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Microbes and their Role in Atrial Fibrillation: A Literature Review

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ABSTRACT

Atrial fibrillation (AF) is a prevalent cardiac arrhythmia observed in clinical practice. The gut microbiota (GM) and their byproducts have the potential to activate the autonomic nervous system, which plays a crucial role in the development and maintenance of AF. Recent hypotheses suggest that bacterial infections, such as *Helicobacter pylori* and *Chlamydia pneumonia* might play a role in the development of AF. The emerging evidence suggested that certain patients might develop AF due to bacterial infections. AF patients exhibited a significant increase in species richness and diversity. Specifically, opportunistic pathogenic bacteria such as *Klebsiella*, *Haemophilus*, *Streptococcus* and *Enterococcus* were significantly higher, while symbiotic bacteria such as *Agathobacter* and *Butyrivibrio* were significantly lower in AF patients. Likewise, the development of AF has been linked to infections caused by viruses that have an affinity for the heart. Chronic hepatitis C virus infection appears to be linked to an elevated risk of incidental AF, likely due to the shared underlying pathology of chronic inflammation. Numerous studies have explored the arrhythmogenic effects of SARS-CoV-2, particularly its impact on mortality and its association with AF. Influenza infection was found to be significantly linked to the development of AF, resulting in an 18% increased risk. However, in cases where AF is present and dengue infection is suspected, it is advisable to exercise caution when considering the use of anticoagulants, ensuring that specific serological tests have excluded the presence of this infection.

KEYWORDS: Atrial fibrillation; Microbes; Virus; Bacteria.

INTRODUCTION

A common cardiac arrhythmia observed in clinical practice is atrial fibrillation (AF). According to the most recent epidemiological census, 4.9% of people in the general population who are 60 years of age and older have baseline AF. In addition, a 6-year observation for AF showed a cumulative new incidence rate of 4.1%, or around seven new cases per 1,000 people each year[1]. The age-related increase in AF incidence is substantial. Cardiac insufficiency and ischemic stroke (cerebral infarction) are significant risks associated with AF. Because of its pathological and clinical features, such as atrioventricular dyssynchrony, high ventricular rate, and loss of atrial systolic pump function, the end-diastolic volume is decreased, which lowers cardiac systolic function and heart failure. Patients' prognosis and quality of life are significantly reduced when AF is combined with heart insufficiency[2].

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In addition, ischemic stroke patients with AF had higher chances of death, recurrence, and disability. It is a significant burden on individuals and society because of the high incidence and disability rates associated with AF. That being said, AF treatment and prevention are crucial. Studies on the incidence, development processes and therapeutic approaches for AF have been conducted in large numbers[3].

As bacteria, viruses, or other microorganisms enter your body and begin to multiply, an infection results. When an infection destroys cells in your body, signs and symptoms of the illness appear. This usually affects a small percentage of those who are affected. Your immune system becomes active and deploys itself in response to an infection. The foreign intruder is removed from your body by the combined action of white blood cells, antibodies, and other defensive systems. A multitude of obstacles are posed to the immune system by pathogenic microbes. Viral infections can result in disease by either destroying cells or altering how they normally operate. Our systems respond by either raising our body temperature to the point where many viruses become inactive, releasing a substance called interferon to stop viral reproduction, or bringing our immune system into action by targeting the invading virus with antibodies and other cells. Likewise, other bacteria cause illness by comparable methods, but they also employ alternative tactics. Bacteria can occasionally multiply quickly enough to outcompete host tissues and impair normal function. In addition, they can directly destroy tissues and cells or to create poisons that can injure a cell by paralyzing it, interfering with its metabolism, or inducing an excessive immune response[4].

Though there is a wide variety of microorganisms (Fig. 1), this article solely covers bacterial and viral infections in AF to summarize our current understanding of them. Science Direct, PubMed, and Google Scholar were among the databases used to do the literature review. Up to June 2, 2023, the search was conducted using certain keywords like "Atrial fibrillation," "Microbes," "Virus," and "Bacteria." Clinical research could only be conducted on English-language publications. No time limit was set, even though current research was highlighted. By looking through the reference lists of the chosen papers, further pertinent articles were found.

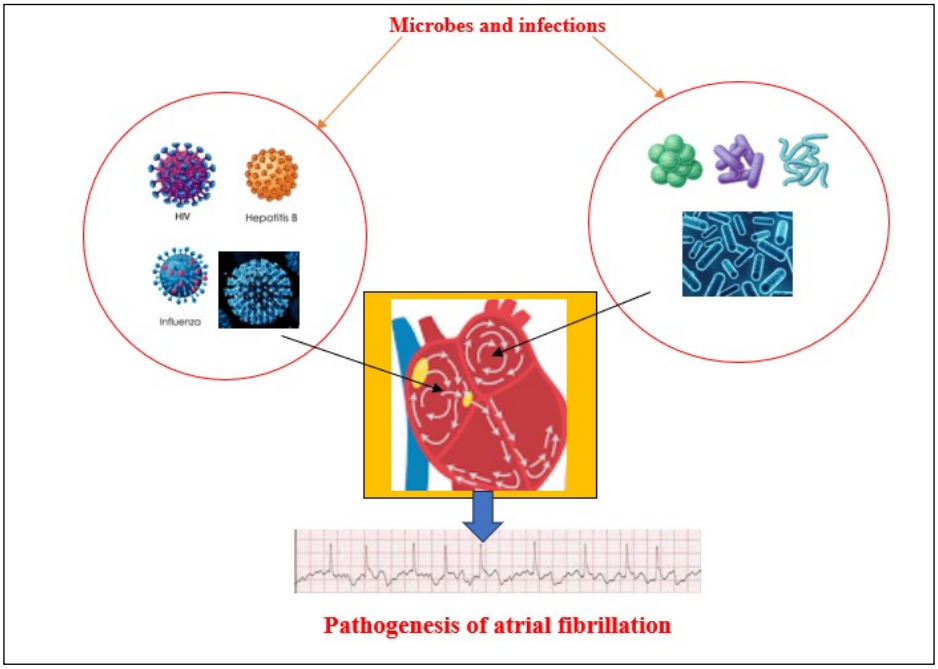

Figure 1. Overview presentation of bacteria and viruses infection in atrial fibrillation
Source: Elaborated by the authors.

Microbial infection in the pathogenesis of atrial fibrillation

Investigating the role of microorganisms in AF can lead to a deeper understanding of the disease's mechanisms and how infections may trigger or exacerbate the condition.

Bacterial infection and AF

Uncertain underlying reasons frequently accompany cardiac arrhythmias, a common cardiac ailment. There is mounting evidence that the GM and its byproducts are important for maintaining cardiovascular health. To identify viable strategies for development, prediction, prevention, and therapy, researchers have been delving into the intricate link between GM and cardiac arrhythmia in recent years. There were explanations for how GM and its metabolites affect cardiac arrhythmia. In particular, the connection between metabolites generated by GM dysbiosis—like bile acids (BA), trimethylamine N-oxide (TMAO), Indoxyl sulfate (IS), lipopolysaccharides (LPS), phenylacetylglutamine (PAGln), and short-chain fatty acids (SCFA), and the established mechanisms underlying cardiac arrhythmias was explored. These include disorders linked to cardiac arrhythmia, aberrant nervous system control, structural remodeling, and electrophysiological remodeling. This microbial-host cross-talk is important because it involves immunological control, inflammation, and several types of programmed cell death. Prospective treatment approaches are also presented, such as the use of immunomodulators, faecal microbiota transplantation (FMT), probiotics, and prebiotics. Over a wide range of possible processes, GM significantly affects cardiac arrhythmia and provides a range of therapy possibilities. But the real issue is to find therapeutic approaches that can successfully lower the risk of ventricular arrhythmia by altering GM and its metabolites[5].

A serious heart rhythm issue that is frequently observed in aging populations is AF. Previous research has linked risk factors for cardiovascular disease to the makeup of the GM. If the gut microbial composition was linked to the chance of developing AF, that connection is not entirely evident. Regression models accounted for in different ways were used to find that, after a median follow-up period of 15 years, particular microbial genera were associated with both new (N = 539) and existing (N = 116) AF cases. Using a statistical adjustment for false discoveries did not affect the significance of the link. Most remarkably, there was a constant correlation between the genera *Enorma* and *Bifidobacterium* and both new and current AF cases. It was shown that there was no significant correlation between AF and markers of bacterial diversity. *Enorma, Paraprevotella, Odoribacter, Collinsella, Barnesiella*, and *Alistipes* were among the top five genera with a consistent shift in abundance in an independent AF case-control cohort utilized for replication. Based on these findings, it may be possible to predict an individual's risk of developing AF using their microbiome profiles. However, a more comprehensive study is required before microbiome sequencing can be used to prevent AF and provide personalized therapy[6].

An important function that the GM and its metabolites play in the formation and maintenance of AF is the autonomic nervous system (ANS), and current research indicates that this system may be activated by the GM. A byproduct that has been connected to cardiovascular disorders is TMAO. Indeed, Yu et al. work was the first to show how stimulating the cardiac autonomic nerve system (CANS) with metabolites produced from gut microbes, Normal dogs and AF models produced by rapid atrial pacing (RAP) after local application of TMAO both showed signs of electrical and autonomic remodeling. Atrial refractory period gradient (ARGP) function was improved, neural activity was increased along with the expression of nerve growth factor (NGF) and c-fos, and the atrial effective refractory period (ERP) was shortened. Additionally, the sum of the window of vulnerability (Σ WOV) was widened and neural activity was increased. By increasing the production of inflammatory cytokines and activating the p65 NF-κB pathway, the injection of TMAO exacerbated these alterations. Increased inflammatory cytokines, autonomic remodeling, and electrical remodeling may all contribute to the maintenance of AF, especially in the first six hours after onset[7].

Since dysrhythmia and certain inflammatory indicators are significantly correlated, recent research has shown a possible connection between inflammation and AF. As a sensitive sign of systemic inflammation, one such measure is the C-reactive protein (CRP). In comparison to a control group without a history of atrial dysrhythmias, patients with AF were shown to have considerably higher levels of CRP. A potential inflammatory basis for AF patients' atria has also been suggested by aberrant tissue alterations seen in these areas. Nevertheless, it's not evident if dysrhythmia results from or is caused by these structural alterations in the atria. Given that inflammation may play a role in AF, scientists have been examining hypoxic factors. The most common cause of both starting and maintaining an inflammatory process is thought to be persistent bacterial infections. Some recent theories propose that *Helicobacter pylori* and *Chlamydia pneumonia* are

examples of bacterial infections that may contribute to the development of angina. According to the research, some people may have bacterial infections and go on to develop AF[8].

Although there is evidence connecting gut bacteria to several cardiovascular disorders, there are few studies on the connection between GM and AF. As such, little is known about the changes that occur in the GM and its metabolites in individuals with AF after catheter ablation. Huang et al. work used non-targeted metabolomic detection and 16S rRNA high-throughput sequencing to examine the GM and metabolites of AF patients both horizontally and longitudinally to fill this knowledge gap. According to the results, there was a notable rise in species richness and diversity among AF patients when compared to the control group. In particular, AF patients had much lower levels of symbiotic bacteria like *Agathobacter* and *Butyrivibrio* and significantly greater levels of opportunistic pathogenic bacteria such *Klebsiella*, Haemophilus, *Streptococcus*, and *Enterococcus*. Following catheter ablation, the majority of patients with AF showed a decrease in harmful bacteria (such as *Ruminococcus*) and an increase in intestine symbiotic bacteria (such as *Lactobacillus*, *Agathobacter*, and *Lachnospira*). Moreover, correlations were found between specific metabolites and particular strains of bacteria[9].

Apart from the downregulation of caffeine, there was a positive association and a negative correlation between it and *Agathobacter*, and individuals with AF also showed positive correlations with estradiol and ascorbic acid. While oleanolic acid was downregulated and had a negative association with *Ralstonia*, citrulline exhibited favourable relationships with *Ralstonia* and *Lactobacillus* after catheter ablation. This illustrates the short-term changes that follow catheter ablation and offers insights into the general changes in the gut flora and metabolites in AF patients. Future therapeutic diagnostic and AF treatment approaches may benefit from these results[9].

A significant incidence of morbidity and disability is linked to AF. An enormous burden is placed on patients and society as a whole by the fast-rising incidence of AF brought on by the aging population. Finding preventative and therapeutic strategies for AF is therefore necessary. Numerous non-pathogenic bacteria comprise the GM, which is found in the human gastrointestinal system. The immunological and metabolic systems are greatly influenced by this microbiota, which is vital to their operation. The GM and its metabolites have been linked to metabolic disorders and chronic inflammatory illnesses, according to recent clinical trials and fundamental research. Additionally, heart failure and hypertension are two cardiovascular disorders that have been linked to GM. The connection between GM and AF is yet unknown, though. The body of research on the relationship between the GM and AF has mostly focused on metabolites including bile acids, lipopolysaccharides, short-chain fatty acids, and trimethylamine N-oxide. By doing this, this aims to move relevant research in this area forward[10].

Similarly, it has been demonstrated that dysbiosis of the GM and AF are related. The link between AF duration and GM profiles, as well as the underlying processes affecting persistent AF (psAF), are yet unknown. Consequently, Zuo et al. examined GM dysbiosis in individuals with varying psAF durations and clarified the relationship between GM and psAF maintenance. Twenty control participants, eight patients with psAF durations greater than 12 months (Pers>12m), and twelve patients with psAF durations less than 12 months (Pers<12m) underwent metabolomic sequencing and analysis[11].

The results showed that both Pers<12m and Pers>12m patients had substantial disruptions in GM composition, which were characterized by enhanced microbial diversity, different structures, and disparate composition. Certain bacteria were variably enriched at different durations of AF, even though Pers<12m and Pers>12m patients shared 84 genera and 404 species of bacteria with the control group. The Pers<12m and Pers>12m groups also showed altered metabolic changes linked to GM and disturbed gut microbial activity. The correlation shown among GM, metabolites, and psAF implies a possible regulation of host metabolic pathways owing to GM dysbiosis, which is linked to the persistence of AF. The research showed that individuals with Pers<12m and Pers>12m have several altered GM and metabolic characteristics in common, which may have happened early in the illness. Extended paroxysmal AF survival was linked to particular, distinct modifications. The results point to the necessity of early intervention in the treatment of AF patients through preventative measures that target GM and microbial metabolites[11].

Global public health continues to face a major issue from cardiovascular diseases (CVDs). Several investigations on the role of gut microbiota (GM) and its metabolites in the pathogenesis of cardiovascular diseases, such as arterial hypertension, AF and congestive heart failure, have been carried out over the previous 20 years. Novel treatment techniques are required

to enhance clinical results, even if a variety of medicines are available to treat CVDs. Effectively managing cardiovascular risk factors presents a problem for researchers working with GM manipulation. Faecal microbiota transplantation (FMT), probiotic and prebiotic supplements, and dietary modifications are among the therapeutic approaches intended to modify the composition of GM and/or its metabolites. Since arterial hypertension, AF and heart failure all share pathophysiological mechanisms and myocardial structural alterations such as inflammation, hypertrophy, fibrosis, and remodelling, these three key cardiovascular disorders are the focus of this discussion[12].

There is a significant amount of research that suggests the GM of AF patients differs from that of healthy controls, however, as of yet, no direct evidence has been found to correlate gut-associated metabolites to AF vulnerability. To offer definitive data, large-scale studies that control for AF risk factors and compare those with and without gut dysbiosis are required. Furthermore, there is little data to determine the effectiveness of therapies such as probiotics, faecal microbial transplantation, and dietary changes in reducing AF risk factors[13].

This question has to be addressed by randomized clinical trials that concentrate on each component of the intervention. Elevated blood concentrations of gut-associated metabolites have also been linked to the recurrence of AF after catheter ablation, according to small observational studies. Adding such metabolites might improve the clinical recurrence prediction methods now in use and help identify individuals who would benefit from AF ablation, however, more research is needed to ascertain this. There is growing evidence of a link between gut dysbiosis and AF due to improvements in molecular diagnostic methods for GM. To determine the molecular connection between gut dysbiosis and arrhythmogenesis in AF, more animal and human experimental research is required. If gut dysbiosis is modifiable as an AF risk factor, this would establish a basis for performing therapeutic interventional research[13].

Viral infection and atrial fibrillation

Up until 2007, incidences of the Zika virus, a recently discovered arbovirus that is a member of the Flaviviridae family and *Flavivirus* genus, were confined to a small number of mild cases in Africa and Asia. A 49-year-old man's acute Zika virus infection resulted in the emergence of atrial fibrillation, as reported by Abdalla et al. For the molecular diagnosis of Zika, a variety of biological samples were analyzed using real-time PCR; however, only the saliva specimen yielded positive results. In the serum sample, the patient's wife tested positive even though she was an asymptomatic carrier. The patient's biomarkers, which included growth factor levels, chemokines, and cytokines, were also thoroughly examined by the researchers[14].

It examined the 95% confidence interval of the mean values and compared these levels to those of other Zika-infected patients and non-infected controls matched for age and gender. In addition, there was just one atrial fibrillation patient, and no other Zika patient showed the same elevated levels of CCL5, IL-1β, TNF-β, IFN-β, IL-9, G-CSF, and GM-CSF. This discovery can be regarded as an unusual Zika virus infection presentation as it is the first recorded case of this specific cardiac condition in Zika-infected individuals[14].

Similarly, viral infections that have a preference for the heart have been connected to the onset of AF. Nevertheless, it is still unclear if a direct viral infection of the atria contributes to the onset of AF. Wu et al. analyzed viral genomes that often impact the heart in individuals with AF to provide light on this issue. Only the genome of PVB19, out of all the viruses examined, was discovered in the atria of 10% of AF patients, including 2 out of 20 who had paroxysmal AF and 3 out of 30 who had persistent/permanent AF for an extended period. In contrast, the PVB19 genome was identified in 7 out of 14 members, or 50%, of the control group. In both the control group and the AF patients, there was no discernible correlation seen between the presence of PVB19 and the presence of CD45+ and CD3+ cells, or between its presence and fibrosis. These results suggest that there was no increase in the amount of viral genomes found in AF patients' atria. Consequently, our findings could not corroborate that a direct viral infection of the atria played a major part in the development of AF[15].

Several research investigations have indicated that inflammation may have a role in the development of non-valvular AF. However, the precise reasons for this inflammation are still a mystery. According to Ichiki et al., viral and bacterial infections considerably raised the levels of Toll-like receptor 2 (TLR2) in monocytes, but not in non-infectious inflammatory circumstances. It comprised 48 consecutive non-valvular AF patients who were hospitalized for catheter ablation; flow

cytometric analysis was used to determine each patient's TLR2 levels. Then, a comparison was made between these levels and a volunteer control group in sinus rhythm[16].

The non-valvular AF group's left atrial volume index (LAVI) and levels of interleukin-6 (IL-6) and CRP were also assessed. Comparing the non-valvular AF group to the control group, the results showed that TLR2 levels were considerably greater in the former. Also, in comparison to the controls, IL-6 levels were noticeably higher in non-valvular AF patients. The CRP levels in the two groups did not, however, differ significantly. TLR2 and IL-6 levels were not substantially altered among the 44 AF patients who had successful pulmonary vein isolation; however, the LAVI dramatically decreased one month following the ablation surgery. According to these results, non-valvular AF may occur as a result of infectious inflammation[16].

A viral infection caused by the hepatitis C virus (HCV) can cause a variety of symptoms outside of the liver and is closely linked to systemic inflammation. Chronic inflammation also increases the chance of getting AF with a fresh start. On the other hand, nothing is known regarding the clinical relationship between HCV infection and the development of new-onset AF. Owing to the same underlying pathophysiology of chronic inflammation, there seems to be a connection between a chronic HCV infection and an increased risk of accidental AF. To ascertain if anti-HCV medication can protect against the onset of AF, more investigation is also required. Clinical observations revealed that a chronic HCV infection was linked to a higher risk of accidental atrial fibrillation, most likely because chronic inflammation is a common underlying pathogenic mechanism[17].

Furthermore, antiviral treatment was proposed as a possible means of lowering the incidence of acquiring new-onset AF. Clinically speaking, it is highly advised to routinely check electrocardiograms to quickly identify any new-onset AF in those with long-term HCV infection. Early intervention and treatment may benefit from this strategy. To ascertain if antiviral medication can successfully prevent and postpone the start of new AF in this group, further research is necessary, either through a bigger population-based study or a carefully planned prospective study[17].

Influenza infection has the potential to increase sympathetic tone and initiate systemic inflammatory responses, two important processes that contribute to the development of AF. Individuals with influenza illness but no immunization (n = 1,369) showed a significantly increased incidence of AF, with an odds ratio of 1.182 after controlling for differences at baseline, compared to a reference group of patients with no influenza infection or vaccination (n = 38,353). On the other hand, those (n = 16,452) who were vaccinated against influenza but did not contract the illness had a decreased risk of AF (odds ratio = 0.881). The risk of AF was comparable to the reference group among patients (n = 696) who both had influenza vaccine and had influenza (odds ratio 1.136; P = 0.214). Subgroup analysis consistently revealed a lower incidence of AF linked to immunization. In conclusion, there is an 18% greater chance of developing AF due to a substantial correlation between influenza illness and AF development. Influenza vaccination may reduce this risk[18].

Although the precise processes leading to the onset of AF remain unclear, inflammation is a significant component. A specific study of the relationship between Herpes Simplex Virus (HSV) infection and the risk of AF has yet to be conducted. A total of 240 participants in the study group (1.6%) and 801 patients in the comparator group (1.1%) experienced their first episode of AF during the three-year follow-up period. Patients with HSV had a significantly higher incidence of developing AF compared to those without HSV, according to analysis using the log-rank test ($p < 0.001$). Using a Cox model to account for established risk factors and comorbidities, it was discovered that HSV infection was independently associated with a higher chance of developing AF (hazard ratios [HR], 1.39; 95% confidence interval [CI], 1.2–1.60; $p < 0.0001$). These results indicate that HSV infection may independently increase the likelihood of AF occurring in the future[19].

Similarly, a 19-year-old man with viral mononucleosis who also had a minor pericardial effusion had AF with a quick ventricular response in one case report[20]. In a different instance, myocarditis was discovered in a patient who had an ongoing, active Epstein-Barr virus (EBV) infection. The first electrocardiogram (ECG) showed evidence of premature ventricular contractions and AF[21].

Herpes zoster (HZ) is a long-term inflammatory disease that can develop into autonomic dysfunction and, in some cases, AF. 8,25 (0.5%) of the 2,204 patients (1.4%) who received an AF diagnosis during the follow-up period did so during the first two years following HZ infection. When comparing the rates of AF development among the patients with severe

HZ (6.4 PTPY) to the patients with moderate HZ (2.9 PTPY) and the patients without HZ (2.7 PTPY), the severe HZ group showed higher rates. During the first two years following HZ diagnosis, the severe HZ group had a 10.6 PTPY risk of developing AF, which was higher than the 2.7 PTPY risk in the moderate HZ group and the 2.6 PTPY risk in the non-HZ group. According to this study, having severe HZ that necessitates hospitalization increases the chance of getting AF, especially in the first two years after HZ diagnosis[22].

Aedes aegypti mosquitoes are the vectors of dengue fever, a viral illness. Though ventricular ectopic beats and atrioventricular blocks, two heart rhythm abnormalities linked to viral myocarditis that have been identified during dengue infection, have not been often documented are supraventricular arrhythmias. In a 62-year-old male patient with dengue hemorrhagic fever, who had no underlying structural heart disease, Veloso et al. reported a case of acute AF with a high ventricular rate. The patient was treated with intravenous amiodarone, which proved an effective course of action. This emphasizes the possibility of acute AF in cases with dengue hemorrhagic fever. Hemorrhagic consequences were not observed in this patient despite the short-term use of an anticoagulant. When contemplating the use of anticoagulants, it is essential to proceed with caution and make sure that specific serological tests have ruled out the existence of dengue infection in situations where AF is present[23].

With 129,650 cases recorded in 2015, dengue fever is quite common in Indonesia. Even though AF in dengue is quite uncommon, as the patient gets well, it usually goes away on its own. Although acute fever in dengue is relatively uncommon, it typically subsides spontaneously as the patient's condition improves. In Case 1, the patient was a 50-year-old male who had been admitted with a fever that had persisted for four days. Both the IgM and NS1 anti-dengue virus assays yielded positive results. Atrial fibrillation with fast ventricular response (AFRVR) was discovered using an ECG. In Case 2, a 53-year-old man complained of palpitations and dyspnea 1 hour before to being admitted[24].

Five days before admission, the patient had been having a fever. Laboratory tests revealed positive results for the IgM antibodies of the Dengue virus, leukopenia, and thrombocytopenia. Additionally, an ECG revealed the presence of AFRVR. Both patients were administered intravenous drips containing digoxin, paracetamol, and normal saline. For close observation, they were admitted. A resolution of AF was observed in Case 1's pre-discharge ECG. Still, AF was seen in the pre-discharge ECG in Case 2. Additionally, doctors should be informed that dengue fever may result in reversible atrial fibrillation. Recurring occurrences should not be written off as "irreversible" AF since they might develop into more serious cardiac problems. In such cases, alertness and sensible handling are essential[24].

The growing amount of data, as noted by Lee et al., suggests a possible link between viral infections and the emergence of arrhythmias. Physicians need to be aware of these infections' potentially fatal consequences, even from quite common ones. To gain a more comprehensive understanding of the complex processes and risk factors associated with the incidence of cardiac arrhythmias in individuals affected by viral infections, more study is necessary. Determining whether these processes can be stopped completely or reversed may be made easier with this knowledge[25]. The extremely pathogenic human coronavirus known as SARS-CoV-2, which produced a broad and catastrophic outbreak, is the source of the infectious disease known as COVID-19[26].

There is no direct effect of the COVID-19 virus on the heart. Nevertheless, it has the potential to induce systemic inflammation and may precipitate significant cardiac complications, including uncontrolled AF. The mortality rate among people with this illness is significant. The case study by Khan et al. concerns an 82-year-old female resident of a nursing home. In addition to other underlying medical issues, she had severe dementia. The initial test conducted at the nursing home yielded a negative result for the presence of SARS-CoV-2. However, a subsequent test yielded a positive result. She was diagnosed with acute respiratory distress syndrome (ARDS) after being admitted to the hospital, where she had low oxygen levels and progressive respiratory failure. As a consequence, she required intubation with a breathing tube. The patient's cardiac rhythm was observed during her hospital stay, and it was found that she suffered from uncontrolled AF. She was initially given intravenous calcium channel blockers to control her heart rate, but this proved ineffective. Consequently, intravenous amiodarone was used as the new form of therapy. After the patient's successful extubation on the fifteenth day of hospitalization, they were transferred to the general medical floor. The antiarrhythmic drugs prescribed for the treatment of atrial fibrillation were continued[27].

Studies on the arrhythmogenic effects of SARS-CoV-2, especially its correlation with AF and mortality, have been conducted in a multitude of ways. According to a review of the 30,999 patients in the American Heart Association COVID-19 Cardiovascular Disease Registry, 5.4% of the patients experienced new-onset AF while they were hospitalized. In comparison to COVID-19 patients without AF, patients with new-onset AF did not have a substantially higher mortality rate after controlling for variables such as demographics data, comorbidities, and disease severity. However, their risk of serious adverse cardiovascular events was significantly elevated. AF may serve as a useful marker of disease severity in the context of SARS-CoV-2 infection[28].

A cohort study with 9,564 individuals found a substantial correlation between mortality among patients with coronavirus disease and the onset of AF[29]. Furthermore, a meta-analysis including 19 observational studies and 21,653 hospitalized patients with confirmed SARS-CoV-2 infection revealed an 11% pooled prevalence of AF, which was substantially associated with an increased risk of death from all causes[30]. Additionally, a retrospective cohort analysis showed that among COVID-19 patients, the presence of atrial arrhythmias was associated with mortality[31].

Similar to this, Stone et al. investigated the function of cardiac microvascular pericytes in in patients with CoVID-19 who express the angiotensin-converting enzyme 2 (ACE2) receptor and their possible effects on the heart. A weakened microvascular support might arise from the malfunctioning of these pericytes or endothelial cells, which could have several negative effects on the heart. These include a elevated risk of AF as a result of increased tissue edema, fibrosis, interstitial hydrostatic pressure, and myocardial inflammation. These elements collectively contribute to the disruption of electrical activity, potentially leading to AF by affecting cells and tissues. Angiotensin, pulmonary hypertension, and regulatory T cells are a few examples of this. Additionally, two commonly prescribed medications, metformin and corticosteroids, and their potential influence on the occurrence of AF were discussed in the context of COVID-19[32].

To determine if having pre-existing AF as a comorbidity may raise the likelihood of developing severe COVID-19 infections, worsen prognoses, or increase death, Russo et al. conducted a study. A total of 467 COVID-19 patients were included in this study. The average age of the participants was 66.88 ± 14.55 years, and 63% of them were male. Of them, 122 patients (26.1%) had a prior history of AF, of which 12 cases (2.6%), 57 cases (12.2%), and 53 cases (11.3%) had paroxysmal, chronic, or permanent AF. Although there were no statistically significant variations in cardiovascular comorbidities or therapies between the two groups, it was found that COVID-19 patients with a history of AF were older (71.25 ± 12.39 vs. 65.34 ± 14.95 years; $p < 0.001$)[33].

It was discovered that a elevated risk of severe ARDS during hospitalization was independently correlated with the presence of AF prior to admission. The risk of in-hospital mortality was not elevated by it, nevertheless. Interestingly, among patients with a history of AF, there were no significant differences in the incidence of ARDS or in-hospital mortality between individuals with a persistent history of AF and those without. Finally, it should be noted that up to 25% of COVID-19 patients who were admitted to the hospital had pre-existing AF. When COVID-19 individuals were hospitalized, it was found to be independently associated with a higher risk of severe ARDS. However, the presence of AF does not appear to affect the likelihood of mortality. Furthermore, it appears that the clinical result in this case is unaffected by the kind of pre-existing AF (permanent or non-permanent)[33].

In individuals with COVID-19, atrial fibrillation and its concomitant conditions can increase the risk of complications, mortality, and morbidity. A comprehensive account of the clinical, epidemiological, radiological, and analytical features of atrial fibrillation patients hospitalized for COVID-19 in Spain was the goal of another study. The SEMI-COVID-19 registry was populated with data from 16,461 patients between 1 March and 1 October 2020. Of these, 1816 (11%) of them had a history of atrial fibrillation, with 738 (41%) of these individuals dying as a result of AF[34].

Age, hypertension, diabetes with target organ involvement, and a history of cardiovascular disease were the only comorbidities in that the dead group had statistically significant differences. The use of oral anticoagulants (DOACs) for therapy exhibited a protective effect against death, according to a multivariate analysis (OR: 0.597; CI: 0.402-0.888; P=0.011). Finally, it can be said that in COVID-19 patients who have atrial fibrillation, the use of DOACs both before and during admission may benefit them. Nevertheless, prospective research should be used to confirm this result[34].

Furthermore, cardiac arrhythmias, namely AF, are often noted in COVID-19 patients, particularly those receiving treatment in the intensive care unit (ICU). Nevertheless, a comprehensive investigation into the precise etiology of this

relationship has not yet been conducted. Furthermore, AF, which is often precipitated by sepsis, is commonly observed in non-COVID ICU patients. In this study, Zakynthinos et al. sought to determine if variables other than cardiac involvement associated with COVID-19 influence the onset of new-onset atrial fibrillation (NOAF) in patients receiving intubation in the intensive care unit. In 52% of cases, there was evidence of modest right ventricular dilatation, while pericardial effusion was observed in 43% of cases. NOAF happened at 8.5 ± 2.1 days after ICU admission and 18 ± 4.8 days after the start of COVID-19 symptoms[35].

It is noteworthy that secondary septic infection episodes occurred in 89.5% of the NOAF group (as opposed to 41.6% in the control group). Furthermore, in 84.2% of cases, NOAF was associated with a subsequent septic episode. The only variable that was demonstrated to be significantly associated with the occurrence of NOAF was the presence of sepsis (OR 16.63, p = 0.002). Inflammation biomarkers, lactate, and noradrenaline levels all progressively increase in the days preceding AF. However, the presence of NOAF did not result in a notable alteration in the echocardiographic findings. According to this, sepsis in particular may operate as a "second hit" on a COVID-19-affected myocardium, hence contributing significantly to the development of NOAF[35].

A recent focus of research has been on arrhythmias, notably AF, among the numerous cardiovascular problems linked to COVID-19. Another study sought to ascertain the incidence of AF formation in COVID-19 patients admitted to the hospital and to evaluate the possibility of AF as a predictor of all-cause death during the hospital stay. Based on the study results, incident AF is a common complication among hospitalized COVID-19 patients, and its incidence is highly correlated with in-hospital mortality[36].

Investigations were conducted to determine the effect of chronic kidney disease (CKD) on in-hospital mortality rates and the onset of AF in SARS-CoV-2. Acute kidney damage (AKI) was another topic of investigation. It was found that having severe CKD was an independent predictor of in-hospital mortality among this sizable group of COVID-19 patients. In addition, the risk of mortality was doubled for those who developed AKI while hospitalized. AKI was substantially correlated with an increase in the incidence of AF, which occurred when the estimated glomerular filtration rate (eGFR) decreased[37].

A deeper comprehension of the microbial factors implicated in AF may facilitate the implementation of preventive measures aimed at reducing the probability of infections, which could, in turn, contribute to a reduction in the risk of developing AF.

CONCLUSION

According to the review paper, AF is significantly influenced by microorganisms, including viruses and bacteria. However, the presence of additional microbes in AF has not been documented. To identify precisely how these microorganisms cause AF, more research is needed. All things considered, research on the role of microbial infections in the pathophysiology of AF is essential for advancing medical knowledge, enhancing of patient care, and developing targeted therapies to treat and prevent the heart arrhythmia.

CONFLICT OF INTEREST

Not applicable.

AUTHOR'S CONTRIBUTIONS

Conceptualization: Rafaqat S; Sharif S and Rafaqat S; **Methodology:** Rafaqat S; Sharif S and Rafaqat S; **Investigation:** Rafaqat S; Sharif S and Rafaqat S; **Writing – Original; Draft:** Rafaqat S; Sharif S and Rafaqat S; **Writing – Review**

and Editing: Rafaqat S; Sharif S and Rafaqat S; **Resources:** Rafaqat S; Sharif S and Rafaqat S; **Supervision:** Rafaqat S; Sharif S and Rafaqat S.

DATA AVAILABILITY STATEMENT

All data sets were generated or analyzed in the current study.

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