Infective Endocarditis and Its Short and Long-Term Prognosis in Hemodialysis Patients: A Systematic Review and Meta-analysis

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Abstract: There are some conclusive evidences on infective endocarditis and its poor prognosis in the background of end-stage renal disease in patients undergoing chronic hemodialysis; however the findings on the risk of infective endocarditis and its long-term prognosis are very diverse, requiring a systematic approach to achieve a global statistic. Our study tried to systematically assess the risk profile as well as short- and long-term prognosis of infective endocarditis among hemodialysis patients. To select our pointed studies, a deeply searching was planned among major articles databases including MEDLINE, Web of Science, SCOPUS, Google Scholar, and Cochrane Central Register of Controlled Trials considering the study keywords. Two high-qualified investigators independently assessed the collected papers. The risk of bias for the studies was also assessed according to the Cochrane's guideline and using the QUADAS-2 tool. In final, 18 articles were eligible for the final analysis. The overall prevalence of infective endocarditis among patients under chronic hemodialysis was estimated to be 2.9% (95% confidence interval [CI]: 2.7%-3.1%). Our assessment revealed an overall in-hospital death rate of 29.5% (95% CI: 26.7%-46.6%) and long-term death rate of 45.6% (95% CI: 41.9%-49.3%) in hemodialysis patients suffering infective endocarditis. Poor

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prognosis with high early and long-term death rates due to infective endocarditis has expected in the background of chronic hemodialysis emphasizing the necessity for its early management by identifying patients which prone to disease along with continuous cardiac monitoring. (Curr Probl Cardiol 2021;46:100680.)

Introduction

The trend of the overall incidence of the end-stage renal disease (ESRD) requiring hemodialysis is increasing rapidly.[1] According to the reports released from the developed countries, the incidence of ESRD has been recently raised at a rate of up to 8% each annually.[2] Not only ESRD can worsen the patient's hemodynamic status and lead to high morbidity and even mortality, but also sometimes predisposes patients to a variety of infectious and inflammatory disorders such as infective endocarditis.[3,4] The first evidences of infective endocarditis due to chronic and persistent hemodialysis have been described in 1966 and after that, several cases of this event were published in the form of case reports and case series.[4–7] In other words, the occurrence rates of infective endocarditis and its related death rate have been reported to be considerable higher in hemodialysis patients than in general population.[8] In a study on French patients, the overall incidence of infective endocarditis among hemodialysis patients was found to be about 2.0 per 1000 patients which have been 50 times higher than in general population.[9] Similar rates have been also released by the United States healthcare systems with an incidence of 18 times of the general population.[10] Accordingly, the increased likelihood of infective endocarditis among chronic hemodialysis patients is absolutely predictable and therefore in the first step, in order to identify the various aspects of this problem, it is very important to evaluate the risk factors and also to evaluate the prognosis of patients, especially in the long time. Regarding the predisposing factors, first, it has been demonstrated high susceptibility of hemodialysis patients to degenerative heart valve disease which in turn is a major risk factor for endocarditis.[11] Also, frequently using intravascular access through vascular graft or catheters provides a source for the transmission of infectious strains to vital organs such as the heart. Moreover, patients with bacteremia are also inherently prone to bacterial infections and also impairment of immune system leading infective endocarditis.[12] As another important point, those ESRD patients undergoing hemodialysis

face frequently with a poor prognosis and high death rate in spite of improvement in therapeutic protocols.[13]

Despite conclusive evidence of ESRD, patients' high susceptibility to infective endocarditis as well as disease-related poor prognosis, the evidences on the risk of disease and its long-term prognosis are very diverse, and therefore, a systematic approach is needed to achieve a global statistic. The present study aimed to systematically assess the risk profile as well as long-term prognosis of infective endocarditis among hemodialysis patients.

Materials and Methods

The Eligibility of Studies

For performing the present systematic review and meta-analysis, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was considered step by step and the study design was initially registered at the PROSPERO database. As the eligibility criteria, all case series, cross-sectional, prospective, or retrospective cohort studies with the aim of assessing the occurrence of infective endocarditis in the background of hemodialysis were considered for initial assessment. In this regard, case reports, reviews, or published letters were not included into the study. The primary endpoint was to identify the main determinants of infective endocarditis in patients undergoing hemodialysis and the second endpoint was to assess the prognosis and outcome of such event.

Data Sources and Search Strategies

For finding our considered studies, a deeply searching was scheduled among major articles databases including MEDLINE, Web of Science, SCOPUS, Google Scholar, and Cochrane Central Register of Controlled Trials considering the study keywords including "infective endocarditis," "hemodialysis," "end-stage renal disease," "outcome," and "risk factor." The search strategy was conducted by an experienced researcher with at least a 10-year experience in library. All English papers with full text availability or the abstracts containing required data and variables were included in study assessment. In the case of missing data, the authors contacted to the corresponding authors of the manuscripts for obtaining additional information and in cases with needed data, the manuscript was excluded from our analysis. Two high-qualified investigators

independently assess the collected papers with the aim of identifying eligible articles. The presence of any disagreement led to assess the papers' eligibility by the third investigator. Or each finally included paper, the following information were extracted: the name of author, the year of publication, inclusion and exclusion criteria, the number of patients and their demographics, any therapeutic intervention, follow-up time, the type of bacterial strains leading endocarditis, duration of dialysis, as well as prognosis-related endpoints. Loss of follow-up and missing data was collected for quality assessment.

Quality Assessment

The quality of studies was assessed independently by the 2 researchers with consideration of the following criteria: allocation concealment, blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias). The risk of bias for the studies was also assessed according to the Cochrane's guideline and by the QUADAS-2 tool and was finally categorized as high risk of bias, low risk of bias, and unclear risk of bias.

Statistical Analysis

Categorical variables were presented as frequency and proportions and quantitative variables as mean ± SD or median. The overall prevalence of infective endocarditis and its related outcome indices was described as the pooled prevalence with 95% confidence interval (95% CI). Risk estimate was also presented by risk ratios with 95% CI, calculated by using the fixed effect modeling or random effect modeling (when the heterogeneity of the studies was calculated to be significant). The heterogeneity among the studies was assessed by using the I^2 statistic that a P-value of less than 0.10 of the Cochran Q-test suggests that the heterogeneity is beyond random error or chance. Statistical analyses were performed using Comprehensive Meta-Analysis Software Version 3.1.

Results

Study Selection and Characteristics of Included Studies

The flow diagram of the study selection is presented in Figure 1. Initially, 54 articles were collected by database searching and other sources. After removing 2 articles due to evidences of duplication, 52 records

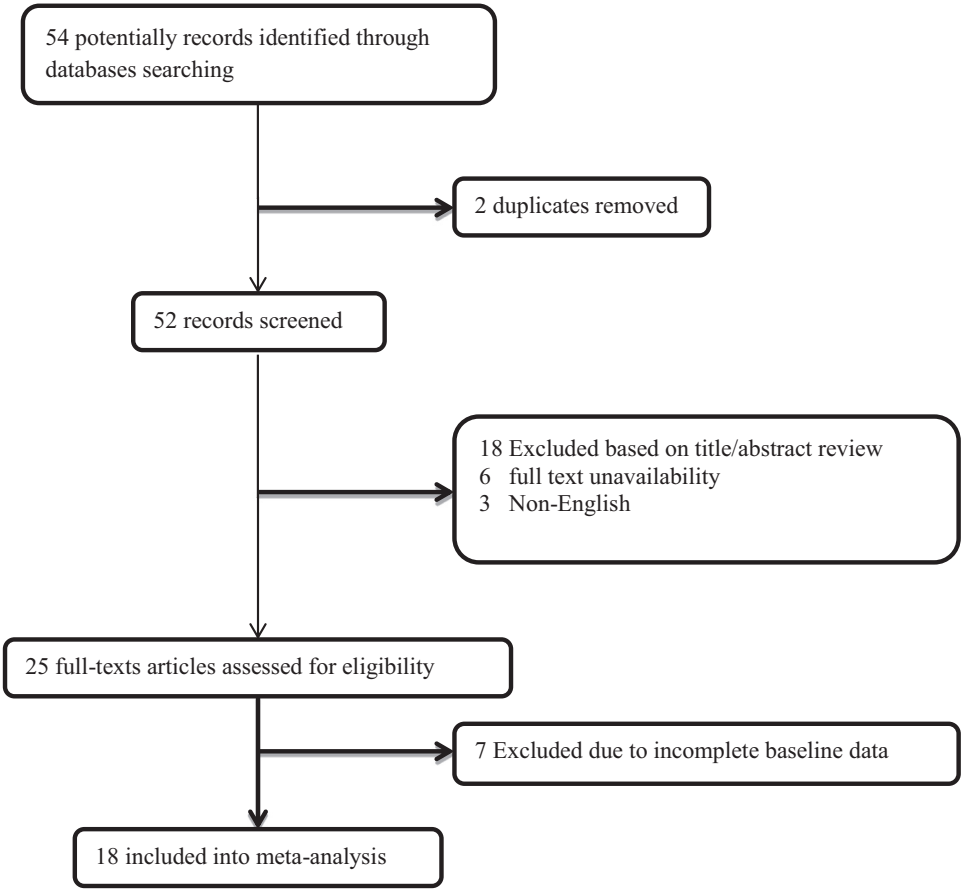

FIG 1. The flowchart of screening the eligible studies.

were primarily under-screened. Based on the titles and abstracts, 27 records were excluded and the remaining 25 citations were assessed for further eligibility. Of those, 7 were also excluded due to incompleteness of the data and contents. In final, 18 articles were eligible for the final analysis.[14−31]

Methodological Quality of the Included Studies

The studies included were assessed qualitatively by the QUADAS-2 tool. According to our risk of bias assessment, all 18 studies yielded good quality and none of the citation was determined to have high risk of bias and therefore the pooled results should be persuasive (Fig 2).

Overall Prevalence of Infective Endocarditis Among Hemodialysis Patients

Of 18 studies finally evaluated, the endpoint of assessing the prevalence of infective endocarditis among hemodialysis patients was considered in only 6 studies[16-26,29,30] (Table 1). According to our meta-analysis, the overall prevalence of infective endocarditis among patients under chronic hemodialysis was estimated to be 2.9% (95% CI: 2.7%-3.1%). The heterogeneity across the studies was insignificant with I^2 value of 17.935 (P= 0.424) (Fig 3).

Early and Late Outcome of Infective Endocarditis Among Hemodialysis Patients

The details of 18 studies included in our systematic review and meta-analysis are summarized in Table 2. In total, 45,799 patients who suffered from infective endocarditis in the background of hemodialysis were included. Overall average age of participants was 56.82 ± 6.77 years (ranged 40.6-66.0 years) and the mean duration of dialysis widely ranged from 24 to 72 months with the mean age of 42.48 ± 14.24 months. Of 18 studies, 7 focused on in-hospital outcome of infective endocarditis. Overall assessment of early outcome of infective endocarditis in hemodialysis patients led to find an overall in-hospital death rate of 29.5% (95% CI: 26.7-46.6%) (Fig 4A). Cochran's Q test showed a significant statistical heterogeneity across the studies for assessing early outcome (I^2 = 93.035, $P < 0.001$) perhaps because of the notable difference weights calculated for the studies due to difference in study sample sizes. Within an overall follow-up time ranged 3-60 months, total death rate was found to be

	Patient selection	Index test	Outcomes measuring	Flow and timing
McCarthy, 2000	+	?	?	+
Fernández-Cean, 2002	?	+	+	+
Maraj, 2002	?	?	+	+
Doulton, 2003	+	+	+	+
Spies, 2004	?	+	+	+
Nori, 2006	+	+	+	?
Kamalakannan, 2007	?	?	?	+
Rekik, 2009	?	?	+	+
Tao, 2010	+	+	+	+
Montasser, 2011	?	?	+	+
Jones, 2013	+	?	?	+
Bentata, 2016	+	+	+	+
Ludvigsen, 2016	+	+	?	+
Durante-Mangoni, 2016	+	+	+	+
Vasudev, 2016	?	+	+	+
Chaudry, 2017	+	+	+	+
Ramos-Martínez, 2017	+	+	+	+
Bhatia, 2017	+	+	+	+

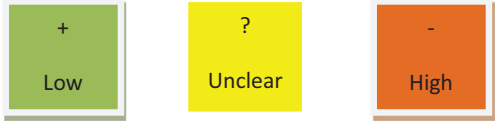

FIG 2. The Assessment of the risk of bias.

45.6% (95% CI: 41.9-49.3%) (Fig 4B), however with a significant heterogeneity between the studies ($I^2 = 89.255$, $P < 0.001$) probably due to wide range of follow-up time as well as different underlying risk profiles prone the patients to poor prognosis. The evaluation of causing agents responsible for endocarditis, staphylococci followed by enterococci strains were prominent. With respect to the main determinants of poor prognosis in patients suffering infective endocarditis, advanced age,

TABLE 1. The prevalence of infective endocarditis in hemodialysis patients

Author, year	No. dialysis patients	No. IE patients	Prevalence rate
Maraj, 2002[16]	2239	31	1.4%
Jones, 2013[24]	1500	42	2.8%
Bentata, 2016[25]	187	11	5.9%
Ludvigsen, 2016[26]	9392	150	1.6%
Chaudry, 2017[29]	7233	241	3.3%
Ramos, 2017[30]	2488	126	5.0%

IE, Infectious endocarditis.

history of diabetes mellitus, severe anemia and hypoalbuminemia, leukocytosis, heart failure, uncontrolled sepsis, valvular abnormalities especially mitral or aortic valves, septic emboli, cerebrovascular events, or infection due to methicillin-resistant bacterial strains could predict long-term poor prognosis (Table 3).

Discussion

The likelihood of infective endocarditis following chronic hemodialysis is dramatically higher than that in general population. The overall incidence of infective endocarditis in the background of hemodialysis ranges between 1.7 and 2.0 cases per thousand patients that seems to be more than 50 times than in people without renal failure.[32,33] Thus, chronic hemodialysis is identified as a major risk profile for infective endocarditis. According to our analysis, we face with high prevalence rate of infective endocarditis following hemodialysis so that about 2.7%-3.1% of hemodialysis group suffer from endocarditis. Although the obtained rate for this event seems to be low, but because of it, related serious morbidity and mortality, this prevalence is also very significant and requires proper management. Aiming to achieve such management, we assessed systematically the adverse outcome of infective endocarditis, its main pathological strains as well as the underlying predisposing factors relating poor prognosis. In the first step, we could show high rates of both early and late mortality rates among patients suffering infective endocarditis due to hemodialysis. In this regard, in-hospital and long-term death rates was estimated to be 29.5% and 45.6%, respectively. In other words, about one-third of patients die within hospitalization and totally half of patients have short-term survival. In other words, the occurrence of infective endocarditis in patients suffering end-stage renal disease requiring chronic and persistent hemodialysis is a catastrophic and deadly event

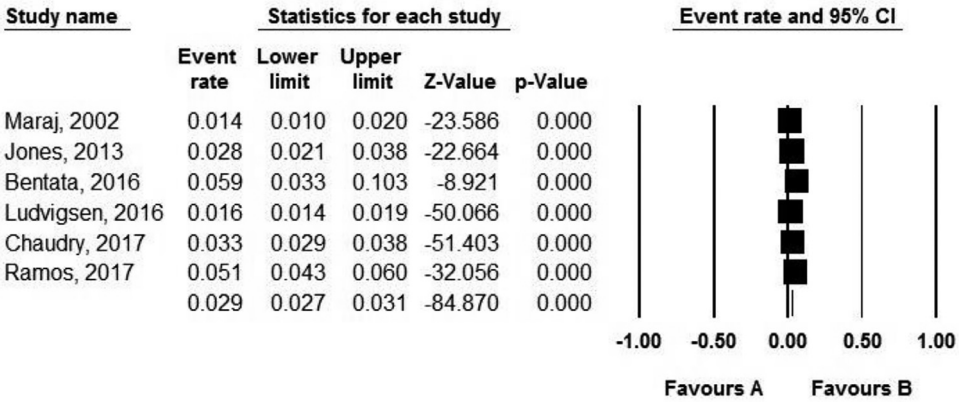

FIG 3. The prevalence of infective endocarditis in hemodialysis patients.

TABLE 2. The details of 18 studies included in systematic review and meta-analysis

Author, year	No. IE patients	Male/Female	Mean age (year)	Diabetes	Mean duration of dialysis (month)	Follow-up time (month)
McCarthy, 2000[14]	20	16/4	63.0	7	24	12
Fernández-Cean, 2002[15]	21	4/17	65.0	2	56	In-hospital
Maraj, 2002[16]	32	—	—	—	37	12
Doulton, 2003[17]	30	18/12	54.1	8	46.3	3
Spies, 2004[18]	40	35/5	59.4	20	39	In-hospital
Nori, 2006[19]	54	29/25	60.0	23	72	3-60
Kamalakannan, 2007[20]	69	31/38	58.0	26	37	In-hospital
Rekik, 2009[21]	16	10	52.5	1	27.3	In-hospital
Tao, 2010[22]	6	4/2	52.3	—	—	3
Montasser, 2011[23]	5	2/4	48.0	—	35.3	10
Jones, 2013[24]	42	20/22	55.2	—	57.4	3
Bentata, 2016[25]	11	8/3	40.6	3	36	21
Ludvigsen, 2016[26]	150	—	—	—	—	3
Durante-Mangoni, 2016[27]	42	—	—	18	—	In-hospital
Vasudev, 2016[28]	52	24/28	55.9	24	—	In-hospital
Chaudry, 2017[29]	267	163/104	63.0	102	—	12
Ramos-Martínez, 2017[30]	126	79/47	66.0	56	—	12
Bhatia, 2017[31]	44816	23877/20939	59.3	9677	—	In-hospital

IE, Infectious endocarditis.

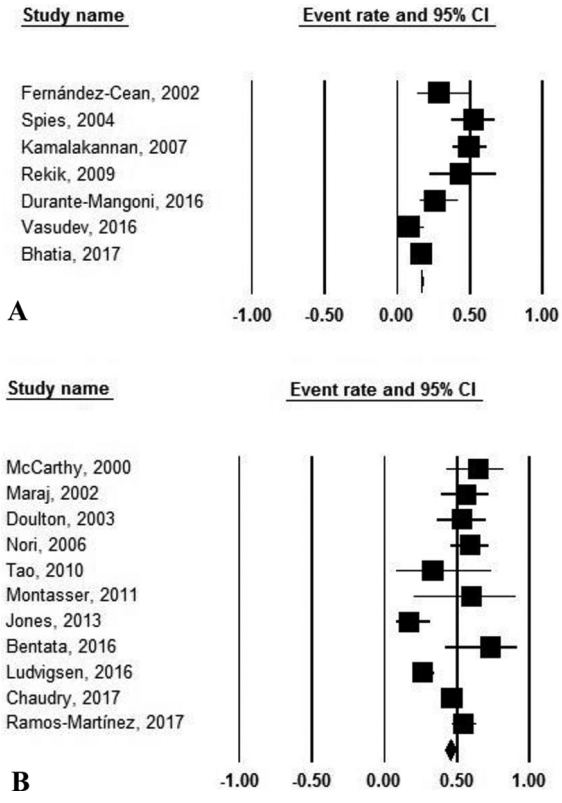

FIG 4. In-hospital (A) and late (B) death rate following infective endocarditis in the background of hemodialysis.

that should be managed with the onset of the first hemodialysis sessions and with the identification of endocarditis-prone factors as well as related bacterial strains related to disease. Thus, managing controllable predisposing factors along with prescribing suitable antibiotics can lead to preventing bacteremia and thus effectively increase the patients' survival. Unfortunately, early episode of bacteremia during hemodialysis is very common[34] and its main reason is to use frequent intravascular access through arteriovenous fistula, vascular graft, or indwelling vascular catheter. In this regard, as shown in our review, staphylococci strains have a central role in dialysis-related bacteremia that can also lead to occurrence of endocarditis. According to some reports, about half of the hemodialysis patients are the nasal carriers of *Staphylococcus aureus* that may be the source of blood stream infection and even sepsis, as a main risk factor for endocarditis.[35-37]

TABLE 3. Early and late outcome of infective endocarditis in the background of hemodialysis

Author, year	No. IE patients	Early death	Follow-up death	Risk factors	Prominent causing agent
McCarthy, 2000[14]	20	6	13	Right-sided IE, vegetation size greater than 2.0, diagnosis of diabetes mellitus, and initial leukocyte count greater than 12.5	*Staphylococcus aureus, Enterococcus, viridans streptococcus*
Fernández-Cean, 2002[15]	21	6	—	Heart failure, uncontrolled sepsis	*Staphylococcus aureus Staphylococcus epidermidis*
Maraj, 2002[16]	32	—	18	Low hemoglobin, elevated leukocyte count, hypoalbuminemia, severe aortic and mitral regurgitation, and annular calcification in mitral valve	*Staphylococcus aureus*
Doulton, 2003[17]	30	16	18	—	*Staphylococcus aureus*
Spies, 2004[18]	40	21	—	fever on admission, fewer negative blood cultures, and bivalvular infective endocarditis	*Staphylococcus aureus*
Nori, 2006[19]	54	19	32	Mitral valve involvement, septic embolism	*Staphylococcus aureus Enterococcus*
Kamalakannan, 2007[20]	69	34	—	valve surgery	*Staphylococcus aureus*
Rekik, 2009[21]	16	7	0	Congestive heart failure, secondary septic localizations, arterial emboli, and cerebral hemorrhage	Methicillin-resistant Staphylococcus aureus
Tao, 2010[22]	6	—	2	—	*Staphylococcus aureus*
Montasser, 2011[23]	5	—	3	Valvular perforations, congestive heart failure	*Staphylococcus aureus, Enterococcus fecalis*

(*continued on next page*)

TABLE 3. (*continued*)

Author, year	No. IE patients	Early death	Follow-up death	Risk factors	Prominent causing agent
Jones, 2013[24]	42	6	7	Age >60 years, septic emboli, and methicillin-resistant S. aureus	*Staphylococcus aureus*
Bentata, 2016[25]	11	—	8	Severe TI, Cardiomyopathy	*Staphylococcus aureus*
Ludvigsen, 2016[26]	150	—	40	—	Coagulase-negative staphylococci
Durante-Mangoni, 2016[27]	42	11	—	—	*Staphylococcus aureus*
Vasudev, 2016[28]	52	4	—	Acute heart failure, heart block	*Staphylococcus aureus, enterococci*
Chaudry, 2017[29]	267	53	124	Aortic valve disease and previous infective endocarditis	*Staphylococcus aureus*, coagulase-negative staphylococci, enterococci
Ramos-Martínez, 2017[30]	126	52	69	Age >70 years, heart failure, central nervous system vascular events, septic shock	*Staphylococcus aureus*, coagulase-negative staphylococci
Bhatia, 2017[31]	44816	7495	—	—	*Staphylococcus aureus*

IE, Infectious endocarditis.

As well shown in our assessment, poor prognosis is expectable in patients suffering infective endocarditis following chronic hemodialysis. In this context, the closest hemodynamic monitoring, repeated echocardiography, early diagnosis of any cerebral, cardiac, and vascular signs, early removing any probable bacterial source such as infectious catheters, compensating anemia and hypoproteinemia especially in older ages is necessary and can be benefitial to minimize early and long-term death.

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