Vaccines and Heart Failure: Analysis of Vaccine Adverse Events Reporting System between 1990-2021

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Abstract

Introduction: the role of vaccines in preventing diseases is well-established. However, the evolving techniques and types of vaccine necessitate the search for its safety more than ever. While cases of takotsubo cardiomyopathy and COVID-19 vaccine have been described, a comprehensive study to investigate the role of vaccination with cardiomyopathy and heart failure is lacking. The aim of this study is to investigate the link between the current vaccines and heart failure. Method: we utilized vaccine adverse event reporting system (VAERS) to search for cardiomyopathy, cardiac failure or ventricular dysfunction. Disproportionality signal analysis was conducted by measuring reporting odds ratio (ROR) with 95% confidence interval (CI). Results: VAERS reported over 1,300,000 adverse events between 1990-2021. Heart failure was reported over 2000 times in association with multiple vaccines. 56% of vaccine-related heart failure reported in males; 88% were serious; 19% mortality rate. The majority of reported heart failure was related to COVID-19 vaccines with ROR of 21.6 (CI: 18.3 to 25.4, P<0.0001). Smallpox was also significant with ROR 7.2 (CI 5.5-9.6, P<0.0001) On the other hand, heart failure was minimally described to be associated with other vaccines (influenza, zoster, tetanus, human papillomavirus (PPV)). Conclusions: Our study showed for the first time that vaccines maybe associated with heart failure. In particular, we show that covid-19 and smallpox vaccines are associated with increased risk of heart failure. Vaccines against Influenza, zoster, tetanus and (PPV) are associated with reduced heart failure. These data warrant longitudinal studies to delineate the association between heart failure and vaccines.

Introduction

Heart failure (HF) is a clinical syndrome caused by malfunction of the heart's ability to pump blood to the rest of the body due to impaired ventricular filling or ejection. Clinical manifestations encompass a large constellation of signs and symptoms of volume overload. HF affects over 6 million Americans(1) and costing the healthcare system up to 32 billion dollars annually(2). When unmanaged, it can be debilitating, rapidly progressive and ultimately fatal.

Throughout decades of research, the scientific community has identified various etiologies of HF that range from common conditions such as coronary artery disease and valvular diseases, to less common conditions such as infections(3, 4). Several studies have repeatedly shown that influenza infection represent a significant hazard for patients with heart failure. Sepsis was shown to increase hospitalization of heart failure and mortality. More recently amidst the COVID-19 pandemic, there have been reports of increased incidence of heart failure in patients with acute COVID-19 infection(5).

Based on the role of infections on heart failure, it was reasonable to hypothesize that vaccines may curb the deleterious effects of infections on heart failure. Indeed, several studies have demonstrated a cardioprotective of annual influenza vaccine(6, 7). Influenza vaccination reduced all-cause mortality in patients enrolled on PARADIGM-HF(8). Additionally, pneumococcal vaccination was associated with lower heart failure incidence and all-cause mortality(9). Based on these studies, the 2022 American College of Cardiology/American

Heart Association/ Heart Failure Society of America HF guidelines encouraged vaccination for heart failure patients(10).

Whereas the previous strongly showed a positive impact of vaccination on heart failure, a comprehensive evaluation of the role of vaccination in heart failure is lacking especially with the evolving techniques and types of vaccines, such as mRNA vaccines. For example, previous case reports described an association between Takotsubo (stress) cardiomyopathy and COVID-19 vaccine(11). Therefore, we decided to analyze VAERS database to provide the first comprehensive evaluation of the association between vaccines and cardiomyopathy/heart failure.

Methods

Vaccine Adverse Event Reporting System (VAERS) is a national warning system established in 1990 to detect the possible safety problems of the US- Licensed vaccines. It is co-managed by the CDC and FDA. VAERS is a passive reporting system where Healthcare professionals, Vaccine manufacturers, and vaccine receivers anonymously report the adverse events that come under their attention. It is a freely and easily accessible platform that collects data from all over the globe and is updated regularly. The primary objectives of VAERS are to detect new, unusual, and rare adverse events of newly licensed vaccines, administration errors, increased monitoring of the known adverse events. The data is limited to vaccine adverse event reports between 1990 to the most recent date for which the data is available. The current study is compendious and exclusive to assess the incidence of Heart failure associated with all the US-licensed vaccines (COVID, Zoster, Influenza, HPV, Tetanus, Meningococcal, Hepatitis-A, Hepatitis-B, MMR)

We obtained information using the standardized medical terms according to the Medical Dictionary of Health Terms like "Cardiac dysfunction, Cardiomyopathy, Ventricular dysfunction, Diastolic dysfunction, Heart failure, Congestive heart failure, Systolic dysfunction, Systolic heart failure, Diastolic heart failure."

The adverse events associated with the vaccines were assessed by disproportionality signal analysis was conducted by measuring Reporting Odds Ratio (ROR). ROR represents the odds of a certain event (Heart failure) occurring with the exposure to vaccine compared to the odds of the same event occurring with all other vaccines in the database. ROR was considered significant with the lower limit of the 95% Confidence Interval (CI) was >1.

Results

Table 1 shows the patient characteristics of reported heart failure cases with all vaccines. Overall, no significant sex differences existed with about 53.8% of cases reported in males compared to 44.4% in females. The age group of 65 years and above constituted about 49.6% of cases while 37.7% and 6.9% lied within the 18-64- and 0-17-years age groups, respectively. Serious adverse events were reported in 86.8% of cases compared to 13.2% of non-serious events.

As shown in Table 2, the highest incidence of reported adverse events was associated with the COVID-19 vaccine (93.9%) with a remarkable significance. A distant second was the incidence associated with the Influenza vaccine (6.9%). Other reported vaccines included in descending order: zoster (3.1%), pneumococcal (2.9%), hepatitis B (2.3%), and smallpox (2.1%) vaccines. Next, we analyzed different types of heart failure associated with vaccines. While 60% of the reported heart failure are poorly defined, left ventricular failure was the most common type (10%) followed by right ventricular failure (5.5%). Acute exacerbation of heart failure reported among 8%. Interestingly, diastolic heart failure was twice more frequently reported (3%) compared to systolic dysfunction (1.5%) as shown in Table 3.

The patient characteristics of COVID-19 associated reported heart failure cases are shown in Table 4. About 55.5% of cases were reported in males compared to 43.5% in females. As with other vaccines, most reported adverse events were serious in about 88.8% of cases compared to 11.5% of non-serious cases. The highest number of reported cases was associated with the use of the Pfizer/Biontech vaccine with 1212 cases (61.93%). The Moderna vaccine was associated with 910 cases (46.5%) while the Jensen vaccine was associated with 169 cases (8.64%). Other manufacturers accounted for 0.36% of cases (Table 5).

Finally, we analyzed the reported odds ratio (ROR) of the most common vaccines compared the entire database. Individuals who received the COVID-19 vaccine had a significantly higher risk of developing heart failure with a ROR (CI 95%) of 21.6 (18.3 to 25.4) with P<0.0001. The second highest incidence was reported in association with the smallpox vaccine (7.2, 5.5-9.6, P < 0.0001). Interestingly, the risk of heart failure was significantly decreased in those receiving the hepatitis B (0.73, 0.6-9.22, P=0.0242), Influenza (0.71,0.6-0.8, P < 0.0001), and Zoster (0.6, 0.5-0.77, P < 0.0001) vaccines denoting possible cardioprotective properties. PPV vaccine recipients had the least likelihood of developing heart failure with an ROR of 0.1 (0.08-0.13, P<0.0001). Notably, the results of the influenza vaccine conform with research studies showing decreased morbidity and mortality among heart failure patients receiving the annual flu vaccine (12, 13).

Discussion

The role of immune based process in heart failure development and progression has shown considerable attention lately. In this paper, we analyzed VAERS database to identify the role of vaccines in heart failure. Our results showed that COVID-19 vaccines were associated the most with heart failure (acute or chronic) with ROR of 21, followed by smallpox vaccine (ROR 7.2). Vaccines for Influenza, zoster, hepatitis, and PPV were associated with reduced incidence of heart failure.

The relationship between infection and heart failure is not very well characterized. While a direct cause of infection in heart failure pathogenesis is ill defined, infection is known to precipitates decompensation and mortality in heart failure patients(14). COVID-19 infection has been implicated in heart failure occurrence. For example, in Wahun, China, heart failure was among the most common outcomes after COVID-19 infection(15). Possible mechanisms have been postulated such as infiltration of inflammatory cells, release of cytokines and endothelial injury(16). Influenza infection is associated with enhanced mortality and morbidity in hospitalized heart failure patients(17). Other types of infections are much less studied in the context of heart failure.

Most of the existing vaccine literature focused on the impact of influenza vaccination on cardiovascular health. For instance, influenza vaccination has been shown to be associated with reduced all-cause mortality and from acute myocardial infarction and stroke in hypertension patients(18). Additionally, the same research group and others elegantly showed that annual influenza vaccination was associated with significant decrease of death among heart failure patients(12, 13). Influenza vaccines reduced death and hospitalization from stroke, acute coronary disease and heart failure and in patients with acute coronary disease(19). Despite the protective effect of influenza vaccines in heart failure, much less is known about the effect of other vaccines on heart failure. Our data corroborated with the current literature by showing significant reduction of heart failure exacerbation or incidence in patients who received influenza vaccines compared to other vaccine. Surprisingly, our results showed a significant increase of heart failure incidence or exacerbation in patients who received COVID-19 or smallpox vaccines. While an explanation for this association is not clear, COVID-19 and smallpox vaccines have been shown to increase the risk of myopericarditis, coronary artery disease and arrhythmia (20-23) which may potentially contribute to heart failure development and progression.

While this study showed a novel association between vaccines and heart failure, further studies are warranted to delineate the molecular mechanisms underlying this association. Additionally, using passive surveillance systems such as VAERS suffer from important limitations including reporting bias and inaccuracy of adverse events reports. Due to the publicity of COVID-19 vaccination adverse events, it is possible that many complications have been reported more frequently. It is also important to mention that studies based on VAERS generally conclude association, however, do not prove causality. Due to these limitations, our results should be interpreted with caution until clinical trials have been conducted.

In conclusion, our results here showed that vaccines against Influenza, zoster, hepatitis, and PPV are associated with reduced heart failure incidence and exacerbation. However, heart failure is associated with COVID-19 and smallpox vaccines. This study serves as a good start to investigate further the association between vaccines and heart failure in longitudinal studies.

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

All the authors contributed to the study design, writing and analysis. Data collection and analysis [Zaki Al-Yafeai David Aziz, and Akhilesh Babbili], design [Zaki Al-Yafeai, David Aziz, Mohamed Ghoweba]. The first draft was written by [Zaki Al-Yafeai, David Aziz, Mohamed Ghoweba] with edits and revision from all the authors. All authors read and approved the manuscript.

Data Availability

The datasets from the current study are available from the corresponding author upon request.

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`Data.pptx` available at https://authorea.com/users/472173/articles/566164-vaccines-and-heart-failure-analysis-of-vaccine-adverse-events-reporting-system-between-1990-2021