Risk of Kidney Injury Requiring Dialysis After Sepsis

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Article

Keywords: Sepsis, acute kidney injury, chronic kidney disease, dialysis

Posted Date: March 28th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1453679/v1

Abstract

Background:

Sepsis-associated acute kidney injury (AKI) can accelerate the progression of chronic kidney disease and lead to permanent kidney damage. However, the relationship between sepsis-associated AKI and dialysis has not been well evaluated. Our study aimed to investigate the risk of AKI requiring dialysis after sepsis.

Methods:

A nationwide population-based case-crossover study comprised all patients requiring their first dialysis from 2004 to 2016 from the database of Taiwan's National Health Insurance. Patients aged <20 years or with missing data were excluded.

Results:

147,201 and 75,031 patients requiring acute temporary and chronic dialysis were included in this study. The odds ratios (ORs) for patients requiring acute temporary dialysis after sepsis were 15.77, 10.67, 9.23, and 8.36 for exposure periods of 1, 2, 3, and 4 weeks, respectively. For patients requiring chronic dialysis after sepsis, ORs were 6.99, 4.12, 4.16, and 3.66 for exposure periods of 1, 2, 3, and 4 weeks, respectively. In analyses using no overlapping time intervals, the risk remained the highest during the time closest to the event.

Conclusions:

This study demonstrated that patients with sepsis had a markedly increased risk of renal failure requiring dialysis and the risk was highest within 1 week of sepsis.

Introduction

Sepsis is a life-threatening organ dysfunction caused by dysregulated host response to infection. Sepsis may progress to septic shock resulting in multiple organ failure and carrying a mortality rate of 54% [1]. Acute kidney injury (AKI) is common in patients with sepsis, occurring in > 50% of cases [2]. In patients with sepsis and septic shock, AKI is a factor in poor prognosis and is associated with high mortality rates, increased intensive care unit and hospital stays, increased risk of progressive chronic kidney disease (CKD), and death [3–5].

CKD is a public health concern because its incidence and prevalence continue to increase, leading to poor outcomes and high costs [6, 7]. Patients with CKD have an increased risk of morbidity and mortality from sepsis [8, 9]. Some studies have suggested that sepsis and septic AKI are markedly influenced by underlying CKD and can also accelerate the progression of CKD [10, 11]. However, the association of sepsis-associated AKI and subsequent acute temporary and chronic dialysis remains unclear.

We conducted a nationwide case-only study based on within-person comparisons by using a large national cohort in Taiwan. The advantage of this approach is that confounding factors that do not vary with time are implicitly adjusted for. The aim of this study was to investigate the risk of sepsis-associated AKI requiring acute temporary dialysis or chronic dialysis. We also explored whether the risk of dialysis after sepsis is moderated by the diagnosis of chronic kidney disease.

Materials And Methods

Study design and data sources

In this study, we conducted a nationwide case-crossover study by using data of patients requiring acute temporary dialysis or chronic dialysis after sepsis from January 1, 2004, to December 31, 2016. Data were retrieved from the Taiwan National Health Insurance (NHI) Research Database. The NHI program covers 99.9% of the Taiwanese population of 23 million, which implemented in 1995. The database contains detailed patient information, including date of birth, sex, residential or work area, dates of clinical visits, *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis codes, prescription details, expenditure amounts, and outcomes at hospital discharge (recovered, died, or transferred). The study was approved after full review by the Joint Institutional Review Board of Taipei Medical University (TMU-JIRB N201909046). The study was conducted in accordance with approved guidelines. Informed consent of the study participants was not required because the dataset used in this study were anonymized before its use.

Study population

We identified all patients who required dialysis, including acute-temporary or chronic dialysis, from January 1, 2004, to December 31, 2016. We defined the primary outcome as the first time of dialysis during admission or at outpatient clinic determined using the procedure codes for dialysis. Acute temporary dialysis was defined as undergoing temporary dialysis for no more than 3 months; in contrast, chronic dialysis was defined as undergoing dialysis for more than 3 months. Patients aged < 20 years or with missing birth date or sex data were excluded. We only included patients who started their first dialysis between January 1, 2006 and December 31, 2015 to facilitate comorbidity evaluation for the self-control group and outcome evaluation for case group.

Exposure Measurement

Exposure measurement was defined as emergency department visit or hospitalization for sepsis (ICD-9-CM codes: 038.xx, 995.91, 995.92, or 785.52).

Case-crossover design

The case-crossover design is used in a special type of case-only study [12, 13] where patients serve as their own controls. This prevents selection bias in the control group, including healthy volunteer bias and confounding bias, such as that related to sex or socioeconomic position. In the case-crossover design, we

identified sepsis exposure during the exposure period for both case and control groups. The exposure period was the period before sepsis up to the index date. The index date for the case group was defined as the date of first dialysis, whereas that for the control group was defined as 6 months before the first dialysis. We studied the exposure period lengths of 1, 2, 3, and 4 weeks before the index date for both case and control groups.

Measurement of covariates

Major risk factors for dialysis were considered, such as diabetes mellitus (ICD-9-CM code: 250), hypertension (ICD-9-CM codes: 401–405), hyperlipidemia (ICD-9-CM codes: 272.0–272.4), Charlson comorbidity index (CCI), and agents related to nephrotoxicity. We identified comorbidities by at least once for inpatient diagnoses with ICD-9-CM codes or three or more times for outpatient diagnoses with ICD-9-CM codes within 1 year before the index date were used. The use of concomitant medications within 1 year before first dialysis was taken as time-varying confounders, including nonsteroidal anti-inflammatory drugs (NSAIDs).

Subgroup and sensitivity analysis

We performed subgroup analyses based on sex and the comorbid condition for CKD, respectively. Patients with CKD (ICD-9-CM codes: 250.4, 274.1, 403.1, 404.2, 404.3, 440.1, 442.1, 447.3, 572.3, 642.1, 646.2, 572.4, 283.11, 580, 581, 582, 583, 584, 585, 586, 587, 588, 589, 403, and 404) were those who were received a CKD diagnosis three times during visits to the outpatient clinic or emergency department or once during admission to the hospital. In sensitivity analysis, we evaluated the risk for different duration of exposure periods before the index date. We assessed the risk of AKI requiring first dialysis within 1,2,3, and 4 weeks after exposure. Furthermore, we assessed the risk of AKI requiring first dialysis at a nonoverlapping time interval after sepsis by investigating the risk at 1–7, 8–14, 15–21, and 22–28 days. Temporary and chronic dialysis were studied separately for each period.

Statistical analysis

A conditional logistic regression model was used in the case-crossover design. All analyses were performed using SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA).

Availability of Data and Materials

The data that support the findings of this study are available from National Health Insurance Research Database in Taiwan but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data cannot be shared from the authors for ethical/privacy reasons. Administrative permissions were required to access the raw data used in this study. Researchers should apply permissions for the raw data from the Health and Welfare Data Science Center, Ministry of Health and Welfare in Taiwan.

Results

Figure 1 illustrates the flow of the case-crossover study. Patients with AKI requiring their first dialysis after sepsis from January 1, 2004, to December 31, 2016, were included in this study (N = 330,026). We excluded patients with their first dialysis before January 1, 2006, or after December 31, 2015 (N = 104,333), with missing age and sex (N = 847) data, or aged < 20 years (N = 2,614), yielding 222,232 eligible patients. In total, 147,201 and 75,031 patients with AKI required temporary and chronic dialysis, respectively. The characteristics of patients with AKI requiring temporary and chronic dialysis after sepsis are shown in Table 1.

Table 1
Characteristics of patients with acute temporary dialysis and chronic dialysis after sepsis

	Acute-temporary dialysis		Chronic dialysis	
	Case	self-control	Case	self-control
N	147201		75031	
Age at first dialysis, mean ± SD, y	68.2 ± 15.7		63.7 ± 14.5	
Age at first dialysis, N (%)				
20–29 y	2482 (1.7)		1287 (1.7)	
30–39 y	5849 (4.0)		3450 (4.6)	
40–49 y	11563 (7.9)		7651 (10.2)	
50–59 y	21178 (14.4)		15796 (21.1)	
60–69 y	26852 (18.2)		18037 (24.0)	
70–79 y	38645 (26.3)		18238 (24.3)	
80–89 y	34529 (23.5)		9646 (12.9)	
≧ 90 y	6103 (4.2)		926 (1.2)	
Male, N (%)	87069 (59.2)		40081 (53.4)	
Year of first dialysis, N (%)				
2006	12659 (8.6)		6290 (8.4)	
2007	13745 (9.3)		6690 (8.9)	
2008	14224 (9.7)		7064 (9.4)	
2009	14554 (9.9)		7329 (9.8)	

	Acute-temporary dialysis		Chronic dialysis	
2010	15237 (10.4)		7706 (10.3)	
2011	15525 (10.6)		7180 (9.6)	
2012	15357 (10.4)		7754 (10.3)	
2013	15173 (10.3)		8092 (10.8)	
2014	15217 (10.3)		8264 (11.0)	
2015	15510 (10.5)		8662 (11.5)	
Comorbid conditions, N (%)				
Diabetes mellitus	68499 (46.5)	60588 (41.2)	43552 (58.1)	40567 (54.1)
Hypertension	94917 (64.5)	82203 (55.8)	65448 (87.2)	53629 (71.5)
Hyperlipidemia	26103 (17.7)	25233 (17.1)	20108 (26.8)	19602 (26.1)
Charlson comorbidity index, N (%)				
≤ 3	68342 (46.4)	86738 (58.9)	28217 (37.6)	33701 (44.9)
4–5	38370 (26.1)	33797 (23.0)	24674 (32.9)	22373 (29.8)
> 5	40489 (27.5)	26666 (18.1)	22140 (29.5)	18957 (25.3)
Charlson comorbidity index, mean ± SD	4.1 ± 2.7	2.5 ± 2.4	4.4 ± 2.1	3.1 ± 2.2
Treatment with NSAIDs within 1 year prior to first dialysis, N (%)	50017 (34.0)	48963 (33.3)	21030 (28.0)	21652 (28.9)

The mean ages of patients with AKI requiring their first dialysis in the temporary and chronic dialysis groups were 68.2 ± 15.7 and 63.7 ± 14.5 years. The frequencies of comorbidities such as diabetes mellitus, hypertension, and hyperlipidemia were higher in patients with AKI requiring temporary or chronic dialysis after sepsis than in patients with sepsis only. The demographic characteristics of patients

receiving temporary or chronic dialysis after sepsis stratified by CKD are shown in Supplementary Tables S1 and S2.

Sepsis was associated with an increased risk of AKI requiring temporary dialysis with odds ratios (OR) of 15.77 (95% confidence interval [CI]: 14.06–17.69), 10.67 (9.81–11.60), 9.23 (8.59–9.91), and 8.36 (7.84–8.91) for exposure periods of 1, 2, 3, and 4 weeks, respectively are shown in Fig. 2. The risk of requiring temporary dialysis after sepsis persisted but the risk magnitude decreased as the time interval increased. The risk of receiving temporary dialysis remained significantly high after increasing the time interval after the sepsis event to 4 weeks. A similar trend was observed in patients with renal failure requiring chronic dialysis after sepsis, where ORs were 6.99 (95% CI: 5.09–8.80), 4.12 (3.47–4.91), 4.16 (3.54–4.89), and 3.66 (3.18–4.20) for exposure periods of 1, 2, 3, and 4 weeks, respectively are shown in Fig. 3. No substantial difference was observed in dialysis risk between male and female patients in subgroup analysis stratified by sex.

In analyses using no overlapping time intervals of AKI requiring temporary or chronic dialysis after sepsis (Supplementary Figs. S1 and S2), the increased risk of requiring temporary dialysis after sepsis was the greatest (15.8-fold) in the first 7 days after sepsis, and this increased risk decreased markedly to 5-fold from 8 to 14 days after sepsis but remained high (4.5-fold) for as long as 22–28 days after sepsis. The pattern for the first chronic dialysis requirement was somewhat different, with a 6.7-fold increased risk in the first 7 days after sepsis and a marked decrease to a 2-fold increased risk from 8 to 14 days after sepsis as well as in the 22–28 days interval.

Discussion

This case-crossover study demonstrated several critical findings. First, patients with AKI exhibited an increased dialysis risk after sepsis of nearly 15.8- and 6.7-fold when requiring temporary and chronic dialysis within 1 week. The risk remained high for up to 4 weeks after sepsis but gradually decreased as the time interval increased. Second, the risk was consistent after stratification based on gender. Third, in analyses using nonoverlapping time intervals, the risk remained the highest during the time closest to the event.

Sepsis severity increases AKI incidence [14, 15]. In a cohort study in Spain, AKI incidence increased significantly depending on sepsis severity (4.2% for sepsis, 22.7% for severe sepsis, and 52.8% for septic shock) [14]. In another prospective cohort study including 1177 patients from 198 intensive care units in 24 European countries, up to 51% patients with sepsis developed AKI [15]. AKI severity is determined on the basis of changes in serum creatinine levels and urine output [16]. Patients with severe kidney injury may require dialysis to improve survival and outcomes. Although a growth in knowledge has illuminated the association between sepsis and AKI [17, 18], investigations regarding the risk of AKI with dialysis among patients with sepsis are limited.

The incidence of AKI requiring dialysis in patients with severe sepsis has increased in recent years, and this may be attributed to the survival advantage associated with early dialysis initiation in patients with

severe AKI, which has been recognized in previous studies [19]. In patients with sepsis-induced AKI, individual differences are variable; therefore, the novelty of our study is the use of a crossover design to minimize within-person confounding biases.

Several pathophysiological mechanisms relatively specific to sepsis-induced AKI have been proposed, including ischemic/hypoxic, nephrotoxic, and inflammatory insults contributing to AKI pathogenesis, and no single pathway can explain all the features of septic AKI [20–22]. Although ischemic injuries are commonly regarded the leading cause of AKI, sepsis-induced AKI may develop in the absence of renal hypoperfusion and clinical signs of hemodynamic instability [23] and in the presence of normal or increased global renal blood flow [24].

Chronic medical conditions, such as diabetes mellitus, hyperlipidemia, and hypertension, are common risk factors for both sepsis and renal failure. The CCI is a commonly used clinical scoring system, which assesses prognosis on the basis of the patient's comorbidities. In a retrospective study, which included 786 critically ill patients who were either admitted with AKI or developed AKI during their hospital stay, a CCI score of > 6 independently predicted poor renal outcomes [25]. Drug toxicity was related to AKI development and dialysis initiation, and NSAIDs were the most commonly used medication, which were frequently associated with AKI. NSAID use is associated with a 3-fold greater risk of acute renal failure in critically ill patients when compared with patients without a history of NSAID use [26], and this may be particularly dangerous in patients with CKD who have sepsis. In our study, major risk factors associated with dialysis initiation, such as common comorbidities and nephrotoxic agents, were further assessed.

Several studies have demonstrated that preexisting CKD is one of the key modifiers in AKI leading to progression of CKD [27, 28]. In a large community-based cohort of patients with CKD, the risk of end-stage kidney disease (ESKD) was found to vary with preadmission renal function: 42% and 63% patients with baseline estimated glomerular filtration rates of 30–44 and 15–29 mL/min per 1.73 m^2, respectively, developed ESKD [27]. Even a single acute insult to already-compromised kidneys may be devastating. Although the mechanism linking CKD progression and AKI is not yet completely understood, recent studies have demonstrated that persistent kidney injury induced by sepsis-associated AKI is coupled with systemic inflammation. Renal repair can lead to malfunctions in inflammation, fibrosis, and vascular rarefaction that lead to continuous cell and tissue disruption [29, 30].

The present study has several strengths. First, this was a national population-based study, which included a sufficiently large sample size, thus increasing the generalizability of the study. Acute temporary or chronic dialysis can be identified correctly by the procedure codes used in the claim database. Second, we used a case-crossover design based on within-individual comparisons, which may implicitly minimize confounding bias through adjusting time-invariant confounding factors. Third, to eliminate the possibility that AKI may be induced by nephrotoxic medications, we also assessed concomitant medications including NSAIDs within 1 year before the first dialysis. Finally, to improve data robustness regarding gradually decreasing dialysis risk after sepsis with increasing time interval, we reassessed data using nonoverlapping time intervals, and the risk remained the highest at the time closest to the event.

This study also has several limitations. First, sepsis diagnosis was identified on the basis of ICD-9-CM codes, and we have no detailed information to define the severity of sepsis. Therefore, we are unable to estimate a severity-related relation between sepsis and the risk of dialysis. Second, the National Health Insurance Research Database (NHIRD) does not provide detailed information on health-related factors, such as body mass index, history of smoking, and dietary habits, all of which may be a confounder. To combat this, we used the case-crossover design to minimize the confounding bias. Third, due to the case-crossover design, all patients who underwent dialysis were 1 year older than those in the control group—age is a major risk factor for CKD and dialysis initiation in these patients. Finally, the NHIRD does not provide detailed information on the severity of sepsis related AKI, and thus, we could not perform a subgroup analysis based on severity. Owing to these limitations, a large prospective study in future may provide helpful information to clinicians.

Conclusion

This study demonstrated nearly 15.8- and 6.7-fold increases in the risks of acute temporary and chronic dialysis within 1 week of sepsis exposure, and patients with sepsis remain at risk of acute temporary or chronic dialysis as long as 4 weeks after sepsis exposure. Patients with sepsis and AKI may require acute temporary dialysis, but some patients may be unable to recover and thus require long-term chronic dialysis. The medical cost of patients with CKD requiring chronic dialysis is enormous and has become a serious public health concern. This study identified a unique group of patients at increased risk of dialysis. To reduce the disease burden of CKD requiring dialysis, taking effective precautions in those with high risk is important. Further studies are needed to confirm these relationships in other populations to determine the exact mechanisms of the increase risk of kidney failure requiring dialysis after sepsis and to develop effective strategies to reduce this risk.

Declarations

Acknowledgments

This work was partly funded by a grant from the National Health Research Institutes (grant no. NHRI-EX110-10926HT) and Ministry of Science and Technology in Taiwan (MOST) (grant no. MOST109-2314-B-038-106-MY3).

Author Contributions

Mei-Yi Wu had full access to all of the data in the study and was responsible for the integrity of the data and the accuracy of the data analysis.

Research idea and study design: Mei-Yi Wu, Chung-Shun Wong, Ping-Jen Hu, Mai-Szu Wu

Data acquisition: Mei-Yi Wu, Tzu-Ting Chen, Chung-Shun Wong,

Data analysis/interpretation: Mei-Yi Wu, Ping-Jen Hu, Chung-Shun Wong, Mai-Szu Wu

Statistical analysis: Tzu-Ting Chen, Chung-Shun Wong

Supervision or mentorship: Mai-Szu Wu, Mei-Yi Wu

Sources of Funding

We have not financial interest and we have not received direct or indirect funding, and there is not conflict of interest.

Disclosures

None disclosed.

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Figures

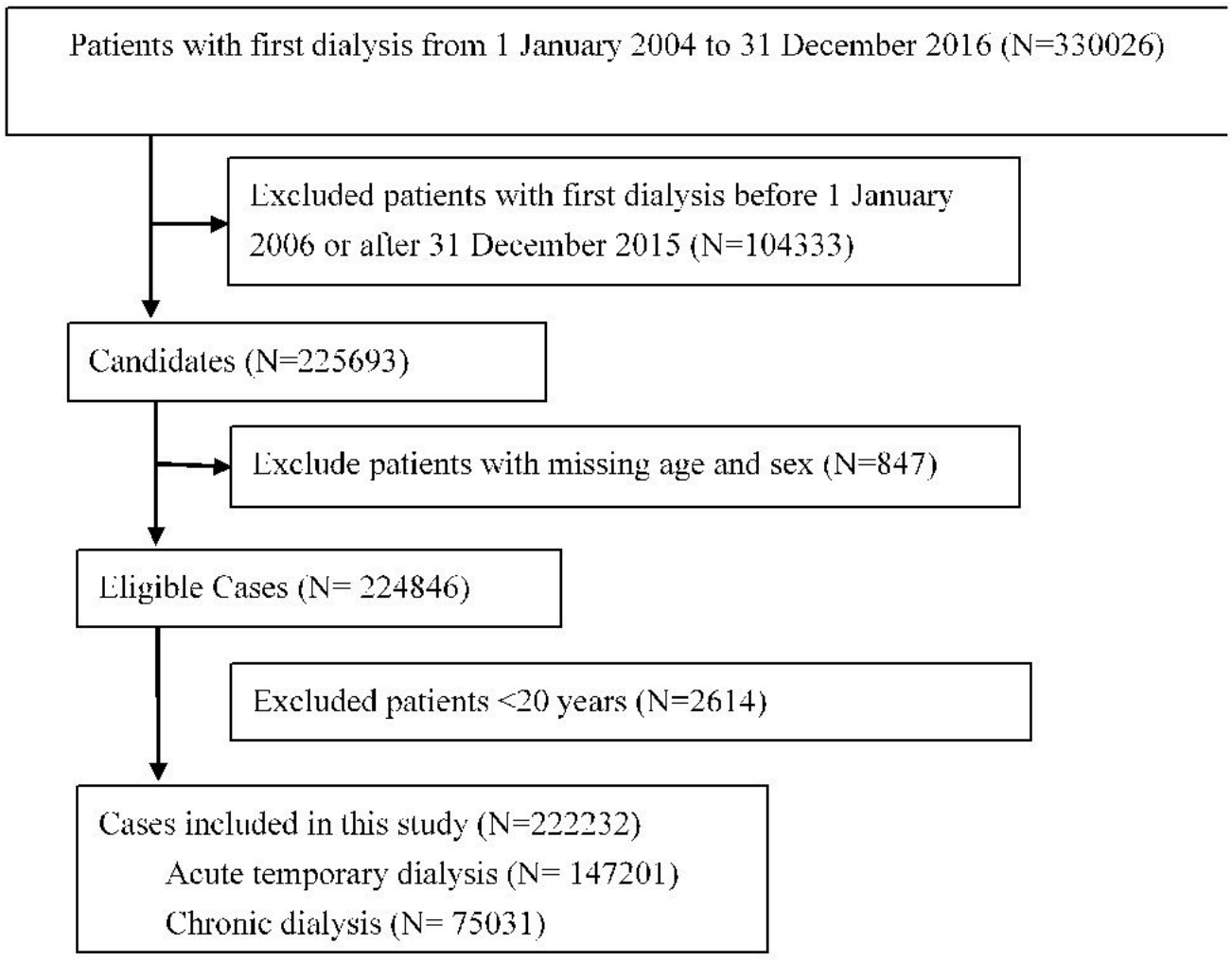

Figure 1

Flowchart demonstrates the selection criteria and process of eligible dialysis patients with sepsis.

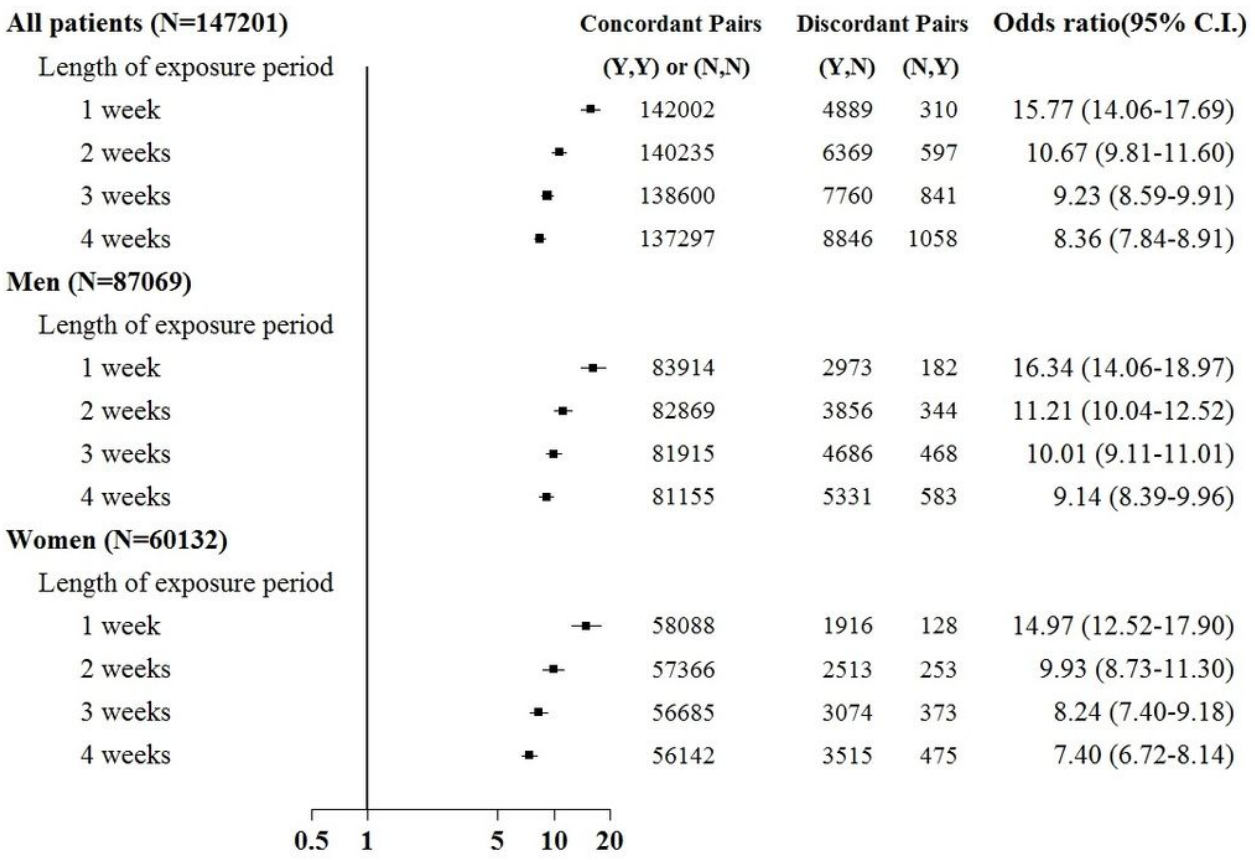

Figure 2

Odds ratios of acute-temporary dialysis after sepsis when control was selected from six months before first dialysis.

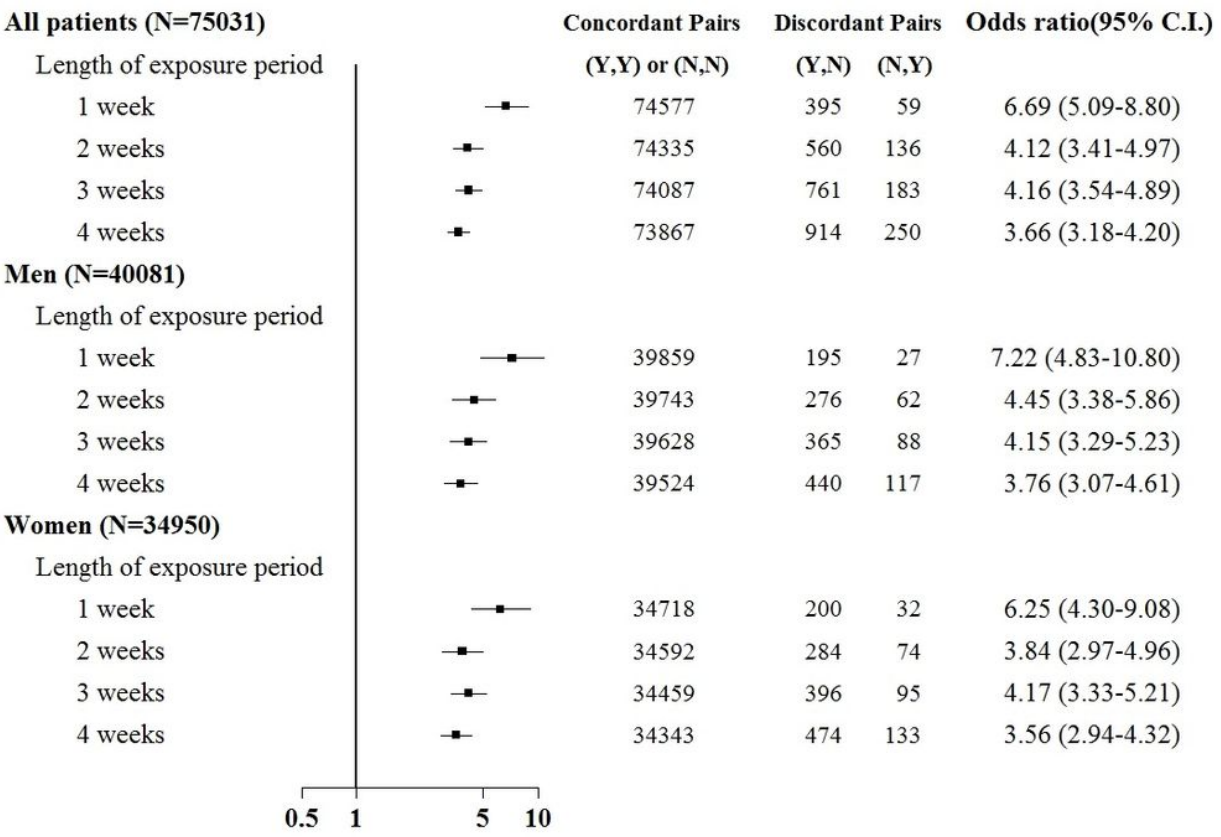

Figure 3

Odds ratios of chronic dialysis after sepsis when control was selected from six months before first dialysis.

Supplementary Files

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