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Original Research

Predictors of 30-day re-admissions in patients with infective endocarditis: a national population based cohort study

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Infective endocarditis (IE) is a life threatening disease requiring lengthy hospitalizations, complex multidisciplinary management and high health care costs. In this study, we analyzed the National Readmissions' Database (NRD) to identify infective endocarditis cases and the causative organisms, clinical determinants, length of stay, in-hospital mortality, and 30-day hospital readmission rates. The study cohort was derived from Healthcare Cost and Utilization Project's National Readmission Database between 2010-15. We queried the National Readmissions' Database using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic code for infective endocarditis (421.0) and identified a total of 187,438 index admissions. SAS 9.4 (SAS Institute Inc., Cary, NC) was utilized for statistical analyses. A total of 187,438 patients with a primary diagnosis of IE were identified over 6 years (2010-2015). Twenty-four percent (44,151 patients) were readmitted within 30 days. Most common etiologies for readmission included sepsis (14%), acute heart failure (8%), acute kidney injury (6%), intracardiac device infection (5.6%) and recurrence of IE (2.7%). Predictors of increased readmissions included female sex, staphylococcus aureus infection, diabetes, chronic lung disease, chronic liver disease, acute kidney injury, acute heart failure and anemia. In-hospital mortality for the readmission of IE was 13%, and average length of stay during the re-admission was 12 days. IE is associated with high rates of index admission mortality and for 30-day readmissions of which are associated with a substantial risk of death.

Keywords

Infective endocarditis; re-admissions; mortality; heart failure

1. Introduction

Infective endocarditis (IE) is a potentially lethal disease, frequently causing morbidity and mortality. IE usually requires lengthy hospitalizations and is associated with high health care costs. Despite aggressive care, the 1-year mortality after IE approaches 30% (Baddour et al., 2015). Currently, there are no large population-based studies that summarize the causative agent, length of stay, etiologies and comorbidities predicting re-admission in patients with IE. To address this knowledge gap, we analyzed the National Readmissions' Database (NRD) to identify these datapoints after an index hospitalization for IE.

2. Methods

The study cohort was derived from Healthcare Cost and Utilization Project's NRD of 2010-15, sponsored by the Agency for Healthcare Research and Quality. The NRD is one of the largest publicly available all-payer inpatient care databases in the United States. The NRD represents 49.3% of total United States hospitalizations. The details regarding the NRD and data extraction methodology are available online (Arora et al., 2017; Chen et al., 2013; Healthcare Cost and Utilization Project, 2014). Patients were tracked during same year using variable "NRD visit link," and the time between 2 admissions was calculated by subtracting variable "NRD Days to Event".

We queried the NRD using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic code for infective endocarditis (421.0). The patients of

Table 1. Multivariate predictors of 30-day re-admission after the index admission for infective endocarditis.

Variable	Odds Ratio	95% Confidence Interval	*P*-value
Age	0.998	0.996-0.999	< 0.001
Female	1.061	1.024-1.099	0.001
Type of infection			
Staphylococcus aureus	1.063	1.021-1.107	0.003
Streptococcal endocarditis	0.994	0.952-1.038	0.79
Gram negative endocarditis	1.1	1.023-1.183	0.01
Comorbidities			
Obesity	1.003	0.951-1.058	0.909
Hypertension	1.018	0.979-1.060	0.366
Diabetes	1.119	1.076-1.163	< 0.001
Chronic lung disease	1.16	1.112-1.210	< 0.001
Chronic Liver disease	1.163	1.096-1.234	< 0.001
Renal Failure	1.317	1.265- 1.372	< 0.001
Anemia	1.099	1.061-1.139	< 0.001
Rheumatological disorder	1.098	1.007-1.197	0.034
Heart failure	1.172	1.123-1.225	< 0.001
Private including HMO	0.865	0.825	< 0.001
Self-pay/no charge/other	0.787	0.736	< 0.001
Disposition to Facility/others	1.099	1.06	< 0.001
Length of stay	1	0.999	0.568

age < 18 years and those missing data for age, gender, or mortality were excluded. The index admissions in the month of December were also excluded as they lacked 30-day follow-up data. We identified a total of 187,438 index admissions. Patients who were readmitted to the hospital within 30 days within the same calendar year (n = 44,151) and were subject to further analysis for predictors of re-admissions.

The primary outcome of our study was 30-day readmission rates after an index hospitalization for IE. Secondary outcomes included trends, etiologies and predictors of re-admission with IE. Causes of re-admission were identified by using the primary diagnosis ICD-9 codes filed during re-admission. NRD variables were used to identify patients' demographic characteristics including age and gender, hospital characteristics such as bed size and teaching hospital status, and other patient-specific characteristics including median household income, category for patient's zip code, primary payer, admission type, admission day, and discharge disposition (Healthcare Cost and Utilization Project, 2014). Using variables provided in NRD which uses ICD-9-CM diagnoses, comorbidities such as obesity, hypertension, heart failure, chronic obstructive pulmonary disease, peripheral arterial disease, diabetes mellitus, anemia, neurological disease or paralysis, hematological or oncological malignancy and acute kidney injury were identified (Healthcare Cost and Utilization Project, 2017). Severity of co-morbid conditions was defined using Deyo modification of Charlson co-morbidity index, which contains co-morbid conditions with differential weights. The score ranges from 0 to 33, with greater scores corresponding to greater burden of co-morbid diseases (Deyo et al., 1992).

SAS 9.4 (SAS Institute Inc., Cary, NC) was utilized for statistical analyses. Chi-square test was used to test for differences between categorical variables. Student t-test was used to test for differences between continuous variables. A hierarchical 2-level logistic regression model with hospital ID as random effect was used to evaluate secondary outcomes. For the 30-day multivariate readmission model, we included hospital level characteristics such as hospital teaching status and bed size, patient's demographics such as age and gender, co-morbid conditions such as obesity, hypertension, heart failure, chronic obstructive pulmonary disease, peripheral artery disease, diabetes mellitus, anemia and acute kidney injury, as well as patient level characteristics such as primary payer, median household income and disposition after hospital discharge. A P-value of less than 0.05 was considered significant in this study.

3. Results

We identified a total of 187,438 patients with primary diagnosis of IE over 6 years (2010-2015). Twenty-four percent (44,151 patients) were readmitted within 30 days. The average age of patients in this cohort was 60 years, and majority were males (60%). Over half of the re-admissions (51%) occurred within the first 11 days of discharge. Amongst the re-admitted patients, 86% had one re-admission, 13% had two re-admissions and 1.5% of patients had three re-admissions in 30 days after discharge.

Most common reasons for re-admission included sepsis (14%), acute heart failure (8%), acute kidney injury (6%), intra-cardiac device infection (5.6%) and recurrence of IE (2.7%) (Fig. 1). Neurological complications and mechanical valvular dysfunction accounted for 2.7% and 1.6% of total 30-day re-admissions. Most prevalent comorbidities included hypertension (56%), anemia (41%), chronic kidney disease (31%), diabetes (30%), valvular heart disease (22%), heart failure (21%) and intravenous drug abuse (15%). Staphylococcus aureus (27%), streptococcus viridians (22%), gram negative species (6%) and fungal species (0.24%)

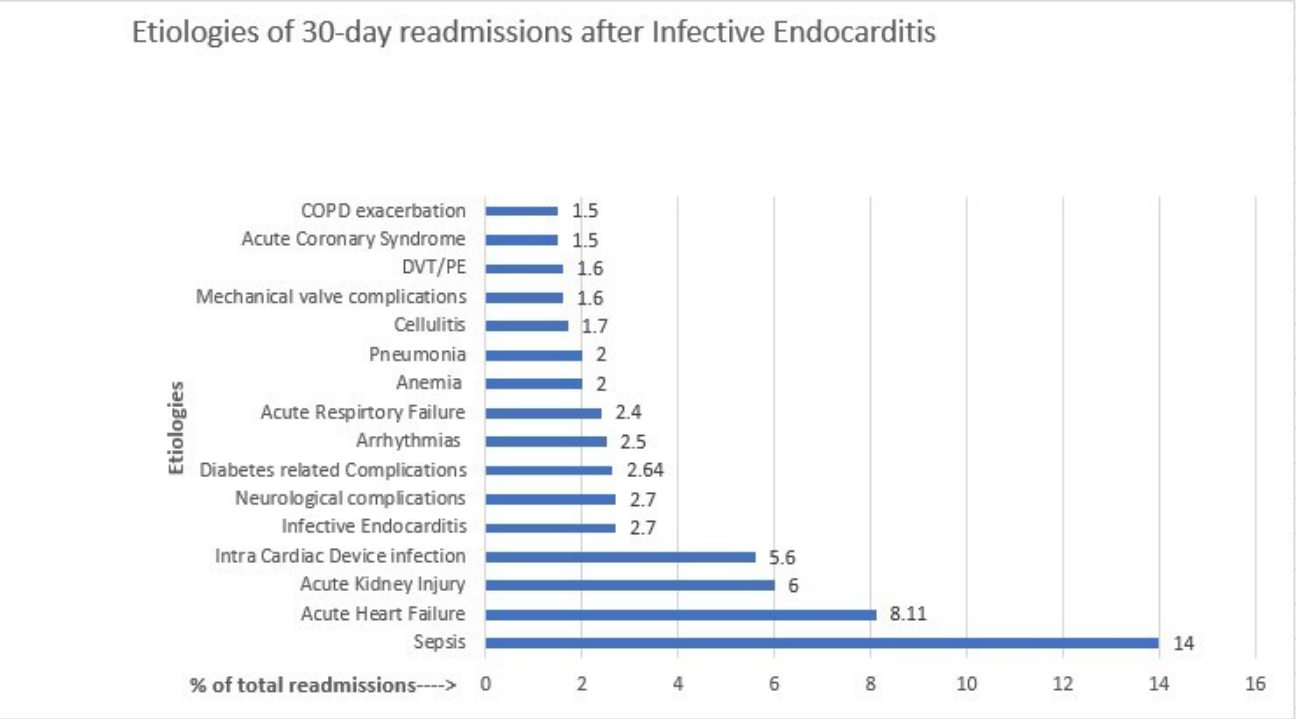

Figure 1. Figure depicting various etiologies for 30-day readmission after an index admission for infective endocarditis with their respective percentages. Sepsis was the most common cause of readmission with about 14% of total readmissions.

Table 2. Studies describing the readmission rate for patients with infective endocarditis.

Study	Year	Location	Number of patients with IE	Percentage of patients readmitted	Follow up duration for readmissions
Rasmussen et al. (2017)	2017	Denmark	347	65%	1 year
Morita et al. (2019)	2019	USA	45214	24.80%	30-days
Kashef et al. (2017)	2018	USA	145	51%	6-month
Amodeo et al. (2009)*	2009	New Zealand	94	10.60%	1 year

* Readmission data only on a subset of cohort receiving outpatient antibiotic therapy.

were identified as causative organisms of IE in this analysis. Within the first 30 days of re-admission after the index admission for IE, 9% of subjects required mitral valve surgery and 5% subjects required aortic valve surgery.

Predictors of higher re-admissions included female sex (odds ratio [OR] 1.06, 95% confidence interval [CI] 1.02-1.1, $P < 0.001$), staphylococcus aureus infection (OR 1.06, 95% CI 1.02-1.1, $P < 0.001$), diabetes (OR 1.11, 95%CI 1.07-1.63, $P < 0.001$), chronic lung disease (OR 1.16, 95%CI 1.11-1.2, $P < 0.001$), chronic liver disease (or 1.06, 95%CI 1.1-1.23, $P < 0.001$), acute kidney injury (OR 1.32, 95%CI 1.26-1.37, $P < 0.001$), acute heart failure (OR 1.17, 95%CI 1.12-1.22, $P < 0.001$) and anemia (OR 1.09, 95% CI 1.06-1.13, $P < 0.01$) (Table 2). In-hospital mortality for re-admission for IE was 13%, and average length of stay during the re-admission was 12 days. Thirty-six percent of patients were ultimately discharged to a facility.

4. Discussion

Infective Endocarditis affects approximately 12.7 cases per 100,000 person -years in the United States (Bor et al., 2013). Despite the improvements in medical and surgical therapies for IE, the incidence of IE has not decreased over the past decades (Moreillon and Que, 2004). The natural history of IE depends on the causative organism, native vs prosthetic valve involvement and right vs left sided endocarditis. Prosthetic endocarditis has been reported to have worse prognosis than native valve endocarditis. About 50% of patients of IE end up needing surgical intervention (Lalani et al., 2010). While there are observational data on prognostic markers and predictors of mortality with IE, the temporal trends in outcomes and predictors of re-admission in patients with IE has been studied only in one population database so far. In this study, we highlight the comorbidities, length of stay, in-hospital mortality, trends and predictors of 30-day hospital readmission after an index admission diagnosis of IE.

In our analysis, we found that 24% of patients (N = 44,151) with IE were re-admitted within 30 days of discharge, and on readmission the in-hospital mortality was 13%. A prior single center experience by Rasmussen et al. (2017) reported mortality and re-admission data on 209 patients in Denmark 12 months post discharge. They found an 18% mortality rate (95% confidence interval (CI): 14%-23%) one-year post-discharge and 65% (95% CI: 59%-71%) re-admission rate within the first year. Table 2 lists all

the studies found in English literature describing the readmission rates for IE (Amodeo et al., 2009; Kashef et al., 2017; Morita et al., 2019; Rasmussen et al., 2017). The study by Morita et al, also a population based study reported a readmission rate of 24.8% in 2010-2014 NRD database (Morita et al., 2019). The most common causes for readmission included infective endocarditis, other infectious causes, and cardiac causes. Our study includes patients from 2010-2015, adding data from additional year to the study by Morita et al. The ICD codes included by Morita et al were 4210, 4211, and 4219, in comparison to all 421 codes in our study. Our data confirms the high re-admission burden and in- hospital mortality rate associated with IE in a large national database, thus highlighting the need for early identification and treatment.

The most common indications for re-admission found in our study included sepsis (14%), acute heart failure (8%), acute kidney injury (6%), intra-cardiac device infection (5.6%) and recurrence of IE (2.7%). Major known complications of IE include heart failure, peri-annular extension of infection, splenic abscess formation, and mycotic aneurysm (Rasmussen et al., 2017). In native valve endocarditis, acute heart failure has been shown to occur more frequently with aortic-valve infections (29%) than mitral (20%) or tricuspid disease (8%) (Bayer et al., 1998). Mills et al showed that patients with normal ventricular function or mild heart failure at the time of the index admission may advance to severe heart failure during the course of treatment. And about two thirds of these patients will progress to severe heart failure during the first month of therapy (Mills and Utley, 1974). Heart failure in IE not only has a grave prognosis with medical therapy, but it is also the strongest predictor of poor outcome with surgical therapy (Stinson, 1979). Recurrent endocarditis has been reported to be as low as 1.12% (N = 212) (Netzer et al., 2002) to as high as 22.5 % (N = 271) (Renzulli et al., 2001). The rates of recurrence of IE were low in our analysis (2.7%).

The most prevalent comorbidities amongst patients readmitted for IE in this study included hypertension (56%), anemia (41%), chronic kidney disease (31%), diabetes mellitus (30%), valvular heart disease (22%), heart failure (21%) and intravenous drug abuse (15%). Predictors of increased risk for re-admission included female sex, staphylococcus aureus infection, diabetes mellitus, chronic obstructive pulmonary disease, chronic liver disease, acute kidney injury, acute heart failure and anemia. In addition to above, the duration of admission was also a risk factor for readmission in the study by Morita et al. (2019). The incidence of *Staphylococcus aureus* IE been steadily rising, and currently *Staphylococcus aureus* is the leading cause of acute IE (Tong et al., 2015). Our analysis confirms the increased disease burden with *Staphylococcus aureus* IE, which was an independent predictor of readmissions after hospitalization for IE. *Staphylococcus aureus* IE has been associated with higher rates of embolic phenomena and mortality as compared to other organisms (Miro et al., 2005). Mortality in IE has been reported to be less than 10% in streptococcal infections, about 25% in non-HACEK gram negative bacilli, 25-40% in staphylococcal infections and unacceptably high for fungal IE (survival rate <20%) (Baddour et al., 2015; Tornos et al., 1998).

In the national population-based Copen Heart IE survey, adults treated for IE experienced lower self- reported health scores as compared to the general population (Rasmussen et al., 2017). In addition, a large proportion of them had clinical signs and symptoms of anxiety and depression. Poor mental health can be one of the additional components predicting re-admission. Understanding all these predictors for readmission is crucial and calls for changes in the in-hospital and post-discharge management of patients with IE.

In a report of IE hospitalizations from 1998-2009 Nationwide Inpatient Sample, the mean length of stay was 15.3 days (Bor et al., 2013). In our study, the average length of stay during the readmission was 12 days. We noted that majority of the readmissions occurred within first 2 weeks post discharge, thereby emphasizing the need for early outpatient follow up for these patients. Since multiple specialties are usually involved in the care of these patients, they should be followed up by an interdisciplinary team of infectious disease specialists, cardiologists and primary care physicians. Identifying high risk patients during the index admission might help reduce the high re-admission rate and ensuring appropriate outpatient management with transdisciplinary efforts targeting modifiable risk factors for re-admission early after discharge.

Our study has all the limitations inherent to analyzing data from large observational databases. Given data was extracted and analyzed from the NRD, the reliability of diagnosis codes entered by different health providers and health systems may be variable across the country. For the same reason, differentiating a new infection from recurrence of same infection as a cause of sepsis is a challenge. We analyzed the 30-day readmissions and its predictors. However, a longer follow up for 6 months to 1 year might shed more light on the cumulative outcomes and cost utilization with IE. The peak of readmissions occurs after 30 days as per one of the studies, and looking at 30-day readmission might be missing on those cases (US National Library of Medicine, 2016). Additionally, we do not have information about the utilization of cardiac surgery or type and duration of antibiotics patients received. Future prospective studies with emphasis on long term outcomes and information on these missing variables might help to understand the morbidity and impact of IE in a more precise way.

5. Conclusions

IE is associated with high in-hospital mortality on the index and subsequent readmission. It is associated with high 30-day readmission rates. The most common reasons for re-admission included sepsis, acute heart failure, acute kidney injury and intracardiac device infection. Female sex, staphylococcus aureus infection, anemia, acute heart failure, chronic obstructive pulmonary disease, chronic liver disease, acute kidney injury and diabetes were independently associated with increased 30-day readmissions in IE patients.

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Conflicts of Interest

There are no conflicts of interest to declare for any of the authors.

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