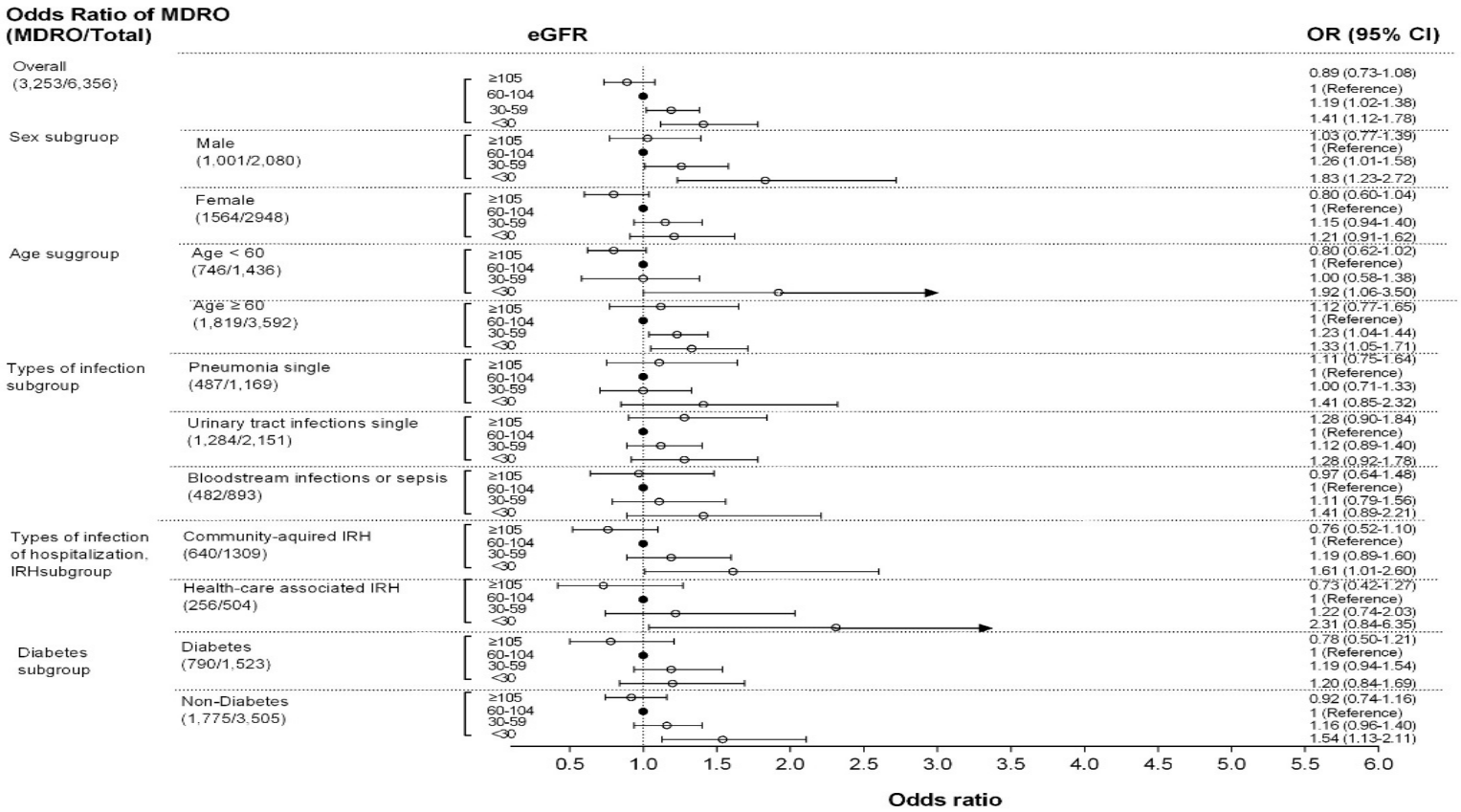


Figure 6.

Odds ratio of MDROs in the first positive culture by patient characteristics and eGFR categories. Sex subgroup adjusted by age and Charlson comorbidity index; Age subgroup adjusted by sex and Adjusted by Charlson comorbidity index; The rest of the subgroups adjusted by age, sex and Charlson comorbidity index. *MDROs: multi-drug resistance organism; Defined by the following bacteria: *Staphylococcus aureus, Enterococcus spp., Enterobacteriaceae, Pseudomonas aeruginos, Acinetobacter spp.*; Resistance to three or more antimicrobial classes; IRH: infection-related hospitalization.

4.2 OUTCOMES IN PATIENTS HOSPITALIZED WITH INFECTIONS AND DIFFERENT KIDNEY FUNCTION (STUDY II & STUDY III)

4.2.1 Intensive care admission (Study II)

ICU admission rates were 5.5% and 12.2% in non-CKD and CKD patients, respectively. The odds of ICU admission were more than two times higher among patients with CKD (AOR=2.18; 95% CI 1.64-2.91). A similar pattern was observed for both HAIRHs (AOR=2.48; CI 1.08-5.70) and CAIRHs (AOR=2.01; 95% CI 1.34-3.02). We further analyzed single infection categories and found that the increased odds of ICU admission in patients with CKD remained statistically significant for pneumonia (OR=2.53; 95% CI 1.64-3.88).

4.2.2 In-hospital medical cost and length of hospital stay (Study II)

The median length of hospital stay (LOHS) for CKD patients was 11 [8-15] days, which was statistically significantly longer ($p<0.001$) than the LOHS for non-CKD patients, 10 [7-14] days. Compared with non-CKD patients, medical expenses in patients with CKD were higher by a median of 2400 RMB (around 350 USD) per hospitalization, corresponding to 20.0% higher in total medical expenses adjusted for inflation rate based on costs in 2012.

4.2.3 Mortality (Studies II, III)

4.2.3.1 In-hospital mortality (Study II)

A total of 115 patients (5.9%) in the CKD group and 166 (3.8%) non-CKD patients died in-hospital. The odds of in-hospital mortality were, therefore, higher among patients with CKD (odds ratio, adjusted OR=1.41; 95% CI 1.02-1.96). In subgroup analysis, ORs for in-hospital mortality were higher among patients with CKD compared with non-CKD patients in CAIRHs, pneumonia, UTIs, although not statistically significant.

4.2.3.2 Cardiovascular mortality and all-cause mortality post-discharge (Study III)

During a median follow-up period of 2 years and five months, 4,781 out of 40,524 patients died. Using multivariable Cox proportional hazards model, all-cause mortality increased with the declining eGFR category. Compared to patients with eGFR values >60 mL/min/1.73m^2, the hazards of all-cause mortality were 19% higher in those with eGFR values between 30-60 mL/min/1.73m^2 (adjusted HR: 1.19, 95% CI 1.11-1.28, P<0.01) and 73% higher in those with eGFR values < 30 mL/min/1.73m^2 (adjusted HR: 1.73, 95% CI 1.59-1.88, *P*<0.01). In the competing risk model, the corresponding sub-distribution HRs for cardiovascular-related mortality were 2.15 (95% CI 1.85- 2.50, *P*<0.01) in patients with eGFR between 30-59 and 3.19 (95% CI 2.68 - 3.80, *P*<0.01) in those with less than 30 mL/min/1.73m^2, respectively.

The risks of all-cause and cardiovascular-related death were highest in the first 7 days following admission and progressively declined thereafter, but remained significantly high at one year following admission **(Table 2**).

Table 2. Hazard ratio of all-cause mortality and sub-distribution hazard ratio of cardiovascular-related mortality at different time points after admission.

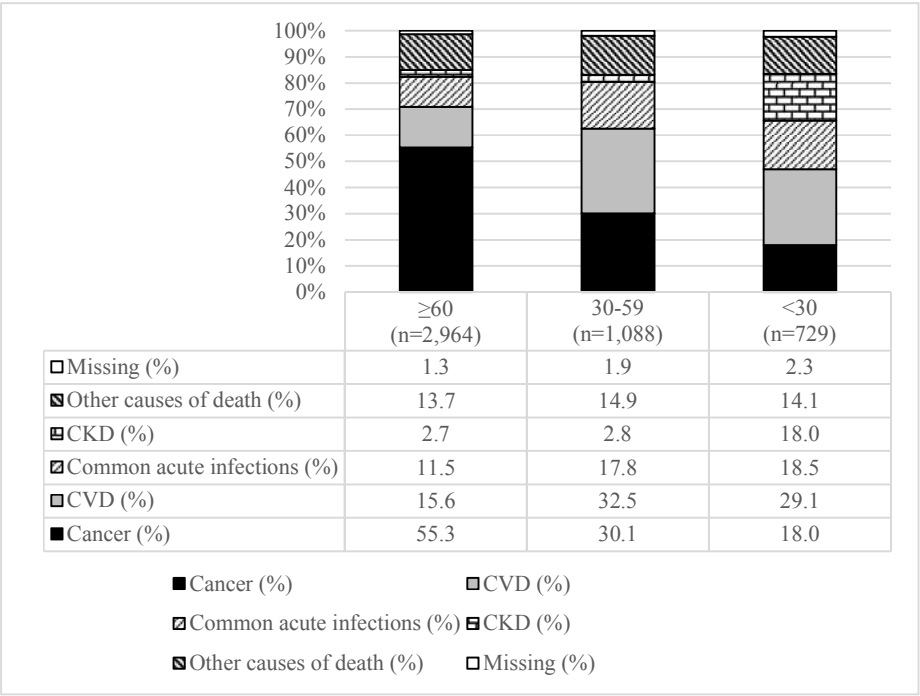
eGFR (mL/min/1.73m^2)	Overall (N=40,524)	7 days after admission	28 days after admission	90 days after admission	365 days after admission
Hazard ratio of all-cause mortality*					
≥60	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
30-59	1.19 (1.11 - 1.28)	2.11 (1.68 - 2.65)	1.54 (1.34 - 1.75)	1.28 (1.16 - 1.42)	1.21 (1.11 - 1.31)
<30	1.73 (1.59 - 1.88)	4.29 (3.40 - 5.41)	2.37 (2.05 - 2.75)	1.86 (1.65 - 2.08)	1.68 (1.52 - 1.84)
Sub-distribution hazard ratio of cardiovascular-related mortality**					
≥60	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
30-59	2.15 (1.85 - 2.50)	3.42 (2.18 - 5.40)	2.95 (2.19 - 3.99)	2.84 (2.27 - 3.56)	2.46 (2.05 - 2.95)
<30	3.19 (2.68 - 3.80)	5.22 (3.17 - 8.60)	4.60 (3.32 - 6.39)	4.30 (3.35 - 5.52)	3.78 (3.08 - 4.63)

*Cox model: Adjusted for age, sex and Charlson comorbidity index.

**Competing risk cause-specific model: Adjusted for age, sex and Charlson comorbidity index.

4.2.4 Cause of death (Study III)

During follow-up, 4,781 patients who hospitalized with infections died due to cancer (43.8%), cardiovascular disease (21.5%), acute infections (14.0%), chronic kidney disease (5.1%) or other causes (14.0%). The cause of death was missing in 1.6% of cases. The proportion of patients dying due to cardiovascular disease increased as the eGFR decreased. (**Figure 7**) Among participants with eGFR>60 mL/min per 1.73m^2, cancer-related death was the most common cause of death: 55.3% (95% CI, 53.5% to 57.0%), which was consistent after adjustment for age and sex. For participants with eGFR values between 30-59 mL/min per 1.73m^2, cardiovascular disease was the most common cause of death, accounting for 32.5% (95% CI, 29.8% to 35.4%). After adjustment for age and sex, cancer was the most common cause of death in this category: 36.0% (95% CI, 33.1% to 38.9%). Among those with eGFR values <30 mL/min per 1.73m^2, CVD was the most common cause of death, accounting for 29.1% (95% CI, 25.9% to 32.5%), which remained similar after adjustment for age and sex.



	≥60 (n=2,964)	30-59 (n=1,088)	<30 (n=729)
Missing (%)	1.3	1.9	2.3
Other causes of death (%)	13.7	14.9	14.1
CKD (%)	2.7	2.8	18.0
Common acute infections (%)	11.5	17.8	18.5
CVD (%)	15.6	32.5	29.1
Cancer (%)	55.3	30.1	18.0

Figure 7. Unadjusted relative percentages for death by all-cause and eGFR. CVD: cardiovascular disease; CKD: chronic kidney disease.

4.3 ROLE OF VITAMIN D IN RELATION TO INFECTIONS IN PATIENTS ON DIALYSIS (STUDY IV)

Of 2,440 reports identified, 17 studies met the inclusion criteria, all with moderate quality. They included 6 cohort studies evaluating 25(OH)D serum concentrations (N=5,714) and 11 (2 RCTs and 9 observational studies) evaluating the use of vitamin D (N=92,309).

4.3.1 25(OH)-Vitamin D concentration and the risk of infection-related outcomes

Compared to individuals with low serum levels of 25(OH)D, the pooled adjusted risk for composite infections was 39% lower (RR= 0.61, 95% CI 0.41-0.89, all were cohort studies) in those with high/normal levels, with moderate heterogeneity (I^2= 60.5%, *P*=0.03) (**Figure 8A**).

In patients undergoing peritoneal dialysis, the risk of peritoneal dialysis-related infections was 66% lower (RR=0.34, 95% CI 0.20-0.58) in those with high/normal levels of 25(OH)D than in those with low levels, with minimal heterogeneity (I^2= 0%, *P*=0.71). In patients undergoing hemodialysis, the risk of infection-related mortality was 12% lower (RR=0.88, 95% CI 0.70-1.08) in those with high/normal levels of 25(OH)D, with minimal heterogeneity (I^2= 0%, *P*=0.43).

Publication bias was indicated in included studies investigating the level of 25(OH)D (*P*= 0.007 in Egger's test).

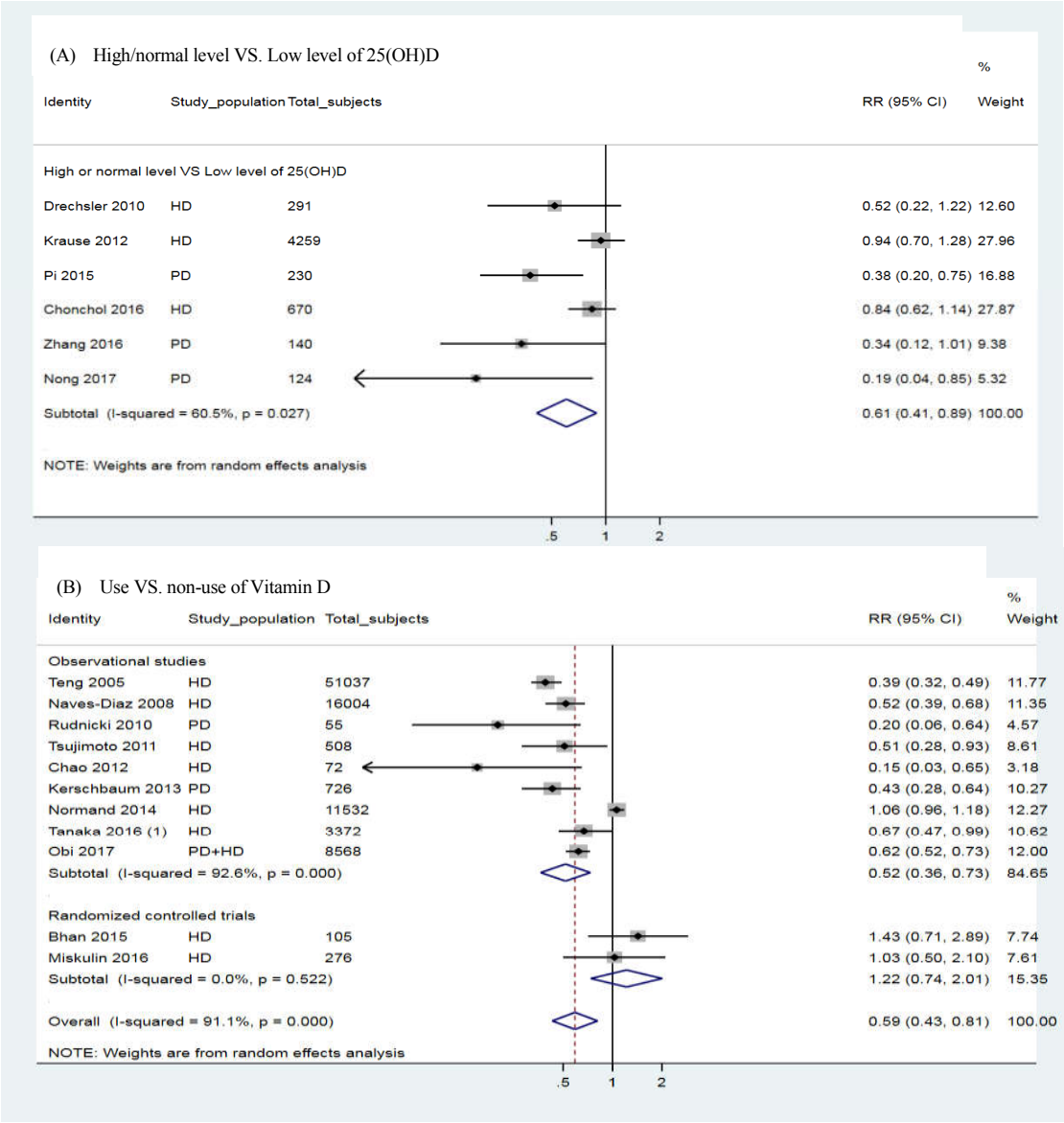


Figure 8. Forest plot using the DerSimonian and Laird random-effects model: (A) The meta-association between high/normal versus low level of 25(OH)D and risk for infection-related outcomes; All the included studies were cohort studies; (B) The meta-association between use and non-use of vitamin D and risk for infection-related outcomes by study design; The observational study group included cohort and case-control studies exploring the association between the use of Vitamin D Receptor Agonists (VDRA) and risk for infection-related outcomes. The randomized controlled trials explored the association between supplemental nutritional vitamin D and risk for infection-related outcomes.

4.3.2 Use of vitamin D and the risk of infection-related outcomes

The pooled adjusted risk for infection-related outcomes was 41% lower in those who used vitamin D (nutritional supplement or VDRA) (RR=0.59, 95% CI 0.43-0.81) compared to those who did not, with high heterogeneity (I^2= 91.1%, *P*<0.001) (**Figure 8B**).

There was no statistically significant difference in infection-related outcomes between supplemental nutritional vitamin D users and non-users (RR=1.22, 95% CI 0.74-2.01, all were RCTs, **Figure 8B**). The pooled adjusted risk for infection-related outcomes was 48%

lower in those who used VDRA (RR=0.52, 95% CI 0.36-0.73, all were observational studies, Figure 3), with high heterogeneity (I^2=92.6%, P<0.001).

A similar association was observed in a meta-analysis of seven cohort studies, which explored the use of VDRA on the risk of infection-related outcomes. Meta-regression analyses suggested that PD patients in studies with larger sample sizes and using intravenous VDRA had lower RRs as compared with their counterparts (**Table 4**).

Publication bias was not indicated in included studies investigating the use of vitamin D (P= 0.12 in Egger's test).

Table 4. Meta-regression Analyses on Association between Use of Vitamin D Receptor Activator and Risk of Infection-related Outcomes

Use VS non-use of VDRA	No. of Studies	Empirical Bayes Metaregression Pooled HR (95% CI)	P	I^2,%
All infection-related outcomes				
Oral vs. Intravenous	9	0.66 (0.24-1.80)	0.36	86.50%
HD vs. PD	8	0.61 (0.20-1.83)	0.32	93.40%
Sample size <500 patients vs ≥ 500	9	0.31 (0.09-1.09)	0.06	93.00%
Non-fatal infections				
HD vs. PD	5	0.57 (0.06-5.53)	0.49	76.97%
Sample size <500 patients vs ≥ 500	5	0.27 (0.04-1.82)	0.12	86.42%

VDRA: Vitamin D Receptor Activator; HD: hemodialysis; PD: peritoneal dialysis; CI: confidence interval; HR: hazard ratio

5 DISCUSSIONS

5.1 SUMMARY OF MAIN RESULTS: WHAT WAS KNOWN BEFOREHAND AND WHAT THESE STUDIES HAVE ADDED

The studies included in this thesis investigated the antibiotic resistant patterns of pathogens as well as short- and long-term outcomes of patients with different kidney functions during and after hospitalization with infections. They also explored the role of vitamin D in the prevention of future infections in patients with chronic kidney disease. We found that the proportion of G- bacteria decreased, while the proportion of G+ increased across decreasing kidney function categories. Poorer kidney function at the time of hospital admission was associated with a higher probability of contracting MDROs (**Study I**). In those hospitalized with infections, CKD patients have increased odds of in-hospital deaths and ICU admissions, resulting in higher health care resource consumption (longer hospital stay and higher medical costs), compared with patients with normal renal function (**Study II**). Lower kidney function on admission was associated with significantly increased hazards of all-cause and cardiovascular-related mortality in those hospitalized with infections (**Study III**). Data from patients undergoing chronic dialysis indicated that the risk of infection-related outcomes was lower in patients with higher serum levels of 25(OH)D. Furthermore, the use of vitamin D, particularly vitamin D receptor activators, was associated with a lower risk of infection-related outcomes in this population (**Study IV**).

5.1.1 MDROs in patients with CKD

5.1.1.1 The underlying mechanism of association between MDROs and CKD

The underlying mechanisms that could explain the association between reduced kidney function and MDROs might include: 1) Immune dysfunction predisposes patients with CKD to infections (125, 126); 2) Higher exposure to antibiotics (either prescribed by physicians or self-prescribed) due to susceptibility to infections, drive antibiotic resistance (127); 3) Patients with more severely reduced renal function had more frequent contact with healthcare personnel and environments (e.g. hospitals) (28).

5.1.1.2 MDROs in dialysis and non-dialysis CKD patients

The presence of infections by MDROs in those requiring dialysis was well documented prior to this study. MRSAs were the most reported MDROs. In a study from the US, 10,517 (14.5%) out of 72,444 invasive MRSA infections were among dialysis patients (128). Among those on dialysis, a meta-analysis by Zacharioudakis et al. reported that the estimated prevalence of

MRSA colonization was 6.2% (95% CI 4.2% to 8.5%) (63). Of haemodialysis patients colonized with MRSA, 19% of the hemodialysis patients colonized with MRSA developed an MRSA infections within 6–20 months. The relative risk of MRSA bacteremia has been found to be approximately 100-fold higher among dialysis patients compared to the general population (128). The prevalence of colonization of MRSA was more common in patients on hemodialysis than in those on peritoneal dialysis (7.2% in HD than 1.3% in PD) (63). Shorr et al. documented that long-term hemodialysis was an independent risk factor associated with infections due to antibiotic-resistant bacteria (129).

In terms of VRE, a meta-analysis of dialysis patients by Zacharioudakis et al. reported that the pooled prevalence of VRE colonization was 6.2% (95% CI, 2.8%-10.8%) (62). Recent use of any antibiotic, particularly vancomycin, and recent hospitalization significantly increased the possibility of a VRE-positive surveillance culture (62).

MRSA and VRE are the antimicrobial-resistant bacteria that have been most extensively investigated in the dialysis population. Infections caused by multidrug-resistant gram-negative bacteria (MDR-GNB) is becoming a concern. Among dialysis patients, MDR-GNB accounted for approximately 25% of isolates in bloodstream infections (130, 131). A study found that the prevalence and incidence of colonization with MDR-GNB were greater than those of colonization with MRSA or VRE in an outpatient hemodialysis facility in the United States (132).

The findings of **Study I** showed that higher odds of infections caused by MDROs were observed as the eGFR declined below 60 ml/min/1.73m^2. The results of this thesis have contributed with the suggestion that the association with MDRO extends to those with less severe levels of reduced renal function who do not require dialysis.

5.1.1.3 Association between MDROs and CKD in the context of China

Our study in China showed a higher prevalence of MDRO infections in non-dialysis CKD patients than what has been reported in studies from Western countries (**Study I**). These studies conducted in Western countries only reported the prevalence of single colonized resistant bacteria, such as MRSA. Johnson *et al* reported that 21.6% of hospitalized dialysis patients were colonized with MRSA in the US (133). The high prevalence of resistant bacteria in our study was comparable to that of other studies from China (95, 134). Yang *et al* reported that the percentage of *Staphylococcus Aureus* identified as MRSA was 73.5% and the percentage of *Acinetobacter Baumannii* isolates identified as multidrug-resistant one was 77.8% in China in 2015 (134). China is one of the countries in the world with high total antibiotic prescribing

(135, 136). Misuse and overuse of antibiotics are driving forces of antibiotic resistance. Self-prescribing and over-prescribing of antibiotics were prevalent in China before stringent antimicrobial stewardship policies were implemented in 2012 (137). These policies may take some time to take effect in terms of containing the high prevalence of MDROs in hospitalized patients.

The finding of an association between kidney function and MDROs infections is of potential clinical relevance. The main clinical application of this study lies in the need to consider the presence of renal dysfunction at admission as a signal to pay closer attention to microbial culture results, given that identified pathogens may be potentially resistant to initial antibiotics. Therefore, subsequent modification of the current therapy is needed if resistance to the current therapy exists. Our study also identifies that patients with impaired renal function as a high-risk group for MDROs infections, with the implication that those patients are in need of close monitoring.

5.1.2 Outcomes in patients hospitalized with infections and CKD

The results of this thesis showed that patients with CKD had higher mortality, a higher rate of ICU admission, longer hospital stay and higher medical costs when they were hospitalized with infections, as compared to patients with normal renal function (**Studies II & III**).

5.1.2.1 Mortality in patients hospitalized with infections and CKD

Increased mortality associated with reduced renal function has also been observed in previous studies (29, 34, 35, 37, 111, 138-142). The Cardiovascular Health Study reported that patients with CKD had a 2-fold greater risk of infection-related mortality (138). This association was further confirmed in the Third National Health and Nutrition Examination Survey (NHANES III) (139). In that study, it was found that not only reduced eGFR, but also albuminuria was associated with increased risk for infection-related mortality (139). In a study conducted in nursing homes in Hong Kong, CKD stage 3B and stage 4/5 CKD were independent predictors of infection-related mortality in adults with a median age of 80 years (111).

The association between reduced kidney function and mortality persisted in patients who had specific infections, such as bloodstream infections (35), sepsis (140) and pneumonia (29, 34, 142). In a cohort of patients 66 years or above, the risk of death within 30 days of onset of community-acquired bloodstream infections was 4.1 times higher in those with an eGFR less than 30 mL/min/1.73m^2 compared to those with an eGFR of 60 mL/min/1.73 m^2 or higher (35). In a Canadian study, compared with participants with an eGFR of 60 to 104 mL/min/1.73 m^2,

an age-dependent inverse relationship also was observed between eGFR and risk of 30-day death from pneumonia (34). In a cohort study from the UK, eGFR <30 mL/min/1.73 m^2 was a risk marker of higher 28-day mortality for pneumonia (RR 1.27: 95% CI 1.12-1.43) and sepsis (RR 1.32: 95% CI 1.07-1.64) (29).

The results of this thesis showed that lower eGFR on admission was associated with significantly increased hazards of all-cause mortality in patients hospitalized with infections. These heightened risks of mortality were highest within 7 days, but remained significantly elevated 1 year following admission. Because of higher mortality in patients hospitalized with infections, analysis of the cause of death in these patients might help risk stratification and help in the planning of intervention strategies.

5.1.2.2 Cause of death in patients hospitalized with infections and CKD

Regarding the cause of death in patients with CKD, a study from Canada used administrative health care data and linked laboratory information to show that the most common cause of death for those with eGFR less than 60 ml/min per 1.73 m^2 was cardiovascular disease (116). Similarly, a study from the U.S. found that cardiovascular diseases were the main causes of death in patients with CKD. After adjusting for covariates, every 5 ml/min per 1.73 m^2 decline in eGFR was associated with a 1.1 fold higher risk of death due to cardiovascular disease (HR, 1.10; 95% CI, 1.08 to 1.12) (143). However, there was little exploration about the cause of death in patients hospitalized with infections. The results of the thesis showed that CVD was the leading cause of death in patients with eGFR less than 60 ml/min per 1.73 m^2 during or after hospitalization with infections (**Study III**).

Previous studies have documented that acute infections triggers a 2 to 8-fold increase in the risk of CVD within the first 30 days (97) as well as after 10 years (98, 144-146). A cohort study from Canada showed that an infectious episode was independently associated with increased risks of mortality and CVD in those with advanced CKD (eGFR between 15 and 45 mL/min/1.73m^2) (43). What is new in our study is that we observed that CVD-related mortality following infections was incrementally higher in those with eGFR<60 mL/min/1.73m^2, not just in those with advanced CKD (**Study III**).

5.1.2.3 Other outcomes in patients hospitalized with infections and CKD

Our study builds on previous findings that CKD is a risk factor for poor outcomes of IRHs in terms of more frequent admissions to ICU, longer hospital stays and higher medical costs, in addition to higher mortality (**Study II**). This finding is clinically important and relevant from a

health policy perspective. Infection is still one of the main causes of hospitalization, consuming a large amount of health-care resources. Our findings highlighted that patients with reduced renal function had poor in-hospital outcomes and higher medical costs. They will inform policymakers that more resources need to be allocated to infection prevention, especially in those with reduced renal function. In the context of DRGs funding system (or so-called single disease reimbursement payment) in China, reimbursement to the hospital is the same if patients are admitted with the same illness, regardless of their comorbidities (87) (147). Our findings suggest that comorbidities, like CKD, should be considered.

5.1.3 The role of vitamin D in relation to infections in patients with CKD

5.1.3.1 The potential mechanism of association between vitamin D and infections

A biologically plausible mechanism by which vitamin D impacts the risk of infections might lie in its role in the innate and adaptive immune systems (148). In the innate immune system, vitamin D promotes the production of β-defensin 2 and cathelicidin which enhances the capacity for autophagy via toll-like receptor activation (149). In the adaptive immune system, vitamin D suppresses the maturation of dendritic cells and weakens antigen presentation (148).

5.1.3.2 Association between vitamin D and infections in the non-dialysis population

Previous studies from the general population have suggested an independent association between low serum concentrations of 25(OH)D and susceptibility to respiratory tract infections, as well as a potentially protective effect of vitamin D against infections (101, 150, 151). In the NHANES III, 25(OH)D levels <30 ng/mL were associated with 56% higher odds of community-acquired pneumonia [OR: 1.56; 95% CI: 1.17-2.07] compared to levels >/=30 ng/mL(151).

Not only lower levels of 25(OH)D, but also lower levels of 1,25-dihydroxy vitamin D ($1,25(OH)_2D$, the activated form of vitamin D) have been associated with infections. In a cohort with a 9.5-year follow-up of 3,292 community-dwelling Japanese subjects, it was observed that death due to respiratory infections increased significantly with lower serum $1,25(OH)_2D$ levels. In the stratified analysis, the association between lower serum $1,25(OH)_2D$ levels and the risk of respiratory infection death was stronger in non-dialysis patients with an eGFR <60 mL/min/1.73 m^2 as compared to those with eGFR >/=60 mL/min/1.73 m^2 (152).

5.1.3.3 Association between vitamin D and infections in the dialysis CKD population

In dialysis populations, however, the evidence of the association between 25(OH)D and infections were conflicting from observational studies (55, 56, 102, 104, 105, 107). In the meta-

analysis of this thesis, it was found that the risk of composite infection-related outcomes (risk of infections, infection-related hospitalization, infection-related death) was lower in patients with higher serum levels of 25(OH)D. In sub group analysis according to different dialysis modalities, we found that this association was not consistent in studies involving hemodialysis patients. One reason for this inconsistency might be that studies involving HD used different infection-related outcomes (mortality or hospitalizations). Studies involving PD patients showed a consistent association between lower level of 25(OH)D and peritoneal dialysis-associated peritonitis.

If the association between vitamin D and infections in dialysis patients was causal, we would expect vitamin D supplementation to lower the risk of infections in this population. The meta-analysis results of this thesis showed that VDRA, but not nutritional supplements, were associated with lower risk of infections. This discrepancy might be related to differences in outcomes ascertainment (infection was not the primary outcome) or in sample size (only 2 studies of nutritional vitamin D supplements). The question remains whether nutritional vitamin D supplementation would reduce the risk of infections. Randomized control trials in the non-dialysis population report inconsistent findings of vitamin D supplementation on the risk of infections (106, 153). This discrepancy of associations might be related to genetic variation in vitamin D metabolism or signaling, which may, in turn, modify the infection prevention effects of vitamin D (154). It should be noted that it is the 1,25-dihydroxy vitamin D ($1,25(OH)_2D$), which is a direct inducer of antimicrobial peptide gene expression, not 25(OH)D (155, 156). Therefore, it might make sense that nutritional vitamin D supplements exert less of an effect on infections than VDRA (149).

Overall, the hypothesis that vitamin D supplementation lowers the risk of infections in dialysis patients is yet to be confirmed in randomized controlled trials.

5.2 METHODOLOGICAL CONSIDERATIONS

5.2.1 Strengths

Studies I, II and III were based on real-world electronic medical data extracted from clinical practice. Many previous studies have analyzed registry data with large sample sizes, but lack detailed information about clinical outcomes and the economic burden of hospitalizations with infections. We were able to 1) comprehensively examine the spectrum of infections, pattern of bacteria and drug sensitivity (**Study I**); 2) explore the associations between kidney function and

a large range of in-hospital outcomes, furthering our understanding of how certain characteristics predispose to in-hospital death, ICU admission, longer hospital stays and higher medical costs (**Study II**); 3) link with the death registry and trace causes of death with a low percentage of missing data (1.6% in **Study III**), furthering our understanding of what characteristics predispose to specific causes of death.

In our systematic review, we were able to capture as many relevant studies as possible via comprehensive searches of four English databases and three Chinese databases; We not only investigate how level of vitamin D [25(OH)D] has an impact on the risk of infections, but also explore the use of vitamin D (both nutritional supplementation and VDRA). This allowed a better understanding of the association of vitamin D with infection-related outcomes, from phenomenon to intervention (**Study IV**).

5.2.2 Limitations

The results should be interpreted considering the following limitations.

5.2.2.1 Selection bias

5.2.2.1.1 Measurement of kidney function

In **Study II**, we included patients with at least one eGFR measurement in outpatient care between one and twelve months before IRHs, to estimate kidney function. The reason why we used outpatient creatinine to estimate kidney function was to avoid the potential shift of eGFR following hospital admission. However, not all patients hospitalized with infections had an outpatient creatinine measurement. In this study, only 11% of all patients hospitalized with infections had outpatient eGFR measurement. Thus, selection bias can not be ruled out. Patients with outpatient eGFR measurements might seek healthcare more frequently than those who do not, or they might be in poorer health. Instead of using eGFR from outpatient visits, we used eGFR at admission to estimate renal function in **Studies I and III**, capturing more than 95% of patients hospitalized with infections. Thus, the representativeness of these study populations might be better.

5.2.2.1.2 Outcome assessment

In **Study I**, the main study outcome was the presence of MDROs in the first positive culture. The presence of MDROs was influenced by culture positive rate, previous antibiotic use, hospitalization or admission from a nursing home (157-159). There was no significant difference in culture positive rates across different eGFR categories in our sample. However,

we did not have access to a regional registry that allowed us to identify previous antibiotic use or hospitalizations.

In **Study II**, all in-hospital outcomes (in-hospital death, ICU admission, length of hospital stay and medical costs) were recorded in the EMR database. There were no missing data. Thus, selective bias due to missing outcomes is unlikely.

In **Study III**, we linked the EMR database with the death registry with only 1.6% of missing data about the cause of death. Selective bias due to missing death status data is thus unlikely. However, the frequency of the death data updated is a concern.

In **Study IV**, we tried our best to identify all relevant articles including those with negative results and grey literature, to avoid selective reporting. Although the tests for publication bias of studies investigating the use of vitamin D were insignificant, its possibility cannot be confidently excluded from observing the funnel plot.

5.2.2.2 Information bias

5.2.2.2.1 Classification of kidney function groups

In **Study II**, we only used the closest serum creatinine 1-12 months before hospitalization as a proxy for kidney function, assuming kidney function to be relatively stable over one year. Misclassification might, however, still exist due to any change of kidney function during this period.

In **Study I** and **III**, we used a single measurement of eGFR at admission to define renal function, which may have resulted in misclassification of true eGFR as patients' renal function might not have been in steady state at the time. Thus, it was not possible to determine with certainty whether patients with low eGFR values at hospital admission had acute kidney injury, chronic kidney disease or a combination of the two. A sensitivity analysis examining the relationship between eGFR values determined 1-12 months prior to hospitalization and MDROs demonstrated consistent findings (**Study I**). Similar sensitivity analysis demonstrated consistently higher hazard ratios for all-cause and cardiovascular mortality in those with low eGFR values at admission, regardless of whether or not reduced renal function existed at a prior outpatient visit (**Study III**).

5.2.2.2.2 Ascertainment of outcomes

In **Study I,** a positive culture could also be related to colonization or contamination and false positives might exist. Frequent cultures might increase the rate of a positive culture. However,

there was no difference in culture positive rates across different eGFR categories. We assume this to be a non-differential classification bias.

There is no universally accepted scheme for classifying cause of death. The groupings that we used in **Study III** were based on previous studies (117). However, it is unlikely that the cause of death would be reported differently due to the kidney function of the patients. We assume this to be a non-differential classification bias.

5.2.2.3 Residual confounding

Despite adjustment for relevant confounders, we cannot exclude the potential effect of residual confounding factors, such as smoking, alcohol consumption, blood pressure, body mass index, the severity of systemic inflammation, or medication (e.g., angiotensin converting enzyme inhibitors), which were not available in our database. In **Studies I, II and III**, very few patients had at least one record of albumin-creatinine ratio or protein creatinine ratio. This introduces additional residual confounding in view of preceding studies suggesting increased infection risk in patients with normal eGFR with albuminuria (36).

In **Study IV**, we used the most adjusted RR presented in the evaluated studies, but the consistency of our results is affected by their implicit residual confounding. The findings cannot prove causality and residual or unmeasured confounding cannot be ruled out.

5.2.2.4 External validity

The findings of **Studies I, II and III** were from Guangzhou and generalization to other populations should be done with caution. We speculate that comparable associations may also be present in other populations with similar social status and income levels.

Study IV was a meta-analysis of available data from chronic dialysis patients. Generalization to other CKD stages cannot be assumed and has yet to be confirmed in future studies.

6 CONCLUSIONS

- Patients with non-dialysis dependent CKD hospitalized with infections:
  - Have a higher likelihood of having infections with multi-drug resistant organisms;
  - Have poorer in-hospital clinical outcomes, resulting in higher health-care resource consumption;
  - Are at significantly increased risk of all-cause and cardiovascular mortality during the following year.
- In patients with CKD receiving chronic dialysis, lower serum levels of 25(OH)-vitamin D and use of vitamin D, particularly vitamin D receptor activators, were associated with a lower risk of infections.

7 IMPLICATIONS AND FUTURE RESEARCH

7.1 IMPLICATIONS FOR CLINICAL PRACTICE

Patients with impaired renal function are a high-risk group for contracting infections by multi-drug resistant organism infections, in need of close monitoring. In patients hospitalized with infections, clinicians should consider the presence of renal dysfunction at admission as a signal to pay closer attention to the results of microbial culture, given that identified pathogens may be potentially resistant to initial antibiotics.

Patients with reduced kidney function at admission have a high risk of cardiovascular-mortality during hospitalization and after one year. Heart status should be carefully monitored following the hospitalization of patients with infections, especially in those with reduced renal function and preexisting ischemic heart disease.

Considering the consistent association between high/normal level of vitamin D and lower risk of infections in patients with CKD receiving chronic dialysis, strategies to increase the serum concentration of vitamin D, such as more sunshine exposure in a certain degree, may be encouraged. The use of vitamin D supplements (nutritional or vitamin D receptor activator) might also reduce the risk of infections in this population. When prescribing vitamin D supplements to these patients, however, their potential adverse effects, such as hypercalcemia leading to vessel calcification, should be considered.

7.2 IMPLICATIONS FOR POLICY AND PUBLIC HEALTH

As a part of China' healthcare reform, DRGs (or so-called single disease reimbursement payment) has been introduced in some cities, such as Guangzhou. By definition, classification of cases in DRGs is based on principal and secondary diagnoses, type of treatment, patient age and sex, surgery, the existence of co-morbidities and complications, discharge status and the procedures performed (160). DRGs payment might work in simple situations such as for patients with appendicitis admitted for surgery. However, patients admitted to hospital for other reasons, such as infections, are more complex, presenting with different comorbidities, especially in the context of increased prevalence of non-communicable disease in China. In fact, the current payment system in China has not established a multi-faceted model that can cope with the complexity of DRGs. Under the current system, the government pays the same fee if patients are admitted with the same illness, regardless of their coexisting comorbidities (82, 147). The findings of our study indicate that patients hospitalized with infections have

higher medical expenses if they also have CKD, which may justify adjustments to the policy of diagnosis-related group payment.

As the global population is aging and kidney function declines with age, we foresee the population of CKD to increase in the future. Not only does infection in patients with CKD induce poor outcomes in this population, requiring more healthcare consumption, but patients with CKD can also be a reservoir of multi-drug resistant organisms, disseminating resistant bacteria to other populations and thus contributing to worldwide antibiotic resistance. Global attention to infections in patients with CKD should thus be encouraged and prioritized.

7.3 IMPLICATIONS FOR FUTURE RESEARCH

Given the significant impact of infections on patients with CKD, research into the underlying mechanisms of high infection risk in this population is warranted, together with identification of strategies to reduce the risk of infections. Also important to explore is how to raise awareness about the importance of infection prevention and associated strategies in the healthcare sector. Although we have observed consistent associations between vitamin D receptor activator and lower risk of infections in patients receiving dialysis, whether the same protection applies to non-dialysis CKD is not known and should be investigated in suitable trials.

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10 APPENDIX

Appendix Table S1. ICD-10 codes for different types of infections.

The following discharge diagnoses were not considered in our study: pregnancy-related infections, delivery-related infections, oral/mouth infections, ear infections, eye infections, pancreatitis, thyroiditis, pituitary gland infections specified as chronic, chronic hepatitis B and C virus, HIV (human immunodeficiency virus), cholecystitis associated with cholelithiasis/choledocholithiasis, sexually transmitted infections, parasitic or protozoal diseases and device-dialysis related infection.

Infection categories	ICD-10 codes
Respiratory tract infections	
Non-pneumonia respiratory tract infections	A06.5 A20.2 A21.2 A36.0 A36.1 A36.2 A36.8 A36.9 A37.0 A37.1 A37.8 A37.9 A38.x B00.2 B08.5 B33.4 B44.2 B48.1 J10.8 J00.x J01.0 J01.1 J01.2 J01.3 J01.4 J01.8 J01.9 J02.0 J02.8 J02.9 J03.0 J03.8 J03.9 J04.0 J04.1 J04.2 J05.0 J05.1 J06.0 J06.8 J06.9 J09.x J10.1 J11.1 J11.8 J20.0 J20.1 J20.2 J20.3 J20.4 J20.5 J20.6 J20.7 J20.8 J20.9 J21.0 J21.8 J21.9 J22.x J34.0 J39.0 J39.1 J40.x J41.1 J44.0 J47.x J85.2 J85.3 J86.0 J86.9 J38.3 J38.7 J39.2 J39.8 J95.0 J98.5 J98.9
Pneumonia	A22.1 A31.0 A42.0 A43.0 A48.1 B01.2 B05.2 B25.0 B37.1 B38.0 B38.2 B39.2 B40.2 B41.0 B42.0 B44.0 B44.1 B45.0 B46.0 J10.0 J11.0 J12.0 J12.1 J12.2 J12.8 J12.9 J13.x J14.x J15.0 J15.1 J15.2 J15.3 J15.4 J15.5 J15.6 J15.7 J15.8 J15.9 J16.0 J16.8 J18.0 J18.1 J18.2 J18.8 J18.9 J85.0 J85.1 J98.4
Genitourinary infections	
Urinary tract infections (UTIs)	N10.x N12.x N13.6 N15.1 N30.0 N30.3 N34.0 N34.1 N34.2 N34.3 N39.0 N15.9 N28.8 N30.8 N30.9
Non-UTIs genitourinary infections	B26.0 B37.3 B37.4 N41.0 N41.2 N41.3 N41.8 N41.9 N43.1 N45.0 N45.9 N48.1 N48.2 N49.0 N49.1 N49.2 N49.8 N49.9 N61.x N70.0 N70.9 N71.0 N71.9 N72.x N73.0 N73.2 N73.3 N73.5 N73.8 N73.9 N75.1 N76.0 N76.2 N76.4 N48.0 N75.8 N76.8 N32.3
Bloodstream infections or sepsis;	A02.1 A20.7 A21.7 A22.7 A26.7 A32.7 A39.1 A39.2 A39.4 A40.0 A40.1 A40.2 A40.3 A40.8 A40.9 A41.0 A41.1 A41.2 A41.3 A41.4 A41.5 A41.8 A41.9 A42.7 A48.3 B00.7 B37.7 R65.1 R65.0 R65.2 U04.9
Abdominal infections	A00.0 A00.1 A00.9 A01.0 A01.1 A01.2 A01.3 A01.4 A02.0 A03.0 A03.1 A03.2 A03.3 A03.8 A03.9 A04.0 A04.1 A04.2 A04.3 A04.4 A04.5 A04.6 A04.7 A04.8 A04.9 A05.0 A05.1 A05.2 A05.3 A05.4 A05.8 A05.9 A06.0 A06.2 A06.3 A06.4 A07.0 A07.1 A07.2 A07.3 A07.8 A07.9 A08.0 A08.1 A08.2 A08.3 A08.4 A08.5 A09.0 A09.9 A21.3 A22.2 A42.1 B05.4 B15.0 B15.9 B16.0 B16.1 B16.2 B16.9 B17.0 B17.1 B17.2 B17.8 B17.9 B19.0 B19.9 B25.1 B25.8 B46.2 K35.0 K35.1 K35.9 K36.x K37.x K57.0 K57.2 K57.4 K57.8 K61.0 K61.1 K61.2 K61.3 K61.4 K63.0 K65.0 K65.9 K75.0 K81.0 K81.8 K81.9 K52.1 K52.9 K57.1 K57.3 K62.8 K63.8 K65.8 K83.0
Skin and soft tissue infections	A06.7 A20.1 A22.0 A26.0 A26.8 A26.9 A31.1 A32.0 A36.3 A43.1 A44.1 A46.x A48.0 B00.0 B00.1 B02.9 B07.x B08.8 B09.x B35.0 B35.1 B35.2 B35.3 B35.4 B35.5 B35.6 B35.8 B35.9 B36.0 B36.1 B36.2 B36.3 B36.8 B36.9 B37.2 B38.3 B40.3 B42.1 B43.0 B43.2 B45.2 B46.3 B48.0 L00.x L01.0 L01.1 L02.0 L02.1 L02.2 L02.3 L02.4 L02.8 L02.9 L03.0 L03.1 L03.2 L03.3 L03.8 L03.9 L04.0 L04.1 L04.2 L04.3 L04.8 L04.9 L05.0 L05.9 L08.0 L08.1 L08.8 L08.9 L30.3 L70.2 R02.x L40.1 L40.3 L70.0 L73.2 L84.x L88.x L98.0
Nervous system infections;	A06.6 A20.3 A32.1 A39.0 A83 A85.8 A86.x A87.0 A87.1 A87.2 A87.8 A87.9 A88.8 A89.x B00.3 B00.4 B01.0 B01.1 B02.0 B02.1 B02.2 B05.0 B05.1 B06.0 B26.1 B26.2 B37.5 B38.4 B43.1 B45.1 B46.1 G00.0 G00.1 G00.2 G00.3 G00.8 G00.9 G04.0 G04.2 G06.0 G06.1 G06.2 G93.7 F05.9 G03.9 G04.8 G04.9 G62.9
Musculoskeletal infections	B33.0 M00.0 M00.1 M00.2 M00.8 M00.9 M46.2 M46.3 M46.5 M60.0 M65.0 M65.1 M71.0 M71.1 M86.0 M86.1 M86.2 M86.8 M86.9 M46.8 M72.8 M94.8
Cardiovascular infections	A39.5 B33.2 B37.6 I01.0 I01.1 I01.2 I01.8 I01.9 I02.0 I02.9 I30.1 I33.0 M05.3 M32.1 I40.0 I410, I411, I412, I430, I39
Other infections of interest	A02.2 A02.8 A02.9 A06.8 A06.9 A20.0 A20.8 A20.9 A21.0 A21.8 A21.9 A22.8 A22.9 A23.0 A23.1 A23.2 A23.3 A23.8 A23.9 A24.0 A24.1 A24.3 A24.4 A25.0 A25.1 A25.9 A27.0 A27.8 A27.9 A28.0 A28.1 A28.2 A28.8 A28.9 A30.0 A30.1 A30.2 A30.3 A30.4 A30.5 A30.8 A30.9 A31.8 A31.9 A32.8 A32.9 A35.x A39.8 A39.9 A42.2 A42.8 A42.9 A43.8 A43.9 A44.0 A44.8 A44.9 A48.2 A48.4 A48.8 A49.0 A49.1 A49.2 A49.3 A49.8 A49.9 A88.0 A88.1 A90.x A91.x A92.0 A92.1 A92.2 A92.3 A92.4 A93.0 A93.1 A93.2 A93.8 A95.0 A95.1 A95.9 A96.0 A96.1 A96.2 A96.8 A96.9 A98.0 A98.1 A98.2 A98.3 A98.4 A98.5 A98.8 A99.x B00.8 B00.9 B01.8 B01.9 B02.7 B02.8 B03.x B04.x B05.8 B05.9 B06.8 B06.9 B08.0 B08.1 B08.2 B08.3 B08.4 B25.9 B26.8 B26.9 B27.0 B27.1 B27.8 B27.9 B33.3 B33.8 B34.0 B34.1 B34.2 B34.3 B34.4 B34.8 B34.9 B37.0 B37.8 B37.9 B38.7 B38.8 B38.9 B39.0 B39.3 B39.4 B39.5 B39.9 B40.0 B40.7 B40.8 B40.9 B41.7 B41.8 B41.9 B42.7 B42.8 B42.9 B43.8 B43.9 B44.7 B44.8 B44.9 B45.3 B45.7 B45.8 B45.9 B46.4 B46.5 B46.8 B46.9 B47.0 B47.1 B47.9 B48.2 B48.3 B48.4 B48.7 B48.8 B49.x B95.0 B95.1 B95.2 B95.3 B95.4 B95.5 B95.6 B95.7 B95.8 B96.0 B96.1 B96.2 B96.3 B96.4 B96.5 B96.6 B96.7 B96.8 B97.0 B97.1 B97.2 B97.3 B97.4 B97.5 B97.6 B97.7 B97.8 B99.x D73.3 E32.1 I00.x I83.2 K11.2 R17.x D76.2

Appendix Table S2. The link between infection diagnosis and culture sample.

Discharge infection diagnosis	Type of culture sample
Respiratory tract infections	Sputum, Nasopharyngeal swab
Urinary tract infections (UTIs)	Midstream urine
Non-UTIs genitourinary infections	Cervical swab, Vaginal Swab
Bloodstream infections or sepsis;	All types of sample
Abdominal infections	Stool, Bile, Ascitic fluid
Skin and soft tissue infections	Wound swab, Skin and soft tissue
Nervous system infections;	Cerebrospinal fluid
Musculoskeletal infections	Joint fluid, muscle tissue
Cardiovascular infections	Pericardial effusion

Appendix Table S3. ICD-10 codes for all causes of death

ICD-10 codes for all causes of death	
Acute infections	Codes from Appendix Table S1
Cardiovascular diseases (CVD)	
All CVD	G45-G46.8,I01-I01.9,I02.0,I05-I09.9,I11-I11.9,I20-I25.9,I28-I28.8,I30-I31.1,I31.8,I31.9,I33-I42.9,I47-I48.92,I51.0-I51.6,I60-I61.9,I62.0-I62.03,I63-I63.9,I65-I66.9,I67.0-I67.3,I67.5-I67.7,I69.0-I69.198,I69.20-I69.398,I70.2-I70.8,I71-I78.9,I80-I83.93,I86-I89.9,I91.9 I51.9,I64, I69.4, I67.4
Arrhythmia	I44.1-I44.3, I45.6, I45.9, 146-149, R00.0, R00.1, R00.8, T82.1, Z45.0, Z95.0
Ischemic heart disease	I20-I25.9
Heart failure	I09.9, I11, I13, I25.5, I42.0, I42.5-I42.9, I43, I50, P29.0
Cerebrovascular disease	G45-G46.8,I60-I61.9,I62.0-I62.03,I63-I63.9,I65-I66.9,I67.0-I67.3,I67.5-I67.7,I69.0-I69.198,I69.20-I69.398
Ischemic stroke	G45-G46.8,I63-I63.9,I65-I66.9,I67.2,I67.3,I67.5,I67.6,I69.3-I69.398
Hemorrhagic stroke	I60-I61.9,I62.0-I62.03,I67.0,I67.1,I67.7,I69.0-I69.198,I69.20-I69.298
Cancer	
	C00-C13.9,C15-C25.9,C30-C34.92,C37-C38.8,C40-C41.9,C43-C45.9,C47-C54.9,C56-C57.8,C58,C58.0,C60-C63.8,C64-C67.9,C68.0-C68.8,C69-C75.8,C81-C86.6,C88-C97.9,D00.00-D00.2,D01.0-D01.3,D02.0-D02.3,D03-D06.9,D07.0-D07.2,D07.4,D07.5,D09.0,D09.3-D09.8,D10.0-D10.7,D11-D12.9,D13.0-D13.7,D14.0-D14.32,D15-D16.9,D22-D25.9,D26.0,D26.1,D27-D27.9,D28.0-D28.7,D29.0-D29.8,D30.0-D30.8,D31-D36,D36.1-D36.7,D37.01-D37.5,D38.0-D38.5,D39.1-D39.8,D40.0-D40.8,D41.0-D41.8,D42-D43.9,D44.0-D44.8,D45-D47.9,D48.0-D48.62,D49.2-D49.4,D49.6,D49.81,K31.7,K62.0,K62.1,K63.5,N84.0,N84.1,N87-N87.9
Chronic kidney disease (CKD)	
All CKD	E10.2-E10.29,E11.2-E11.29,E12.2,E13.2-E13.29,E14.2,I12-I13.9,N02-N08.8,N15.0,N18-N18.9 N13, N12, N19
Chronic kidney disease due to diabetes mellitus	E10.2-E10.29,E11.2-E11.29,E12.2,E13.2-E13.29,E14.2
Chronic kidney disease due to hypertension	I12-I13.9
Chronic kidney disease due to glomerulonephritis	N03-N06.9
Chronic kidney disease due to other causes	N02-N02.9,N07-N08.8,N15.0

Appendix Table S4. Pubmed searching strategy

#1	"Anti-Bacterial Agents"[Mesh] OR "Anti-Bacterial Agents" OR antibiotic*
#2	amoxicillin OR ampicillin* OR bacitracin OR cephalothin OR cefazolin OR cefotaxime OR cefoperazone OR ceftazidime OR ceftriaxone OR cefuroxime OR chloramphenicol OR ciprofloxacin OR clarithromycin OR clindamycin OR cloxacillin OR colistin OR colimycin OR erythromycin OR flucloxacillin OR furazolidone OR "fusidic acid" OR gentamicin OR gramicidin OR imipenem OR "mafenide acetate" OR mupirocin OR natamycin OR neomycin OR nitrofurazone OR oxacillin OR penicillin OR piperacillin OR polymyxin OR rifam* OR "silver nitrate" OR "silver sulfadiazine" OR "sulfacetamide sodium" OR tobramycin OR amphotericin OR tazocin OR teicoplanin OR tetracycline OR trimethopri* OR sulfamethoxazole OR vancomycin
#3	"Infection"[Mesh] OR "Infecti*" OR "infectious" OR "infection-related"
#4	"Catheter-related infection"[Mesh] OR "Peritonitis"[Mesh] OR "Catheter-related infection" OR "Peritonitis"
#5	"sepsis"[Mesh] OR sepsis OR "Systemic Inflammatory Response Syndrome"[Mesh] OR "Systemic Inflammatory Response Syndrome" OR sirs
#6	"Bacterial Infections and Mycoses"[Mesh] OR "Virus Diseases"[Mesh] OR bacterial*
#7	"pneumonia"[Mesh] OR "Respiratory Tract Infections"[Mesh] OR "respiratory tract infection*" OR "respiratory infection*" OR pharyngit* OR tracheit* OR bronchit* OR pneumon* OR "common cold"[Mesh] OR "common cold*" OR coryza OR influenza* OR flu OR "otitis media*" OR sinusit* OR tonsillit* OR laryngit* OR pharyngit* OR bronchit* OR pneumon*
#8	cystitis[Mesh] OR "Urinary Tract Infections"[Mesh] OR pyelonephritis[Mesh] OR "cystitis*" OR "urinary tract infection*" OR "UTI*" OR pyelonephritis
#9	("1966/01/01"[Date - Publication] : "2017/12/30"[Date - Publication])
#10	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8) AND #9
#11	"Vitamin D"[Mesh] OR "vitamin D" OR "vitamin d2" OR "vitamin d3"
#12	"Cholecalciferol"[Mesh] OR "Calcitriol"[Mesh] OR "25-Hydroxyvitamin D3 1-alpha-Hydroxylase"[Mesh] OR "Ergocalciferols"[Mesh] OR "Hydroxycholecalciferols"[Mesh]
#13	"25-hydroxyvitamin D" OR "25-hydroxyvitamin d*" OR "1,25-dihydroxy Vitamin D*" OR "1alpha-hydroxy Vitamin D3" OR "19-nor-1,25-dihydroxy Vitamin D*" OR "cholecalciferol*" OR "colecalciferol*" OR "hydroxycholecalciferol*" OR "falecalcitriol*" OR "calcitriol*" OR "alfacalcidol*" OR "alphacalcidol*" OR "calcipotriol*" OR "epicalcitriol*" OR "22-oxa-1alpha, 25-dihydroxy Vitamin D" OR "F6-1alpha, 25-dihydroxy Vitamin D*"
#14	"25-Hydroxyvitamin D 2"[Mesh] OR "Calcifediol"[Mesh] OR Dihydrotachysterol[Mesh] OR "dihydrotachysterol*" OR "1alpha-hydroxyergocalciferol" OR "dihydrotachysterol*" OR "calciferol*" OR "doxercalciferol*" OR "dihydroxyvitamin D*" OR "hydroxyvitamin D*" OR "calcifediol*" OR "ergocalciferol*" OR "calcifediol lactol" OR "calcifediol lactone"
#15	"maxacalcitol*" OR "oxacalcitriol" OR "paricalcitol*" OR "lexacalcitol*" OR "seocalcitol*" OR "VDRA"
#16	("1966/01/01"[Date - Publication] : "2017/12/30"[Date - Publication])

#17	(#11 OR #12 OR #13 OR #14 OR #15) AND #16
#18	"Kidney Failure, Chronic"[Mesh])
#19	"Renal Insufficiency, Chronic"[Mesh]
#20	"chronic kidney disease" OR "renal failure*" OR "CRF" OR "kidney failure*" OR "renal insufficien*" OR "kidney dysfunction" OR "renal dysfunction" OR "reduced kidney function" OR "reduced renal function" OR "chronic kidney" OR "chronic renal"
#21	"estimated glomerular filtration rate" OR "eGFR" OR "reduced eGFR"
#22	"end-stage renal disease*" OR ESRD OR "End-Stage Kidney Disease" OR "ESKD" OR "CKD" OR "CKF" OR "CRD" OR "CRF" OR "ESKF" OR "ESRF" OR "uremia"[Mesh]
#23	"predialysis" OR "dialysis" OR "haemodialysis" OR "hemodialysis" OR "dialysis*" OR "Renal Replacement Therapy"[Mesh] OR "Renal Dialysis"[Mesh] OR "Hemofiltration"[Mesh] OR "hemodialysis" OR "Hemofiltration" OR hemodiafiltration OR "peritoneal dialysis" OR "continuous renal replacement therapy" OR "CRRT" OR "Hemodialysis, Home"[Mesh] OR "Hemodiafiltration"[Mesh] OR "Hemofiltration"[Mesh] OR "Peritoneal Dialysis"[Mesh] OR "Peritoneal Dialysis, Continuous Ambulatory"[Mesh]
#24	"CAPD" OR "CCPD" OR "APD"
#25	"kidney transplant*" OR "Kidney Transplantation"[Mesh]
#26	"glomerular disease*" OR "glomerular nephritis" OR "nephritis" OR "nephrotic syndrome*" OR "nephropathy" OR "podocyte disease*" OR "Proteinuria" OR "Albuminuria" OR "Proteinuria"[Mesh] OR "Albuminuria"[Mesh]
#27	("1966/01/01"[Date - Publication] : "2017/09/30"[Date - Publication])
#28	(#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26) AND #27
#29	#10 AND #17 AND #28