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MINIREVIEWS

New-onset atrial fibrillation among COVID-19 patients: A narrative review

Fahimeh Talaei, Akshat Banga, Amanda Pursell, Ann Gage, Namratha Pallipamu, Amith Reddy Seri, Ramesh Adhikari, Rahul Kashyap, Salim Surani

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Abstract

Over the last three years, research has focused on examining cardiac issues arising from coronavirus disease 2019 (COVID-19) infection, including the emergence of new-onset atrial fibrillation (NOAF). Still, no clinical study was conducted on the persistence of this arrhythmia after COVID-19 recovery. Our objective was to compose a narrative review that investigates COVID-19-associated NOAF, emphasi-

zing the evolving pathophysiological mechanisms akin to those suggested for sustaining AF. Given the distinct strategies involved in the persistence of atrial AF and the crucial burden of persistent AF, we aim to underscore the importance of extended follow-up for COVID-19-associated NOAF. A comprehensive search was conducted for articles published between December 2019 and February 11, 2023, focusing on similarities in the pathophysiology of NOAF after COVID-19 and those persisting AF. Also, the latest data on incidence, morbidity-mortality, and management of NOAF in COVID-19 were investigated. Considerable overlaps between the mechanisms of emerging NOAF after COVID-19 infection and persistent AF were observed, mostly involving reactive oxygen pathways. With potential atrial remodeling associated with NOAF in COVID-19 patients, this group of patients might benefit from long-term follow-up and different management. Future cohort studies could help determine long-term outcomes of NOAF after COVID-19.

Key Words: COVID-19; SARS-CoV-2; New-onset atrial fibrillation; Atrial fibrillation

Core Tip: In this literature review, we have observed resemblances between the fundamental pathophysiology of coronavirus disease 2019 (COVID-19)-related new-onset atrial fibrillation (NOAF) and the mechanisms proposed for the persistence of AF, particularly those involving oxidative stress and reactive oxygen species. The mechanisms responsible for the development of AF following a COVID-19 infection could potentially contribute to atrial remodeling, further perpetuating AF. However, while short-term outcomes of COVID-19-related NOAF have been well-studied, as we transition into an endemic era of COVID-19, there is a need for more research to investigate the long-term outcomes of patients who develop NOAF after COVID-19 infection.

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INTRODUCTION

Background

As atrial fibrillation (AF) incidence was approaching an epidemic proportion[1], in January 2020, the world health organization announced the preliminary determination of a novel coronavirus in Wuhan, China. By March 2020, the novel virus was recognized as a global pandemic[2,3]. AF was reported as the most common arrhythmia in a multicenter review of coronavirus disease 2019 (COVID-19) cases in 76 countries, with a prevalence of 19% to 21% of all hospitalized cases[4]. The new onset of AF (NOAF) among COVID-19 patients (referred to as COVID-19-related NOAF) raises concerns for unfavorable outcomes, especially in critically ill patients, regarding in-hospital mortality, length of stay in the intensive care unit, and survival[5,6].

In individuals whose AF has progressed, it has previously been observed that various factors, such as oxidative stress, atrial dilatation, calcium overload, inflammation, and myofibroblast activation, interact in a way that significantly contributes to the remodeling of the atrial extracellular matrix (ECM) and electrical properties. This ultimately results in the continuous presence of AF. Nevertheless, the possibility of AF persisting following a COVID-19 infection has not undergone comprehensive investigation, and there is currently a dearth of prolonged studies that evaluate the consequences of COVID-19-related NOAF[7,8]. Furthermore, maintaining sinus rhythm is generally more challenging in patients with persistent AF compared to those with paroxysmal AF, and persistent AF is associated with higher thromboembolic risks [9]. However, there is a paucity of the data regarding persistence of AF after COVID-19 infection. The innate tendency of COVID-19 for coagulopathy, characterized by elevated D-dimer and a significant increase in peripheral thromboembolic events observed in NOAF patients, calls for further investigation of the management of COVID-19-related NOAF[10,11].

Similar to past pandemics in history, the COVID-19 pandemic presents a chance to broaden our knowledge despite the challenges it poses[3]. Our objective was to explore the underlying mechanisms of NOAF in COVID-19 patients, with a particular emphasis on factors that could sustain the occurrence of this arrhythmia. To peruse this, a comprehensive, structured literature search was conducted through EMBASE and MEDLINE for articles published between December 2019 and May 20, 2023, that reported the pathophysiology of NOAF after COVID-19 and those persisting AF. Also, the latest data on incidence, morbidity-mortality, and management of NOAF in COVID-19 were investigated. The search terms include each of the following terms individually and in combination: "new-onset atrial fibrillation", "NOAF", "AF persistence", "persistent atrial fibrillation", "SARS-CoV-2", "COVID-19", "SARS", coronavirus as described in the Supplementary Table 1[12]. Two investigators (Talaei F and Banga A) independently screened studies for eligibility. We focused primarily on published research articles, systematic reviews, and observational cohorts. The title, abstract, and keywords were checked for relevance initially. Studies were excluded if not written in English.

NOAF

NOAF is defined as AF detected after diagnosis of COVID-19 without a prior history[13]. In the course of the disease, AF might indefinitely appear as short (< 7 d) self-limiting episodes (*i.e.*, paroxysmal). However, it is more likely to transform into long-lasting forms of AF[14]. AF is considered persistent when perpetually lasting more than seven days[15,16].

Epidemiology

An October 2021 meta-analysis involving over 21000 hospitalized COVID-19 patients revealed that NOAF had a prevalence of 11%. Elderly COVID-19 patients (aged ≥ 60) had a higher NOAF prevalence (13%) compared to younger patients (5%). Among different ethnic subgroups, Europeans (15%) and Americans (11%) had the highest NOAF prevalence, while Africans had the lowest (2%). Additionally, NOAF was significantly linked to a higher risk of all-cause mortality among COVID-19 patients (odds ratio = 2.32)[17].

A report from the American Heart Association COVID-19 Cardiovascular Disease Registry revealed that 5.4% of patients hospitalized for COVID-19 infection developed NOAF during their hospital stay. Moreover, NOAF was associated with higher rates of death (45.2% *vs* 11.9%) and major adverse cardiovascular events of cardiovascular death, myocardial infarction, cardiogenic shock, and heart failure (23.8% *vs* 6.5%) compared to those who did not develop NOAF. The unadjusted hazard ratio for mortality was 1.99 [95% confidence interval (CI): 1.81-2.18], and for major adverse cardiovascular events was 2.23 (95%CI: 1.98-2.53) for patients with *vs* without new-onset AF[18].

COVID-19-related NOAF was demonstrated to be an independent prognostic factor for in-hospital embolic events, irrespective of anticoagulant use and prolonged hospital stay. Potential co-factors contributing to the development of NOAF could include older age, arterial hypertension, a history of myocardial infarction, renal dysfunction, and elevated D-dimers[19], which align with previously reported risk factors associated with the emergence of NOAF in critically ill patients[20].

Etiology and pathophysiology

There are ongoing debates regarding underlying mechanisms involved in provoking arrhythmias in COVID-19 infection. While some attribute arrhythmias and hence AF directly to the virus itself[21]; others highlight the connection between inflammatory markers and arrhythmias, considering it as a consequence of a systemic illness not exclusive to COVID-19 [11,22]. A third group points towards the long-term changes required to make atrial structural abnormalities and the relatively short incubation period of COVID-19 and concludes that it might be a symptom of prior undetected structural heart diseases[23,24].

There are limited studies concerning the pathophysiology of NOAF in COVID-19; nonetheless, several of them are built upon earlier research conducted on severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) or Middle East respiratory syndrome coronavirus (MERS-CoV). Considering the resemblances in structure and potential pathogenicity among MERS-CoV, SARS-CoV-1, and SARS-CoV-2[25], various mechanisms have been suggested to elucidate the processes that might trigger arrhythmia in the context of COVID-19[26,27].

Angiotensin-converting enzyme-2 (ACE2)-related signaling pathways, endothelial dysfunction, spike protein interaction, cytokine storm, hypoxia, alteration in the autonomous nervous system, and metabolic disarray in the setting of viral infection are some proposed mechanisms[21,23].

Modulation of myocardial ACE2 expression: ACE2 is found in abundance in the lungs. It is thought to play an essential role in the pathogenesis of SARS-CoV-2-associated severe acute respiratory syndrome by acting as a receptor for this family of viruses. However, this enzyme is not exclusive to the lungs, as it is also highly expressed in the heart and kidneys[19,28].

The catalytic action of this enzyme in the heart leads to the degradation of angiotensin-II (Ang II) to cardioprotective Ang1-7. In doing so, ACE2 plays a cardioprotective counterbalance role in the renin-angiotensin-aldosterone system (RAAS)[19].

Binding the viral spike protein to the ACE2 receptor activates catalytic processes that lead to ACE2 shedding, decreasing antifibrotic Ang1-7. Consequently, the Ang II/Ang1-7 ratio will move toward Ang II production, which is a growth factor for fibroblasts, and promote inflammation, fibrosis, oxidative stress, and vasoconstriction[19,29,30]. Decreasing Ang1-7 also leads to an increase in disintegrin and metalloproteinase 17, which will prompt further cardiac injury and subsequent potential AF[23,27].

Endothelial dysfunction: The cardioprotective role of ACE2 has been discussed, yet it extends beyond that by serving as a regulator of the kallikrein-bradykinin pathway, imparting a significant vasodilator effect. This effect acts as a counterbalance to the vasopressor effect of RAAS[19,31]. Declined vascular levels of ACE2 in COVID-19 patients lead to overactivation of the kallikrein-bradykinin system and increased permeability[31]. The heightened permeability leads to the recruitment of diverse immune cells, inflammatory cytokines, and vasoactive molecules to the site. Consequently, the production of reactive oxygen species (ROS) and other cytotoxic mediators by activated neutrophils synergizes with the release of vasoactive molecules, including thrombin, histamine, bradykinin, thromboxane A2, and vascular endothelial growth factor. This, in turn, enhances the contractility of endothelial cells and the loosening of inter-endothelial junctions, ultimately leading to vascular leakage[32]. Also, interleukin (IL)-1β and tumor necrosis factor (TNF)-α are recognized for their ability to promote fluid retention by increasing glycocalyx degradation and upregulating hyaluronic acid synthesis, the ultimate result of which is an increased deposition of hyaluronic acid in the compromised ECM, promoting fluid retention[32]. Both mechanisms ultimately converge on vascular impairment as an endpoint.

While the impact of AF on the vasculature has been better studied, recent discoveries indicate a bidirectional relationship between the two[33,34]. Endothelial dysfunction would further increase oxidative stress, proinflammatory cytokines, and impaired nitric oxide-dependent vasorelaxation[29]. Excessive production of endothelial ROS has been linked to atrial oxidative injury, resulting in structural and electrical remodeling, contributing to AF. Interestingly, there is evidence that patients with coronary endothelial dysfunction are at increased risk for developing persistent AF[33,34]. Up to date, no similar human studies are available, and the current pandemic could present an opportunity to investigate this link.

Spike protein binding to cardiomyocyte: Spike protein of COVID-19 plays an essential role in host cell invasion, including cardiomyocytes[35]. Viral spike protein interacts with CD147 as an ECM metalloproteinase inducer. CD147 is a potent stimulator of several cytokines, including IL-18, *in vitro,* and IL-18 is an essential element of the inflammatory cascade, acts as a cardiotropic metalloproteinase, and correlates with cardiac remodeling and AF[36,37].

Spike protein also binds to N-acetylneuraminic acid (Neu5Ac), the predominant sialic acid in human cells, including cardiomyocytes. Higher levels of Neu5Ac are associated with left atrial enlargement, and it plays a crucial role in severe coronary artery diseases (CAD) and cardiac fibrosis[38], but how this cardiac fibrosis could lead to AF is under study[23].

Cytokine storm: The sustained infiltration of neutrophils, macrophages, and CD4+ T-lymphocytes associated with the COVID-19 cytokine storm can promote the transformation of fibroblasts to myofibroblasts, which in the long run could lead to pathological cardiac remodeling and fibrosis[39].

On the other hand, atherosclerotic plaques in the coronary artery are more prone to rupture in the state of inflammation anticipated by cardiac injury and arrhythmias. Production of several cytokines, either by inducing direct myocardial necrotic effect or releasing pro-atherogenic cytokines like IL-6, will develop proliferation in vascular smooth muscle accompanied by endothelial cell and platelet activation[40,41].

Hypoxemia: COVID-19 causes hypoxia by several different mechanisms that can transform into acute respiratory syndrome[42]. Pneumonia in COVID-19 deteriorates gas exchange and complicates cell metabolism. This enhances anaerobic fermentation, resulting in intracellular acidosis and oxygen free radicals destroying the phospholipid layer of the cell membrane. Meanwhile, the hypoxia-induced influx of calcium ions also leads to injury and subsequent apoptosis of injured cardiomyocytes[43]. Also, COVID-19 systemic infection, being a situation of increased cardiometabolic demand, collaterals with hypoxia caused by an acute respiratory illness. This coincidence leads to an unmatched myocardial demand-supply ratio and subsequent acute myocardial injury[44].

The above should also add hypoxemia-induced dynamic changes in transmural pressure gradients, promoting increased pulmonary pressure, which leads to tricuspid regurgitation and further impairment in the right atrium, followed by possible changes in atrial conduction properties and refractoriness[45].

Gramley *et al*[46] previously observed a close association between prolonged hypoxic and increased angiogenic markers in the atrium with AF. With the persistence of hypoxia, an endoglin called CD105 would up-regulate, which is a homolog to the type III receptor of transforming growth factor-β, leading to ECM formation. It was hypothesized that cardiac hypoxia could provoke AF through the hypoxia-inducible factor pathway and over-expression of connective tissue growth factor and angiogenic genes like vascular endothelial growth factor[46].

Autonomic nervous system alteration: Severe infections generally activate the sympathetic nervous system (SNS), which also relates to AF[23]. Among cytokines released in COVID-19 infection, IL-6 can hyperactivate SNS, either centrally by a hypothalamus-mediated mechanism or peripherally *via* the left stellate ganglia[47].

SNS activation likely increases calcium influx into the cardiomyocytes and calcium overload in the sarcoplasmic reticulum, further increasing the frequency of spontaneous diastolic calcium releases, resulting in delayed afterdepolarizations and triggered action potentials, increasing the likelihood of AF induction[48].

On the other hand, hypoxemia might activate the parasympathetic system. Combined sympathetic and vagal activation creates a more pronounced AF substrate than sympathetic or parasympathetic stimulation alone. In an experimental animal model, changes in intrathoracic pressure, dynamic hyperinflation, and obstructive respiratory events that were followed by hypoxia-activated the parasympathetic nervous system, reducing the right atrial effective refractory period and increasing the susceptibility to AF. Autonomic nervous system (ANS) activity and AF have a reciprocal interaction that could help the arrhythmia continue to evolve[49].

Fluid and electrolyte abnormality: Renal dysfunction in COVID-19 can lead to a decrease in serum potassium levels due to increased excretion[50]. Increased ACE/ACE2 ratio imbalance would also affect the RAS and potassium metabolism [51]. Increased ACE2 degradation augments RAS activity, increasing sodium and water reabsorption and collateral increase potassium excretion[52]. Hypokalemia frequently happens in hospitalized patients with COVID-19, with reported rates ranging from 41% to 55% of cases[53]. The occurrence of hypokalemia, which increases resting potential, leads to cell membrane hyperpolarization, thus accelerating atrial conduction and potentially creating a susceptibility to AF. Hypokalemia, by increasing resting potential, leads to cell membrane hyperpolarization, thus accelerating atrial conduction, which could possibly predispose to AF[54]. Hypokalemia frequently happens in hospitalized patients with COVID-19, reported in 41% to 55% of cases[55].

Association with CAD

Growing evidence highlights a strong link between CAD and AF, and several observational studies have indicated that CAD and AF aggravate each other. Shared risk factors encompassing hypertension, diabetes mellitus, and obesity substantiate this linkage. Notably, AF incidence has been found to be higher in people with CAD compared to age-matched

adults without CAD[56].

Evidence points to an intricate relationship between atrial tissue excitability and neuronal remodeling with ischemia at the microcirculatory level. CAD adversely affects AF by promoting progression *via* re-entry and increasing the excitability of atrial tissue as a result of ischemia and electrical inhomogeneity. AF, in turn, accelerates atherosclerosis and, together with enhanced thrombogenicity and hypercoagulability contribute to micro and macrothrombi throughout the cardiovascular system. Inflammation and endothelial dysfunction remain central to both disease processes[57].

Patients with CAD associated with NOAF or persistent AF have significantly higher morbidity and mortality, predisposing to heart failure, life-threatening ventricular arrhythmias, and major adverse cardiovascular events[57]. A recent comprehensive analysis supports heightened AF risk in CAD patients, yet a causal AF-to-CAD link remains unestablished[56]. Management of concurrent CAD and AF centers on anti-thrombotic strategies, balancing stroke prevention and stent thrombosis avoidance while cautiously mitigating bleeding risk. Current guidelines recommend up to one year of combined oral anticoagulant (OAC) and antiplatelet therapy, preferably P2Y12 inhibitors or OAC monotherapy. However, the limited quality of evidence in these guidelines and persistently high bleeding risk constrain their clinical applicability[50,52].

Management of NOAF

Recognition: NOAF recognition in patients with COVID-19 can be done with electrocardiography, telemetry, or implantable device interrogation. Close observation of vital signs and regular electrocardiograms help monitor for dysrhythmias such as AF in patients with COVID-19[51].

Evaluation: The initial evaluation of COVID-19-related NOAF parallels the standard management for AF. This involves conducting a routine two-dimensional transthoracic echocardiogram to assess for structural irregularities. However, if indications of heart failure, hemodynamic instability, unexplained clinical deterioration, or planned cardioversion are pre-sent, expedited evaluation is warranted[15].

Transesophageal echocardiography should be obviated by the early start of anticoagulation in NOAF to detect left atrium thrombi as a potential source of systemic embolism in AF and can be used to guide the timing of cardioversion or catheter ablation procedures[53].

Treatment goals: Treatment goals are regardless of the type, treatment goals encompass three primary objectives: Managing heart rate during episodes of AF; and achieving the restoration, sustained maintenance of normal sinus rhythm (rhythm control), and mitigating the risk of systemic or cerebral embolism linked to the heightened embolic risk associated with AF all while minimizing the impact of drug interactions[15,58].

Rate and rhythm control: The contemporary therapy of AF with rate control *vs* rhythm control strategies is still disputed, there is a scarcity of data regarding the effectiveness of rhythm and rate control approaches for COVID-19-related AF. Current recommendations are based on acute management of AF in COVID-19 disease and long-term data is not available[53,58]. Enhancing the treatment of underlying factors such as hypoxemia, inflammation, and potentially reversible triggers (like hypokalemia, hypomagnesemia, and acidosis) seems to form the empirical foundation for managing these cases. As with other setting, if NOAF is suspected to be a contributing factor to hemodynamic instability immediate cardioversion should be considered. Although, for the remaining patients who do not urgently require cardioversion, the decision to proceed should be weighed against the availability of necessary equipment and medical personnel, as well as the potential risk of virus transmission with intubation. In critically ill patients with compromised hemodynamics due to NOAF, intravenous amiodarone is the preferred antiarrhythmic medication for rhythm control[59].

Hospitalized patients who have developed COVID-19-related NOAF and are undergoing antiviral treatment while maintaining hemodynamic stability should give precedence to discontinuing their anti-arrhythmic medications. Instead, the preferred approach involves initiating rate control therapy using beta-blockers or non-dihydropyridine calcium channel blockers, along with or without digoxin, unless contraindicated[58]. This approach ensures the safe administration of antiviral medication without the potential risk of QT prolongation[53,58].

Amidst a COVID-19 infection, the potential for QT interval-related risks could be heightened due to the simultaneous utilization of anti-arrhythmic medications with other QT-prolonging medications (such as hydroxychloroquine, azithromycin, lopinavir/ritonavir), along with factors like myocardial inflammation and electrolyte imbalances (like hypokalemia, hypomagnesemia, and/or hypocalcemia)[60]. It's crucial to assess potential drug interactions, including those between antiviral and antiarrhythmic drugs, prior to initiating therapy[53].

Unless dealing with highly symptomatic AF cases, such as individuals with AF-related heart failure or those experiencing medically refractory AF resulting in frequent emergency room visits, all AF ablation procedures ought to be delayed for a minimum of three months after recovering from a COVID-19 infection[53].

Prevention of thromboembolic events: As a general guideline, for patients with a history of prior stroke, transient ischemic attack, or a CHA2DS2-VASc score > 2 who subsequently develop AF, oral anticoagulation is recommended[15]. Given that hospitalized COVID-19 patients are generally over the age of 65 and often have multiple underlying health conditions, a significant proportion of individuals with AF necessitate prolonged anticoagulation therapy[11]. Hemodynamically stable COVID-19 patients presenting with atrial AF during their hospitalization have treatment including unfractionated heparin, low molecular weight heparin, or direct OACs (DOACs). The specific choice among these options is influenced by factors like the suitability of oral administration, renal function, and additional clinical aspects. It's important to highlight that certain medications for COVID-19 treatment could potentially interact with DOACs. Lopinavir/ritonavir may create a potential interaction with DOACs through cytochrome P450 CYP3A4 interaction, and antimalarial drugs could influence DOACs *via* P-glycoprotein inhibition. If such interactions are pertinent, there may be

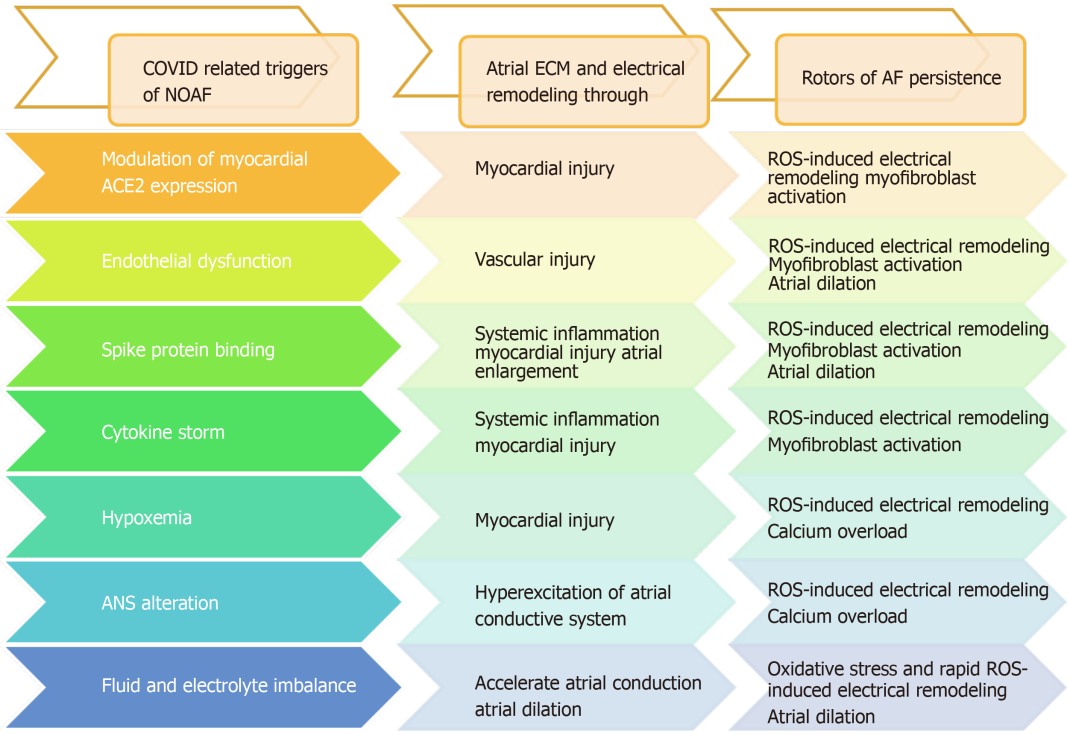

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Figure 1 Comparing available studies on new-onset atrial fibrillation pathophysiology in coronavirus disease 2019 patients and rotors of atrial fibrillation persistence (including oxidative stress, calcium overload, atrial dilation, micro-RNA, inflammation, and myofibroblast activation. COVID: Coronavirus disease; ECM: Extracellular matrix; NOAF: New-onset atrial fibrillation; AF: Atrial fibrillation; ROS: Reactive oxygen species; ACE2: Angiotensin-converting enzyme-2; ANS: Autonomic nervous system.

an increased risk of bleeding, underscoring the need to avoid DOACs. Given this scenario, DOACs are favored over vitamin K antagonists (VKAs) due to their more favorable safety profile and standardized dosing schedule[58].

VKAs are also considered for specific subsets of patients, including individuals with mechanical prosthetic valves or antiphospholipid syndrome. While VKAs typically induce a temporary deficiency of vitamin K, the observed lower levels of vitamin K in patients with COVID-19 compared to healthy individuals suggest a need for additional investigation regarding the utilization of VKAs in COVID-19 patients[61]. The precise mechanisms driving this connection are yet to be fully understood.

The innate tendency of COVID-19 for coagulopathy, characterized by elevated D-dimer and a significant increase in peripheral thromboembolic events observed in NOAF patients, calls for further investigation of the management of COVID-19-related NOAF[10,11]. Since heparins are unlikely to interact with drugs used in COVID-19 treatment, they represent a safe and attractive option for stroke prevention in AF patients who are hospitalized due to COVID-19. Remarkably, beyond their antithrombotic effects, heparins also possess anti-inflammatory properties that could be pertinent in this context[53]. Following recovery from COVID-19, the continuation of long-term anticoagulation should be based on the CHA2DS2-VASc score.

Discussion

COVID-19-related NOAF is still not well studied. Mechanisms involved in the development of NOAF after COVID-19 infection could potentially lead to atrial remodeling and fibrosis, which can further perpetuate AF, as shown in Figure 1. Clinical studies suggested that the majority of the patients with AF remain paroxysmal, though the electrophysiological substrate underlying AF in those who progress to sustained forms may differ from that of those who remain paroxysmal [62]. However, in this study, a sizable overlap was noted in mechanism inducing COVID-19 associated NOAF and those persisting AF.

The mechanism involved in the progression of AF is a constellation of oxidative stress, inflammation, atrial dilatation, calcium overload, and myofibroblast activation, all of which are likely to be involved in one way or another in AF-induced ECM and electrical remodeling[7,8]. Interestingly, many of these mechanisms seem to be mutual with suggestive models of COVID-19-related NOAF (Figure 2), and looking back to the mutual mechanisms of persistent AF and COVID-19-related NOAF could explain the possible risk of developing persistent AF after NOAF in COVID-19 patients (Table 1 and Figure 2).

In the working model of AF perpetuation by Jalife and Kaur[8], oxidative stress and ROS are the cornerstones of maintaining AF. In that model, a putative mechanism of AF perpetuation involves Ang II stimulation, which triggers the release of ROS from activates nicotinamide adenine dinucleotide phosphate oxidases 2/4. This process leads to a rapid reduction in L-type Ca^{2+} current and an increase in inward rectifier K^{+} current within a short timeframe (*i.e.*, hours or

Table 1 Comparing coronavirus disease 2019-related new-onset atrial fibrillation and persistent atrial fibrillation in terms of etiology, pathophysiology, contributing risk factors, outcome, and management

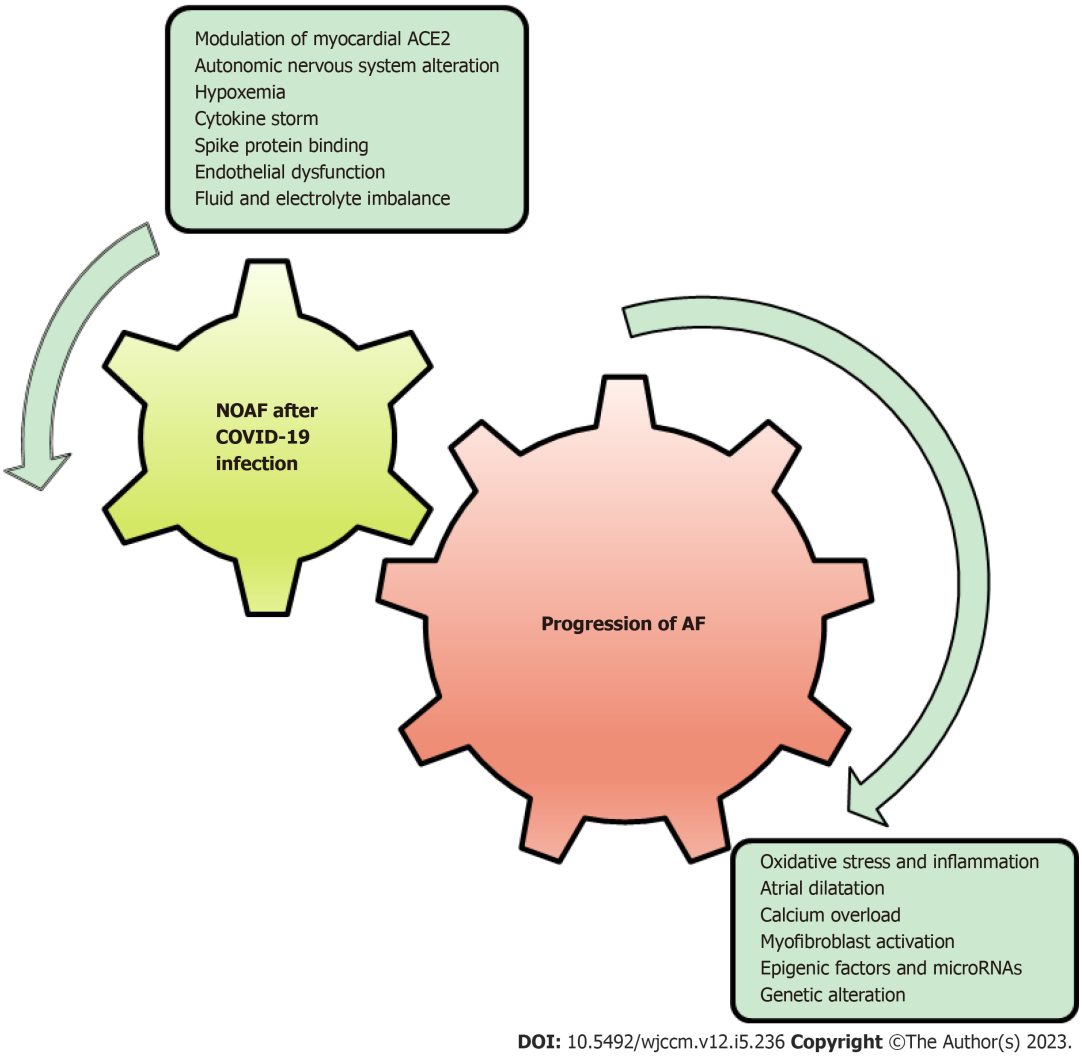
	COVID-19-related NOAF	Persistent AF
Etiology and pathophysiology	(1) Diminished availability of ACE-2 receptors contributes to myocardial hypertrophy, vasoconstriction, ROS production, oxidative stress, tissue inflammation, and fibrosis, all of which play a role in the development of AF; (2) Endothelial dysfunction leads to increased vascular permeability and leakage culminating in an overproduction of ROS leading to structural and electrical remodeling predisposing to AF; (3) CD147- and myocyte's sialic acid-spike protein interaction upregulate the expression of several cytokines and ROS that induce extracellular matrix degradation, cardiac remodeling, and fibrosis; (4) Excessive release of proinflammatory cytokines in cytokine storm leads to ROS production, progressive myocardial cell apoptosis or necrosis, which may lead to conduction disturbances leading to AF; (5) Impaired gas exchanges and intrathoracic pressure swings lead to cardiomyocyte injury and increased frequency of premature atrial beats and induce AF; (6) ANS alteration: SNS-mediated calcium influx increases the frequency of delayed afterdepolarization and triggers AP; PNS activation mediated by intrathoracic pressure swing leads to shortening of right atrial ERP, and APD both induce AF; and (7) Sodium and water resorption increases blood pressure and excretion of potassium increase the resting membrane and enhances depolarization predisposing to AF	Steady generation of ROS triggered by sustained high-electrical activity, followed by intracellular Ca^{2+} overload together with atrial dilatation, mitochondrial ROS and activation of inflammatory and pro-fibrotic pathways progressively alters gene expression clinically relevant sheep model of persistent AF, leading to myocyte hypertrophy, interstitial fibrosis, and ion channel remodeling, all of which would occur relatively slowly but reach critical levels when AF becomes persistent at a median time of about 2 mo: (1) Oxidative stress by ROS released either by NOX2/4 or mitochondria is the first consequence, the persistence of which leads to shortened APD and RF through reducing rapid L-type Ca^{2+} current and increasing inward rectifier K^{+} current promoting the formation and stabilization of rotor that world in a vicious cycle to preserve sustained high electrical activity; and (2) Inflammation leads to profibrotic signaling in response to cardiac injury by promoting fibroblast-to-myofibroblast trans-differentiation leading to either through increased expression of TRP channels or miR-21 resulting in structural remodeling by atrial dilation and fibrosis that maintains AF
Risk factors	(1) Older age; (2) A history of myocardial infarction; (3) Renal dysfunction; (4) Raised D-dimer levels; and (5) Hypertension	Risk factors for progression to more persistent forms of AF among patients with paroxysmal AF and varying degrees of CVD per HATCH score is[62]: (1) Heart failure; (2) Older age; (3) Previous transient ischemic attack or stroke; (4) Chronic obstructive pulmonary disease; and (5) Hypertension
Outcomes	Among patients hospitalized with COVID-19 infection, 5.4% could develop NOAF. All-cause mortality rates are 45.2% *vs* 11.9% and MACE is 23.8% *vs* 6.5% for patients with *vs* without NOAF[67]	Among patients with persistent AF all-cause mortality rate is 4.41% and MACE is 5.09%[67]
Treatment	The initial approach is to enhance the treatment of underlying factors. Hemodynamic instability warrants immediate cardioversion, provided that the risk of embolism is low	Hemodynamic instability warrants immediate cardioversion provided that the risk of embolism is low[15]
	Rate control therapy is preferred over rhythm control unless hemodynamic instability warrants the addition of rhythm control *e.g.*, with amiodarone	A similar efficacy of rate *vs* rhythm control in all-cause mortality and MACE had been noted. Thus, current guidelines recommend an individualized decision taking into consideration that a rhythm control is most likely to fail in patients with long-term persistent AF (> 1 yr), in whom atrial substrate alteration is greatest
	Anticoagulation: Unfractionated heparin, LMWH is safe to use. Use DOACs with caution as interact with some antiviral medications. VKAs induce a state of vitamin K deficiency that could potentially influence susceptibility to contracting COVID-19	The choice of anticoagulation should be individualized based on the patient's comorbidities, like other indications for anticoagulation and renal function

COVID-19: Coronavirus disease 2019; ECM: Extracellular matrix; NOAF: New-onset atrial fibrillation; AF: Atrial fibrillation; ROS: Reactive oxygen species; ACE2: Angiotensin-converting enzyme-2; SNS: Sympathetic nervous system; AP: Action potential; PNS: Peripheral nervous system; ERP: Effective refractory period; APD: Action potential duration; TRP: Transient receptor potential; CVD: Cardiovascular disease; MACE: Major adverse cardiovascular events; LMWH: Low molecular weight heparin; DOAC: Direct oral anticoagulant; VKA: Vitamin K antagonist; ANS: Autonomic nervous system.

days). These alterations result in the shortening of the atrial action potential duration and refractory period, promoting the formation and stabilization of rotors of persistent AF. Subsequently, intracellular Ca^{2+} overload ensues, promoting triggered activity and apoptosis[63,64].

Nevertheless, Ca^{2+} overload, together with atrial dilatation, mitochondrial ROS, and activation of inflammatory and pro-fibrotic pathways, progressively alters gene expression. The eventual outcomes of these persistent alterations entail myocyte hypertrophy, interstitial fibrosis, and ion channel remodeling. When these processes collectively escalate to a critical threshold, it could lead to the persistence of AF. In an animal study, after two months of tachypacing, the arrhythmia progressed to persistent AF[65]. However, no study is available on the same time frame in COVID-19 patients.

In addition to Ang II, sustained AF is fostered by the release of proinflammatory cytokines and tissue injury mediators such as TNF-α, IL-6, and IL-8. While the initial purpose of this cascade is to facilitate a beneficial "self-destroy and rebuild" process[66], its continuous activation is a widely recognized initiator of fibroblast-to-myofibroblast transformation leading to atrial remodeling[8]. Therefore, the prolonged presence of inflammatory cascades and myocyte apoptosis, whether through spike protein binding to cardiomyocyte, cytokine storm, prolonged hypoxemia, or altered ANS, could also potentially lead to ion channel dysfunction and excessive matrix production, likely generating electrical and structural remodeling and predisposing persistent AF.



DOI: 10.5492/wjccm.v12.i5.236

Figure 2 Long-term studies needed to assess progression from coronavirus disease 2019-related new-onset atrial fibrillation to more sustained forms of atrial fibrillation. COVID-19: Coronavirus disease 2019; NOAF: New-onset atrial fibrillation; ACE2: Angiotensin-converting enzyme-2; AF: Atrial fibrillation.

Conversely, potential risk factors associated with COVID-19-related NOAF, such as advanced age, hypertension, and a previous myocardial infarction, exhibit resemblances to independent factors that are linked with the progression toward persistent AF[62].

Progression from paroxysmal to more sustained forms of AF is associated with increased adverse events, including thromboembolic events, although the long-term outcomes of COVID-19-related NOAF infection are unknown (Figure 1) [67]. Early recognition of COVID-19-related NOAF is essential due to the high mortality risk associated with it. It is unknown if the management of COVID-19-related NOAF should follow the same pattern as routine management of paroxysmal or persistent AF. The disturbed coagulation system resulting from COVID-19 infection appears to elevate the potential for thromboembolic events in individuals with NOAF, although this necessitates additional research and confirmation.

While the conclusions drawn from this review are limited due to its non-experimental nature, it is evident that among various factors contributing to the development of COVID-19-related NOAF, some have the potential to perpetuate AF. These factors include modulation of myocardial ACE2 expression, spike protein binding, cytokine storm, endothelial dysfunction, increased permeability, and hypoxemia, which have the potential to induce atrial, ECM, or electrical remodeling, thereby perpetuating AF. To gain a more comprehensive understanding, further fundamental studies are required to explore the interplay between these factors. Additionally, prospective long-term studies are necessary to investigate the outcomes of patients who develop NOAF after experiencing COVID-19 infection in the long run (Figure 1).

CONCLUSION

Among several mechanisms that contribute to COVID-19-related NOAF, those exerting oxidative stress, such as modu-

lating myocardial ACE2 expression, endothelial dysfunction, spike protein binding, and cytokine storms, have the potential to contribute to changes in atrial structure, ECM, and electrical characteristics, which are common factors perpetuating AF. The electrophysiological substrate underlying AF in those who progress to sustained forms may differ from that of those who remain paroxysmal as maintaining sinus rhythm is generally more challenging in patients with persistent AF compared to those with paroxysmal AF, and persistent AF is associated with higher thromboembolic risks. The long-term outcomes of NOAF, including the persistence of AF after COVID-19 infection, remain unknown. Long-term prospective studies are needed to follow up on patients with COVID-19-related NOAF to address this knowledge gap.

FOOTNOTES

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MINIREVIEWS

Narrative review of traumatic pneumorrhachis

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Abstract

Pneumorrhachis (PR) is defined as presence of free air in the spinal canal. Traumatic PR is very rare, and its exact incidence and pathogenesis is unknown. A comprehensive literature search was performed using the PubMed, Cochrane Library, Google Scholar and Scopus databases to identify articles relevant to traumatic PR published till January 2023. A total of 34 resources were selected for inclusion in this narrative review. Traumatic PR can be classified anatomically into epidural and intradural types. In the epidural type, air is present peripherally in the spinal canal and the patients are usually asymptomatic. In contrast, in intradural PR, air is seen centrally in the spinal canal and patients present with neurological symptoms, and it is a marker of severe trauma. It is frequently associated with traumatic pneumocephalus, skull fractures or thoracic spine fracture. Computed tomography (CT) is considered to be the diagnostic modality of choice. Epidural PR is self-limited and patients are generally managed conservatively. Patients with neurological symptoms or persistent air in spinal canal require further evaluation for a potential source of air leak, with a need for surgical intervention. Differentiation between epidural and intradural PR is important, because the latter is an indication of severe underlying injury. CT imaging of the entire spine must be performed to look for extension of air, as well as to identify concomitant skull, torso or spinal injuries Most patients are asymptomatic and are managed conservatively, but a few may develop neurological symptoms that need further evaluation and management.

Key Words: Pneumorrhachis; Trauma; Intraspinal air; Spinal emphysema

Core Tip: Traumatic Pneumorrhachis (PR) is defined as presence of free air in the spinal canal, and is very rare. Differentiation between epidural and intradural PR is important, because the latter is an indication of severe underlying injury. Computed tomography imaging of the entire spine must be performed to look for extension of air, as well as identify concomitant skull, torso or spinal injuries. Most patients are asymptomatic and are managed conservatively, but a few may develop neurological symptoms that need further evaluation and management.

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INTRODUCTION

Pneumorrhachis (PR) is defined as presence of free air in the spinal canal. The term was coined by Newbold *et al*[1] in 1987, but the pathology was first described by Gordon in 1977[1,2]. The etiology of PR could be iatrogenic, non-traumatic or traumatic[3]. Iatrogenic causes include lumbar puncture, epidural anesthesia or spinal surgery. Non-traumatic causes include violent coughing or vomiting, spinal dural arteriovenous fistula, gas-producing infections, epidural abscess, malignancy, radiotherapy or drug use[4-6].

Traumatic PR is very rare, and its exact incidence is not known[7]. It has been mainly described in the radiology and spine surgery literature, and the emergency medicine specialists are less familiar with this rare presentation. This clinical review discusses the etiology, pathogenesis and management of traumatic PR.

METHODOLOGY

A comprehensive literature search was performed using the PubMed, Cochrane Library, Google Scholar and Scopus databases to identify articles and case reports relevant to traumatic PR published till January 2023. The following search terms were used: "traumatic pneumorrhachis", "spinal emphysema", "epidural emphysema", "intraspinal air", "spinal pneumatosis" and "pneumomyelogram". Studies published in English were included, and the reference lists of relevant articles were also searched. A total of 34 resources were selected for inclusion in this narrative review. Of these, there was 1 systematic review, 2 retrospective studies, 2 narrative reviews and 29 case reports/series. Publications due to non-traumatic or iatrogenic causes were excluded from this review.

DISCUSSION

Classification and etiology

Traumatic PR is very rare. Blunt trauma accounted for 80% of cases of traumatic PR, while the remaining were secondary to penetrating trauma. PR can be classified anatomically into epidural and intradural (subdural/subarachnoid) types, based on location of air in the spinal canal. In the epidural type, air is present peripherally in the spinal canal (Figure 1), while in intradural PR, the air is seen centrally within the spinal canal in the subarachnoid space[8].

There was no correlation between the type of PR and the mechanism of injury, with 60%-65% of the traumatic PR cases being epidural PR, and the remaining 35%-40% cases had intradural PR[4]. Traumatic PR is often localized to isolated cervical, thoracic or lumbar regions, but there are have been limited case reports of PR in two contiguous spinal regions, or even along the entire spinal canal[3].

The location of air within the spinal canal depends on the site of injury causing the air leak, volume of air, capacity of the intraspinal space, and patient position. In epidural PR, air usually collects in the posterior epidural space as result of reduced resistance from the connective tissue, compared to the rich vascular network in the anterior epidural space[9]. But epidural air can also be present in the anterior or lateral epidural space (Figure 2).

There has been a reported case of PR secondary to penetrating spinal injury without an associated skull fracture[10]. In absence of penetrating injury, it can be seen in patients with head injury and basal skull fracture, likely secondary to accompanying tear in the dura mater[11]. PR was reported in a paediatric patient with associated T3 spine fracture, highlighting the need for evaluation for occult spinal fractures in patients without a clear etiology of PR[12]. The presence of traumatic PR is associated with significant injury of the skull, chest, abdomen, pelvis or spine[13], and the patient may have concomitant pneumocephalus, pneumothorax, pneumomediastinum, or subcutaneous emphysema.

Pathophysiology

The exact pathophysiology of traumatic PR is not known. One of the possible mechanisms is that in patients with base of skull fracture, air in the cranial cavity (pneumocephalus) extends inferiorly through the foramen magnum in the spinal canal leading to PR[14]. In patients with pneumothorax or pneumomediastinum, air migrates along fascial planes of mediastinum into the epidural space through the neural foramina alongside the neurovascular bundle. Due to lack of a

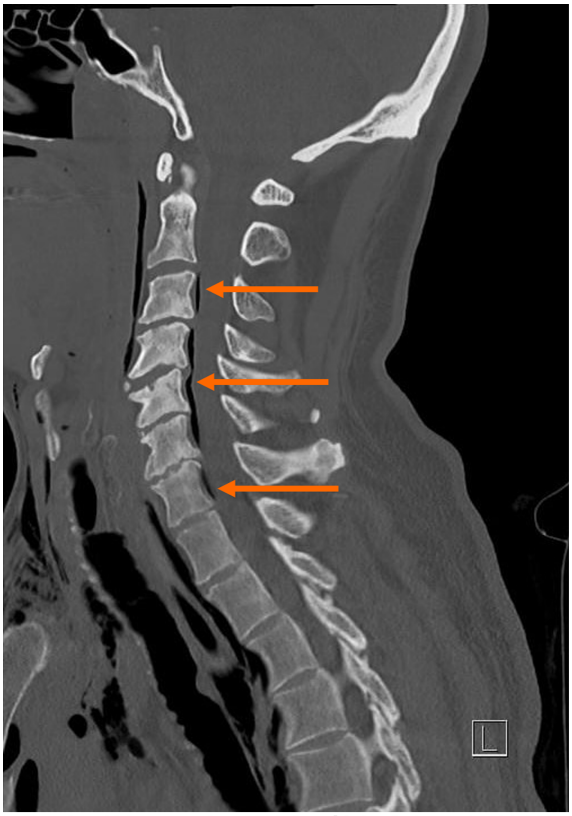

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Figure 1 Sagittal computed tomography scan demonstrating peripheral pneumorrhachis in the spinal canal from the level of C3 to C7 (marked by arrows), suggestive of epidural pneumorrhachis.

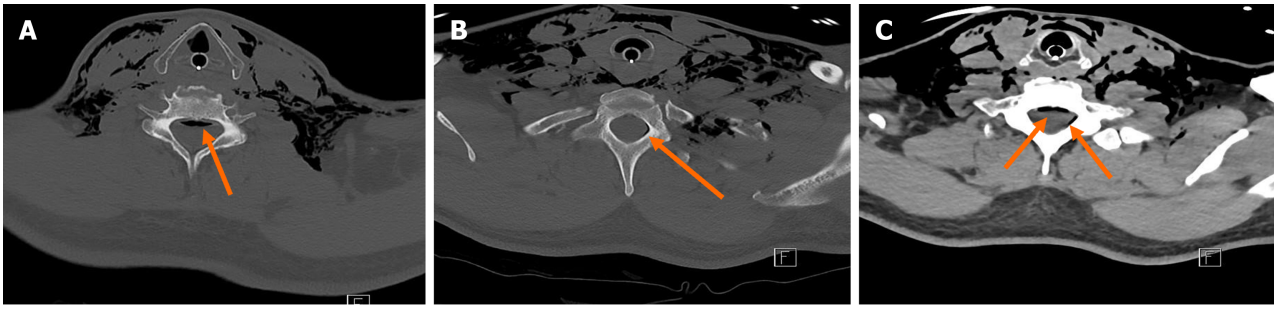

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Figure 2 Axial computed tomography scan demonstrating epidural pneumorrhachis (marked by arrows) in the anterior spinal canal, left lateral spinal canal and both anterior and lateral part of spinal canal. A: Anterior spinal canal; B: Left lateral spinal canal; C: Both anterior and lateral part of spinal canal.

fascial barrier between the posterior mediastinum and the spinal canal, air can enter the epidural space without any significant trauma to the surrounding structures[15,16]. Another proposed theory is entry of air in the epidural venous plexus due to embolization of small mediastinal veins[3]. It could also occur due to dural tear following blunt trauma to the trachea or the lungs[17,18]. Air can reach the spinal canal *via* the intervertebral veins which anastomose with the lumbar veins which are damaged due to pelvic fracture[19,20]. Hollow viscus injuries, like oesophageal perforation associated with cervical spine fractures, or duodenal or jejunal rupture after seat belt injuries and associated spine fracture can also result in PR[21,22]. There has also been a report of intradural PR secondary to subarachnoid- pleural fistula after blunt thoracic trauma[23].

Clinical presentation

Although challenging, it is important to differentiate between epidural and intradural PR, because the etiology, pathogenesis and clinical presentations are different[15]. Epidural PR is relatively less common, and is associated with traumatic pneumothorax, pneumomediastinum or subcutaneous emphysema[24]. These patients are usually asymptomatic, with only two cases reported in the literature who suffered from neurological deficits[25]. In contrast, intadural PR is frequently associated with traumatic pneumocephalus, skull fractures or thoracic spine fracture, and is a

marker of severe trauma. These patients often experience associated neurological symptoms like radicular pain, limb weakness, paraesthesia, and sphincter dysfunction. Some authors suggest that the presence of PR with neurological deficit suggests a focal spinal instability due to an initial fracture-dislocation which reduced spontaneously[14,26,27]. These patients may suffer from potential complications such as tension pneumocephalus or meningitis[28]. Although tension PR has not been reported in trauma patients, intraspinal air can be trapped in the spinal canal due to a one-way valve mechanism, leading to increased pressure, which in turn causes progressive worsening of the neurological deficits.

Diagnosis

The majority of the cases of traumatic PR are asymptomatic, thus making its clinical diagnosis extremely challenging. It is usually diagnosed incidentally during radiological evaluation for other injuries[4]. On plain radiography, PR appears as a linear lucency along the spinal canal in the lateral views of cervical and thoracic spine or chest radiographs. It has a sensitivity of about 48% and is only able to detect large volume PR[29]. Computed tomography (CT) is considered to be the diagnostic modality of choice, with a sensitivity of 100%[11]. Even on CT scan, it may sometimes be difficulty to differentiate between intradural and extradural PR, and additional testing with magnetic resonance imaging or intrathecal contrast CT can help in this differentiation[8,29].

Management

As the incidence of traumatic PR is rare with varied underlying etiology, there are no definitive guidelines for its management, and the current management strategies are based on individual case reports[30]. Upon identification of this condition on the initial CT scan, PR is usually managed conservatively if patients are asymptomatic. Traumatic PR usually resolves spontaneously in 96% of the cases[4]. However, the patient requires monitoring for development of any new neurological symptoms[30]. There is no indication for repeat imaging as air in the spinal canal absorbs spontaneously in majority of the patients.

If PR is detected, the physician should evaluate the patient for major underlying injuries such as base of skull fracture, pneumocephalus, pneumothorax, pneumomediastinum or hollow abdominal viscera[4]. Also, in a rare instance, if the patient develops neurological symptoms or signs of raised intracranial pressure, further evaluation for a potential source of air leak is needed. Early surgical or neurosurgical consultation for surgical intervention may be required in these patients to treat the underlying causes of traumatic PR. Routine use of prophylactic antibiotics with an aim to prevent meningitis in these patients is not recommended in both epidural and intradural PR[4,13]. Rarely, traumatic PR can serve as a potential entry point for infection in the spinal canal, and antibiotics should be initiated if the patient shows any signs or symptoms of systemic infection (meningitis) or sepsis[5].

Epidural PR is generally benign and self-limiting, and the air gets spontaneously reabsorbed into the blood without any recurrence. Patients are generally managed conservatively, and they recover without any neurological sequelae[4,31]. The management of epidural PR depends on management of the underlying cause like pneumothorax or pneumomediastinum. In the case of traumatic pneumothorax, the patient may need to be undergo chest tube insertion or surgery in case of persistent air leak[32].

Presence of intradural/subarachnoid air in the spinal canal is a marker of concomitant major trauma like base of skull fracture, spinal fracture, or lung or hollow abdominal viscus injury[32]. These cases need to be referred promptly to the relevant specialty like neurosurgery or cardio-thoracic surgery for definitive management of the associated serious injuries. Persistent cerebrospinal fluid leak can be treated by repair of dural tears or placement of a lumbar spinal catheter [12]. Intradural PR may be complicated by tension pneumocephalus and meningitis[33]. Tension PR can occur rarely due to the unidirectional valve mechanism, wherein the air can occupy a significant portion of the intradural space increasing the intraspinal pressure, and by extension leading to raised intracranial pressure as well[27]. This can lead to increasing pain or development of neurologic deficits in the patient, requiring urgent treatment by neurosurgery or interventional radiology, with interventions such as air decompression using a Tuohy needle, surgical decompressive laminectomy or repair of the dural tear[34].

CONCLUSION

Traumatic PR is a rare phenomenon, often found incidentally on CT scan. Differentiation between epidural and intradural PR is important, because the latter is an indication of severe underlying injury, with potential complications of tension pneumocephalus or meningitis. CT imaging of the entire spine must be performed to look for extension of air, as well as identify concomitant skull, torso or spinal injuries. Traumatic PR is usually self-limiting, with most patients being managed conservatively, but a few may develop neurological symptoms that need further evaluation and management.

FOOTNOTES

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MINIREVIEWS

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Nishant Kumar

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Abstract

As the treatment options, modalities and technology have grown, mortality in intensive care unit (ICU) has been on the decline. More and more patients are being discharged to wards and in the care of their loved ones after prolonged treatment at times and sometimes in isolation. These survivors have a lower life expectancy and a poorer quality of life. They can have substantial familial financial implications and an economic impact on the healthcare system in terms of increased and continued utilisation of services, the so-called post intensive care syndrome (PICS). But it is not only the patient who is the sufferer. The mental health of the loved ones and family members may also be affected, which is termed as PICS-family. In this review, we shall be reviewing the definition, epidemiology, clinical features, diagnosis and evaluation, treatment and follow up of PICS. We shall also focus on measures to prevent, rehabilitate and understand the ICU stay from patients' perspective on how to redesign the ICU, post ICU care needs for a better patient outcome.

Key Words: Post intensive care syndrome; Post intensive care syndrome-family; Guidelines; Post intensive care syndrome clinics; Impediments

Core Tip: Core priorities of critical illness survivors should be a part of the stakeholder-driven clinical guidelines and quality measures for post-intensive care unit (ICU) care. Future research should extend these findings among other stakeholders (*e.g.*, family members and healthcare providers) and determine barriers and facilitators to patient-centered post-ICU care. It is not too far-fetched to think of a multi-professional patient centric critical care team that provides the right care to the right patient at the right time throughout and after the acute illness is over. What we need to change to bring in the future is how we use data, devices, and new technologies to continue to strive toward that goal.

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INTRODUCTION

As the treatment options, modalities and technology have grown, mortality in intensive care unit (ICU) has been on the decline[1]. More and more patients are being discharged to wards and in the care of their loved ones after prolonged treatment and sometimes in isolation. These survivors have a lower life expectancy and a poorer quality of life. They can have substantial familial financial implications and an economic impact on the healthcare system in terms of increased and continued utilisation of services[2].

Though the intensivists may have cured the underlying disease, the process and time spent in the ICU far from family and loved ones predispose them to a new set of diseases which warrant special attention in terms of prevention, recognition, diagnosis, treatment and support of the so-called post intensive care syndrome (PICS)[1,2]. But it is not only the patient who is the sufferer. The mental health of the loved ones and family members may also be affected, which is termed as PICS-family (PICS-F)[1,2].

In this review, we shall be reviewing the definition, epidemiology, clinical features, diagnosis and evaluation, treatment and follow up of PICS. We shall also focus on measures to prevent, rehabilitate and understand the ICU stay from patients' perspective on how to redesign the ICU, post ICU care needs for a better patient outcome.

Definitions

PICS may simply be defined as a new or worsening function in one or more following domains: Cognitive, psychiatric and/or physical. This includes all adult patients who after being discharged from the ICU reside in acute rehabilitation units, nursing facilities or at home. Patients with traumatic brain injury and stroke are excluded, and since this is a relatively new concept, the timeline for the occurrence after discharge is not defined[1].

PICS-F encompasses the acute and chronic psychological effects among a patient's family members that occur during the critical care or following death or discharge of the patient from the ICU[1,2]. An expansion of PICS has been proposed with a focus on the contributing factors, addition of potential new components which include: Osteopenia, metabolic disorders, endocrine dysfunction, vulnerability, fatigue, sleep disorders and chronic pain, and consequences thereof (Figures 1-3)[2].

Epidemiology

Approximately 50% of ICU survivors, while out of those requiring life support, 64% at three months and 56% at 12 mo, suffer from either one or more of the three components of PICS[3-8]. Impairment of the cognitive domain has been reported with an incidence of 25%-78%[4]. The BRAIN-ICU study has reported that while 6% had cognitive impairment at baseline, 40% had impairment similar to traumatic brain injury and 26% similar to mild dementia at three months. These deficits persisted for most patients at 12 mo post discharge[6].

Depression, anxiety and post-traumatic stress disorder (PTSD) are the most common psychiatric disorders reported among survivors of critical illness. The absolute risk varies from 1%-62% in literature, with higher rates in acute respiratory distress syndrome (ARDS) survivors[9]. The reported incidence of depression is 28% and that of PTSD is 22% respectively in systematic reviews[10-12].

Twenty five percent or more ICU survivors are left with ICU acquired weakness as the most common form of physical impairment. Mobility at six months was problematic in 64%[3], while 73% complained of moderate or severe pain. As much as 26% of patients could not perform normal daily activities fully and this persisted in most patients at the end of one year[5,6]. The presence of neuropsychological and functional disability that occurs after survival leads to substantial public health burden and a negative impact on the family income[3].

Risk factors

These can be broadly classified into either pre-existing or ICU specific factors. Any of the factors responsible may be preexisting or acquired during or after the ICU stay[8]. It is not clear however, whether ICU related factors introduce morbidity or merely enhance the pre-existing neuropsychological and functional decline and to what extent[13].

Risk factors for the cognitive domain are: delirium[5], prior cognitive deficit[14], sepsis[15], ARDS[16] and others such as alcoholism, hypoxemia, hypotension, glucose dysregulation, respiratory failure, blood transfusions, benzodiazepines, transfusions and renal replacement therapy[5,15-20]. The possible mechanisms include ischemia, neuroinflammation and disruption of white mater integrity in areas involved in memory[16,21-23].

The psychiatric factors are similar to cognitive dysfunction, pre-existing anxiety, depression and PTSD. Female sex, tall stature in males, age < 50 years and low level of education increase the risk. Glucocorticoid administration during critical illness may reduce the levels of cortisol, hence offering protection against development of PTSD[16,24-30].

The physical factors include pre-existing functional disability, fraility, cognitive impairment, prolonged mechanical ventilation (> 7 d), sepsis, multi-organ failure, prolonged bed rest[31-33], and others like ARDS, hyperoxia, use of vasoactive agents and steroids[15,30,34]. The role of neuromuscular blockers in developing physical component of PICS is under suspicion and more studies are required to prove it conclusively[31,35,36].

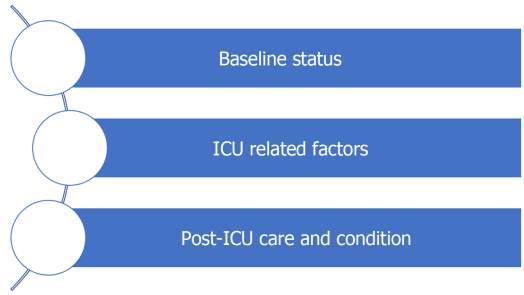

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Figure 1 Contributing factors for post intensive care syndrome. ICU: Intensive care unit.

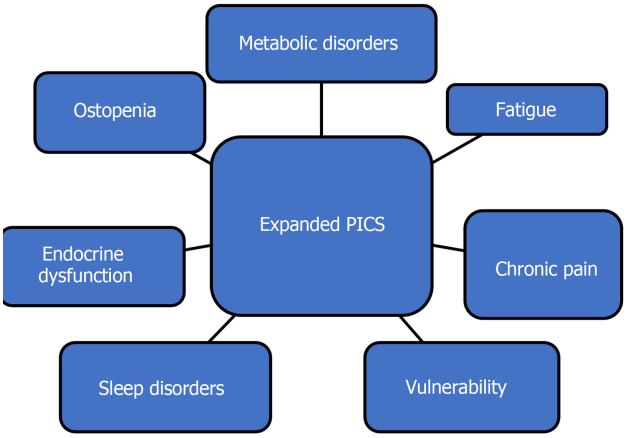

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Figure 2 Potential new components of post intensive care syndrome. PICS: Post intensive care syndrome.

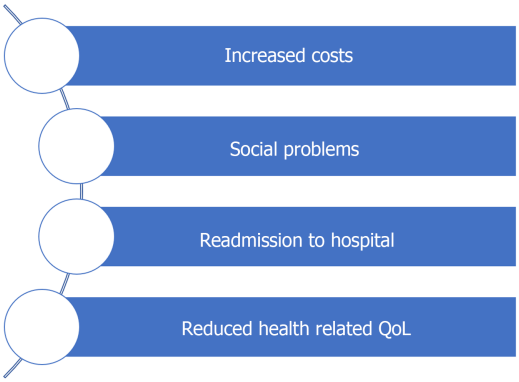

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Figure 3 Consequences of post intensive care syndrome. QoL: Quality of life.

Clinical presentation

The common symptoms include weakness, poor mobility, poor concentration, fatigue, anxiety, and depressed mood. These symptoms are either new or represent worsening after the critical illness. The clinical features are depicted in Figure 4[1,7,16,31,32,37].

Diagnosis

A high index of suspicion is required for its identification. There are no formal screening or definitive tests available for its diagnosis[38,39]. The society of critical care medicine advocates an early and serial assessment which begins at admission to ICU, as a part of ICU to ward over and involves predischarge functional assessment, followed by 2-4 wk post discharge and throughout recovery. Those at high risk due to pre-existing or ICU related risk factors should be prioritised for evaluation[40]. All three domains are evaluated using a systematic screening approach beginning two to four weeks after hospital discharge (Figure 5)[33,40-44].

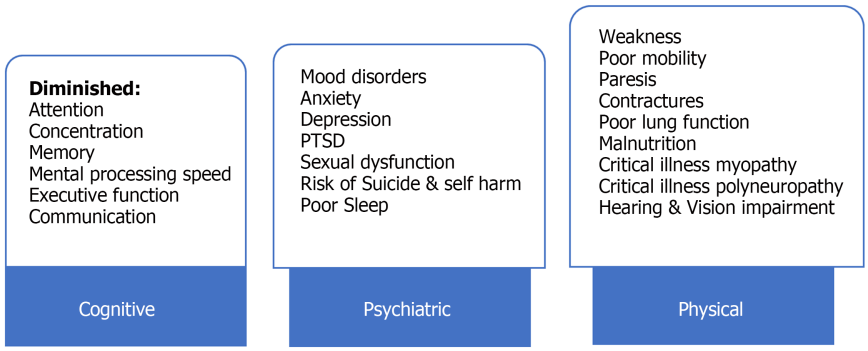

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Figure 4 Clinical features of post intensive care syndrome. PTSD: Post-traumatic stress disorder.

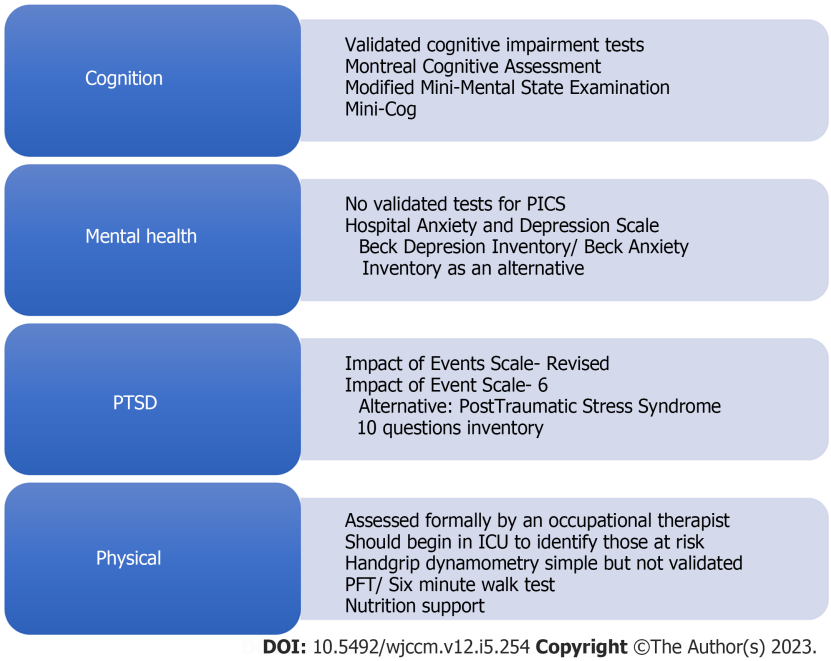

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Figure 5 Evaluation tools for diagnosis of post intensive care syndrome. PTSD: Post-traumatic stress disorder; PICS: Post intensive care syndrome; ICU: Intensive care unit; PFT: Pulmonary Function Test.

It is also important to rule out other causes which may cause disability and loss of function after ICU discharge. Most important of these include pre-existing illness which may persist and remain unchanged, thus excluding a diagnosis of PICS. The worsening or appearance of new illness may be difficult if the pre-existing illness is not known. Help may be sought from family members to obtain an extended history and pre admission status may help confirm the diagnosis. Apart from above, certain conditions may mimic PICS, including but not limited to stroke, hypo/hyper-thyroidism, vitamin B12 deficiency, anaemia, malignancy and obstructive sleep apnoea. These can usually be detected by routine laboratory testing or imaging, but should be directed based on history and examination findings. Rhabdomyolysis, cachetic myopathy and Guillain Barre syndrome may be mistaken for ICU acquired weakness, but usually obvious on admission[40].

A transient hospital- associated disability (post-hospital syndrome) may be confused with PICS. However, this is transient, seen in elderly and associated with a number of functional disabilities. PICS, on the other hand, may afflict all ages and runs a protracted course[45].

Prevention

All patients being admitted into the ICU facility should undergo a psychological evaluation that includes pre-admission history, ability to adapt to stress in past, medication history, current mental and clinical status and environmental and family factors[46].

An ABCDEF bundle approach is warranted to prevent PICS especially in patients receiving mechanical ventilation. This approach includes: (1) Awakening (minimal, light sedation, daily interruption, minimising use of benzodiazepines); (2) Breathing (disease appropriate ventilation, ventilator liberation practices including spontaneous breathing trails); (3) Coordination of care and communication among various disciplines; (4) Delirium monitoring and management; (5) Early

ambulation/exercise; and (6) Family empowerment and engagement[47-49].

Additional interventions to prevent PICS include avoiding hypoglycaemia and hypoxemia, maintenance of ICU diary prospectively by the family members, health care providers, or both during the patient's ICU stay, has shown to decrease symptoms of PTSD, and can be used as a holistic tool to provide support and care to the patient and family[50]. Creating post-ICU clinics to provide follow-up counselling and support to the patients and family[51]. Maintaining good nutritional status and adequate sleep of the patient. Progressive feeding in the early phase for both proteins and calories is essential to prevent overfeeding and high caloric intake. After 4-7 d, high-protein intake and sufficient calories, essential to prevent further loss of muscle mass and function, should be initiated. High-protein targets either by prolonged tube feeding or by enhanced high-protein oral nutrition (supplement) intake should be ensured post discharge [52].

The different phases of critical illness and recovery can be classified as acute illness, hospital recovery, and early and late post discharge recovery. Table 1 summarizes the various phases of critical illness and its consequences, which may be amenable to interventions that attempt to prevent, ameliorate, or treat the underlying impairments of PICS. Identification of the issues associated with each phase encourages development of targeted strategies to mitigate the impediments to complete recovery[53].

Treatment

The clinician should endeavour to treat each component and seek appropriate post ICU discharge services such as cognitive, mental health, physical therapy, occupational rehabilitation and social/family support. Early physical rehabilitation and nutrition along with psychological and familial support right from the early recovery phase within the ICU itself may improve outcomes (Figure 6)[54-57]. Of late, the primary involvement of rehabilitation therapists and psychosocial support have emerged to be the mainstay of the treatment. While the intensivist may ameliorate and prevent the development of PICS, therapy beyond the walls of ICU lies outside the domain of the intensivist[40].

Follow up

The exact period for follow up is not known, but may extend up to years every 2-3 mo post discharge. There is no set protocol and it should be individualised to the disease and needs of each patient. The multidisciplinary team should include specialist providers, social services, occupational and physical therapists[40].

Communication between the care givers and patients should be optimised. PICS clinics are specialised clinics which recognise the need for the care of patients and families with medical, mental health, social support and counselling requirements. Post pandemic, e surveys and tele-medicine have been incorporated for far to reach areas or where expert consultation is required in the absence of available specialists[40]. Peer support groups much like alcoholic anonymous, is being attempted to mitigate PICS and may go a long way in providing help and therapy to these patients[58,59].

PICS-F

Family provides an unyielding and strong support to the individual. Just as the family has an effect on individual, the family itself cannot remain unaffected by the suffering of the individual. Over half of the family can be affected psychologically by the critical illness in of a member, which may persist for months to years. This is termed as PICS -F.

The risk factors may be lower educational level, being the decision maker, child or spouse of the patient, long term stay, less social and financial support, death of the patient and poor communication between the staff[60,61]. Usually family members present with anxiety, depression, PTSD, sleep deprivation, complicated grief, and financial stress[60]. Diagnosis is based on presence of any psychological sequelae that is directly attributable to the critical illness of a loved one. This can however be prevented while the patient in still in ICU by liberalised family presence, structured communication approaches and increasing access to information[62-64]. Additional measures which may reduce the incidence are use of a trained nurse though that may induce additional financial burden, participation in bedside care and keeping a diary to reduce PTSD[65]. The treatment modalities remain the same as for the patients suffering from PICS.

FUTURE TRENDS

Seamless care integration appears to be a key factor in ensuring optimal continuum of care for survivors of critical illness. With growing ICU survivorship and increasing burden of PICS, it is imperative to integrate post-acute care services targeting residual impairments into the discharge process. It may aid post-discharge recovery, but also optimize resource use utilising bundled episode-based care[66].

Patients' ICU and post-ICU experiences are challenging, with little or no preparation or support. There are no evidence-based, patient-centered guidelines for the interdisciplinary care teams to develop and execute care plans meeting patients' medical, social, and rehabilitation needs. Before these guidelines can be developed, it is necessary to understand patients' priorities during recovery. The patients want to feel safe, be comfortable, engage in mobility, participate in self-care, resume normal roles and routines, connect with people, assert personhood, ensure family well-being, go home, restore physical and psychological health and seek new experiences[66].

These core priorities of critical illness survivors should be a part of the stakeholder-driven clinical guidelines and quality measures for post-ICU care. Future research should extend these findings among other stakeholders (*e.g.*, family members and healthcare providers) and determine barriers and facilitators to patient-centered post-ICU care[66].

Table 1 Various phases of critical illness, its consequences amenable to interventions[53]

Phase of critical illness	Acute illness	Recovery	Early post-discharge recovery	Late post-discharge recovery
Desired outcome	Survival	Discharge home	Stay home and improving	Return to baseline
Location	ICU	Hospital ward	Home	Home
Impediments	(1) Late antibiotics or source control for sepsis; (2) Hospital-onset infection (*e.g.*, VAP, CABSI, CAUTI); (3) Lack of venous thromboembolism prophylaxis; and (4) High-tidal volume ventilation for ARDS	(1) Immobility; (2) Delirium; (3) Lack of rehabilitation; (4) Polypharmacy; (5) Prolonged catheterization; and (6) Disruption of circadian rhythm	(1) Post-intensive care syndrome; (2) Caregiver misinformation; (3) Fragmented care or inadequate follow-up; (4) Vague or incomplete discharge instructions; (5) Non-compliance to medication; (6) Absence of ME; (7) Inadequate rehabilitation; (8) Lack of subspecialist follow-up; and (9) Polypharmacy	(1) Post-intensive care syndrome; (2) Inadequate vocational rehabilitation; (3) Disrupted employment; (4) Patient and family financial burden; (5) Socioeconomic barriers to care (insurance, transport); (6) Fragmented or inadequate family support; and (7) Polypharmacy

The table was adapted from Brown SM *et al*[53]. VAP: Ventilator associated pneumonia; CABSI: Catheter associated blood stream infection; CAUTI: Catheter associated urinary tract infection; ARDS: Acute respiratory distress syndrome; ICU: Intensive care unit; ME: Medical equipment.

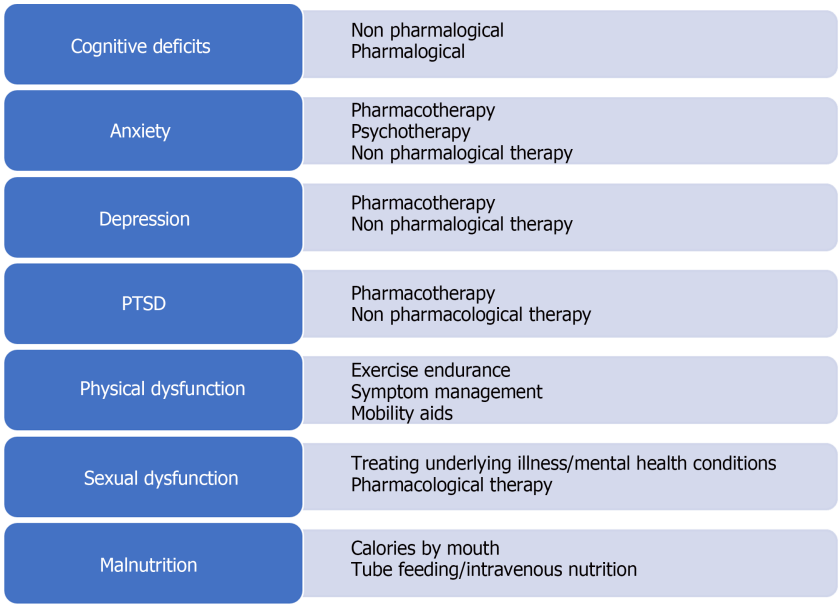

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Figure 6 Treatment modalities for post intensive care syndrome. PTSD: Post-traumatic stress disorder.

Some of the barriers that are needed to be crossed before a critical care team of the future can be created are: Enhancing collaboration and communication, evolving technologies, enhanced security of health data, evolving research techniques, provider responsibilities to improve patient care and innovative educational models[67]. To achieve this, the role of professional societies would be equally important to improve outcomes for a diverse population of critically ill and injured patients, expand and support a global network of critical care professionals and advocate for patients, families, and critical care professionals[67].

CONCLUSION

It is not too far-fetched to think of a multi-professional patient centric critical care team that provides the right care to the right patient at the right time throughout and after the acute illness is over. What we need to change to bring in the future is how we use data, devices, and new technologies to continue to strive toward that goal.

FOOTNOTES

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META-ANALYSIS

Systematic review and meta-analysis of seroprevalence of human immunodeficiency virus serological markers among pregnant women in Africa, 1984-2020

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Abstract

BACKGROUND

Human immunodeficiency virus (HIV) is a major public health concern, particularly in Africa where HIV rates remain substantial. Pregnant women are at an increased risk of acquiring HIV, which has a significant impact on both maternal and child health.

AIM

To review summarizes HIV seroprevalence among pregnant women in Africa. It also identifies regional and clinical characteristics that contribute to study-specific estimates variation.

METHODS

The study included pregnant women from any African country or region, irrespective of their symptoms, and any study design conducted in any setting. Using electronic literature searches, articles published until February 2023 were reviewed. The quality of the included studies was evaluated. The DerSimonian and Laird random-effects model was applied to determine HIV pooled seroprevalence among pregnant women in Africa. Subgroup and sensitivity analyses were conducted to identify potential sources of heterogeneity. Heterogeneity was assessed with Cochran's Q test and I^2 statistics, and publication bias was assessed with Egger's test.

RESULTS

A total of 248 studies conducted between 1984 and 2020 were included in the quantitative synthesis (meta-analysis). Out of the total studies, 146 (58.9%) had a low risk of bias and 102 (41.1%) had a moderate risk of bias. No HIV-positive pregnant women died in the included studies. The overall HIV seroprevalence in pregnant women was estimated to be 9.3% [95% confidence interval (CI): 8.3-10.3]. The subgroup analysis showed statistically significant heterogeneity across subgroups ($P < 0.001$), with the highest seroprevalence observed in Southern Africa (29.4%, 95%CI: 26.5-32.4) and the lowest seroprevalence observed in Northern Africa (0.7%, 95%CI: 0.3-1.3).

CONCLUSION

The review found that HIV seroprevalence among pregnant women in African countries remains significant, particularly in Southern African countries. This review can inform the development of targeted public health interventions to address high HIV seroprevalence in pregnant women in African countries.

Key Words: Human immunodeficiency virus; Pregnant women; Africa; Prevalence; Review; Meta-analysis

Core Tip: A meta-analysis reveals a 9.3% Human immunodeficiency virus (HIV) seroprevalence among pregnant women in Africa, with regional variations. Southern Africa reports the highest rates at 29.4%, whereas Northern Africa shows the lowest at 0.7%. These findings underscore the need for targeted public health interventions to tackle high HIV seroprevalence in pregnant women, especially in Southern African countries.

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INTRODUCTION

Human immunodeficiency virus (HIV) treatment guidelines, increased use of testing and counselling have resulted in a significant decrease in HIV rates in the general population during the 2010s, including in Africa[1-4]. Unfortunately, the impact of these interventions on pregnant women is less clear. According to the UNAIDS report (2023), 39 million people globally were living with HIV in 2022, and around 65% of these people lived in sub-Saharan Africa[5]. According to the same report, women and girls accounted for 63% of all new HIV infections in sub-Saharan Africa. A meta-analysis of participants recruited from 1984 to 2012 showed that HIV acquisition during pregnancy and postpartum was estimated at

3.8 [95% confidence interval (CI): 3.0, 4.6] per 100 person-years[6]. HIV incidence was higher during pregnancy and in Africa. A more recent meta-analysis revealed HIV incidence among pregnant women in sub-Saharan Africa remained significant at 3.6 (95%CI: 1.2-11.1)[7]. HIV causes maternal deaths between 5.9% and 17.9%[8-10]. HIV-positive pregnant and postpartum women are more likely to die than those without HIV. Moreover, the study estimated that 994 deaths per 100000 were caused by HIV in pregnant and postpartum women[11]. A more rapid progression of HIV-related illness or obstetric complications may contribute to this higher morbidity in HIV-positive pregnant women[12,13]. Besides health risks for mothers, HIV infection also increases the risks of mother-to-child transmission. HIV transmission from mother to child is also increased during pregnancy and after delivery[6,7]. A study has shown that the risk of mother-to-child HIV transmission during pregnancy is higher than that of chronic infections during pregnancy and postpartum[6]. A separate study found that mothers infected with HIV who don't receive antiretroviral therapy have an increased chance of having a preterm birth, a low birth weight, a small for gestational age, and a stillbirth in sub-Saharan Africa[14]. Several studies have explored the HIV seroprevalence among pregnant women in Africa, but a comprehensive review is needed. A meta-analysis of 15 studies found that 5.74% (95%CI: 3.96-7.53%) of pregnant women in Ethiopia had HIV with a high level of regional heterogeneity[15]. To guide future research and policy, it is essential to better understand the characteristics contributing to variations in HIV estimates among pregnant women. Furthermore, it is vital to develop effective strategies to reduce horizontal and vertical transmission of HIV during pregnancy and breastfeeding. We have summarized estimates of HIV seroprevalence among pregnant women in Africa and identified regional and clinical characteristics that contribute to variation in study-specific estimates.

MATERIALS AND METHODS

Study design

This study complied with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [16]. Study protocol was registered in PROSPERO (CRD42021272440). The registered protocol specifies objectives, inclusion and exclusion criteria, search strategy, data extraction, and statistical analysis plan.

Eligibility criteria

This systematic review and meta-analysis assessed the seroprevalence of HIV serological markers among pregnant women in 54 African countries up to February 2023. The study included pregnant women from any African country or region, irrespective of their symptoms, and any study design (cross-sectional, cohort, clinical trial, or case-control) conducted in any setting (hospital-based, antenatal clinics, or community-based). All laboratory diagnostic methods using any sample type to detect HIV serological markers were eligible. Studies with a sample size greater than 10, with enough data available, written in English and French were included. We chose studies with more than 10 samples for statistical robustness and reliability. When overlapping data appeared in different articles, the most recent or complete study was used. Review articles, comments, case reports, and studies with inaccessible full-text or abstracts were excluded from the study.

Article search strategy

Using Pubmed and Web of Science, African Index Medicus, and African Journal online, we reviewed the electronic bibliography for articles published till February 2023. Search terms related to HIV, pregnant women, and Africa were used (Supplementary Table 1). The reference lists of all relevant articles were reviewed to complete searches in the bibliographic database and identify possible additional data sources.

Article selection

Two investigators (Ebogo-Belobo JT and Kenmoe S) independently screened titles and abstracts of articles retrieved from electronic literature searches, and full texts of those eligible were obtained and assessed further for final inclusion. A PRISMA flow diagram was used to document the screening process. Consensus was reached between reviewers to resolve disagreements.

Data extraction from the included articles

Data extraction for this systematic review was conducted using a Google form by 14 study authors and verified by Ebogo-Belobo JT. The extracted data included information on the first author's name, year of publication, and participants' inclusion period. We also collected information about the study design and countries. A number of websites were used to obtain the WHO region, United Nations region, and World Bank Income Group from country information [17,18]. Other extracted information included single HIV diagnostic methods or algorithms of diagnostic methods, parity, gravidity, gestational age, educational level, sample size, HIV positive number, and type of HIV. In studies reporting results with undetermined HIV status, we excluded these patients from our estimations. In cases where detection algorithms were used, we considered the number of positives from the group of detection methods constituting the algorithm, not the results of the individual detection methods. Discrepancies encountered during data extraction were resolved through discussion and consensus among the authors.

Assessment of study quality

The risk of bias assessment was conducted using the Hoy *et al*[19], tool, which is designed to assess the risk of bias in

prevalence studies (Supplementary Table 2). This tool includes ten items related to the study's external and internal validity. Each item is scored as either low risk, high risk, or unclear risk of bias. Scores range from 0 to 10, with higher scores indicating lower bias risk. Each study included in the review was assessed for bias using the tool, with disagreements resolved through discussion and consensus.

Statistical analysis

This meta-analysis used the DerSimonian and Laird random-effects model to determine pooled HIV seroprevalence among pregnant women in Africa[20]. This was done by inputting numerators (HIV positive) and denominators (HIV tested) extracted from selected studies. Using the Clopper-Pearson method, we calculated 95%CI for individual studies. The results of individual studies were summarized using forest plots. The analysis was conducted with the 'meta' package in R v4.0.3 (R Foundation for Statistical Computing, Vienna, Austria), and the 'metaprop' function was applied to conduct the meta-analysis of single proportions to obtain HIV pooled seroprevalence[21,22].

Sub-group, metaregression, and sensitivity analyses

A subgroup meta-analysis and metaregression analysis were conducted to identify potential sources of heterogeneity. Several covariates were considered, including: (1) Regional characteristics such as countries, United Nations regions, WHO regions, and World Bank Income Groups; (2) HIV characteristics such as type of HIV and HIV diagnostic method; (3) participant characteristics such as gestational age, parity, gravidity and educational level; and (4) studies characteristics such as sample size, risk of bias, and study period. Only covariates with at least three data points were considered in the subgroup analyses. We included only cross-sectional studies and those with low bias risks in the sensitivity analyses.

Heterogeneity and publication bias

Heterogeneity was assessed using Cochran's Q test and I^2 statistics[23]. A statistically significant Cochran's Q test ($P < 0.05$) was indicative of true heterogeneity of effect sizes between studies. The I^2 statistic was calculated as an estimate of between-studies variance using the maximum likelihood method. I^2 values of 50% or higher indicate substantial heterogeneity. Publication bias was assessed with Egger's test, with a statistically significance ($P < 0.05$) suggesting evidence of funnel plot asymmetry[24].

RESULTS

Selection of included articles

We conducted a comprehensive search of relevant databases for studies on HIV seroprevalence and case fatality rates in pregnant women. After deduplication and initial screening, 619 full-text articles were evaluated. Ultimately, 248 articles met our inclusion criteria and were incorporated into the meta-analysis (Figure 1)[25-272].

Included article characteristics

We conducted a systematic review of studies published from 1987 to 2023 and reviewed 248 studies. The selected studies encompassed a total of 1374392 participants, with individual studies ranging from 11 to 243302 participants. There were no cases reported of HIV-positive pregnant women dying in the included studies, which only reported HIV seroprevalence among pregnant women. Included studies recruited participants between 1984 and 2020, with unclear inclusion periods in 25 studies (Supplementary Table 3). The studies were conducted in 37 African countries, with the majority being from Nigeria (23.0%), followed by Tanzania (8.5%), Ethiopia (7.3%), and South Africa (7.3%). The studies were mostly conducted in lower-middle-income countries (58.5%), followed by low-income countries (32.3%) and upper-middle-income countries (8.9%). Most studies were hospital-based (99.2%), with only one community-based study. The HIV diagnostic methods used in the studies varied, with the most common methods being algorithm of rapid antibody tests (29.0%), single rapid antibody test (14.9%), and indirect enzyme-linked immunosorbent assay (ELISA) (11.7%).

Risk of bias in the included studies

Out of the total number of studies included in the review (248), 146 (58.9%) were deemed to have a low risk of bias, while 102 (41.1%) were categorized as having a moderate risk of bias (Supplementary Table 4).

Meta-analysis

A meta-analysis was performed to estimate the overall HIV seroprevalence in pregnant women, as well as the seroprevalence among cross-sectional studies, among studies with sample size ≥ 100 and those with a low risk of bias. The overall HIV seroprevalence in pregnant women was estimated to be 9.3% (95%CI: 8.3-10.3). The seroprevalence among cross-sectional studies and among studies with a low risk of bias were slightly lower at 8.8% (95%CI: 7.7-9.8) and .8% (95%CI: 7.5-10.2) respectively, while the seroprevalence among studies with sample size ≥ 100 was 9.1% (95%CI: 8.1-10.2). All three analyses exhibited high heterogeneity ($P < 0.001$). The analysis of publication bias using the Egger test indicated evidence of significant publication bias ($P < 0.001$) in the meta-analysis (Supplementary Figure 1).

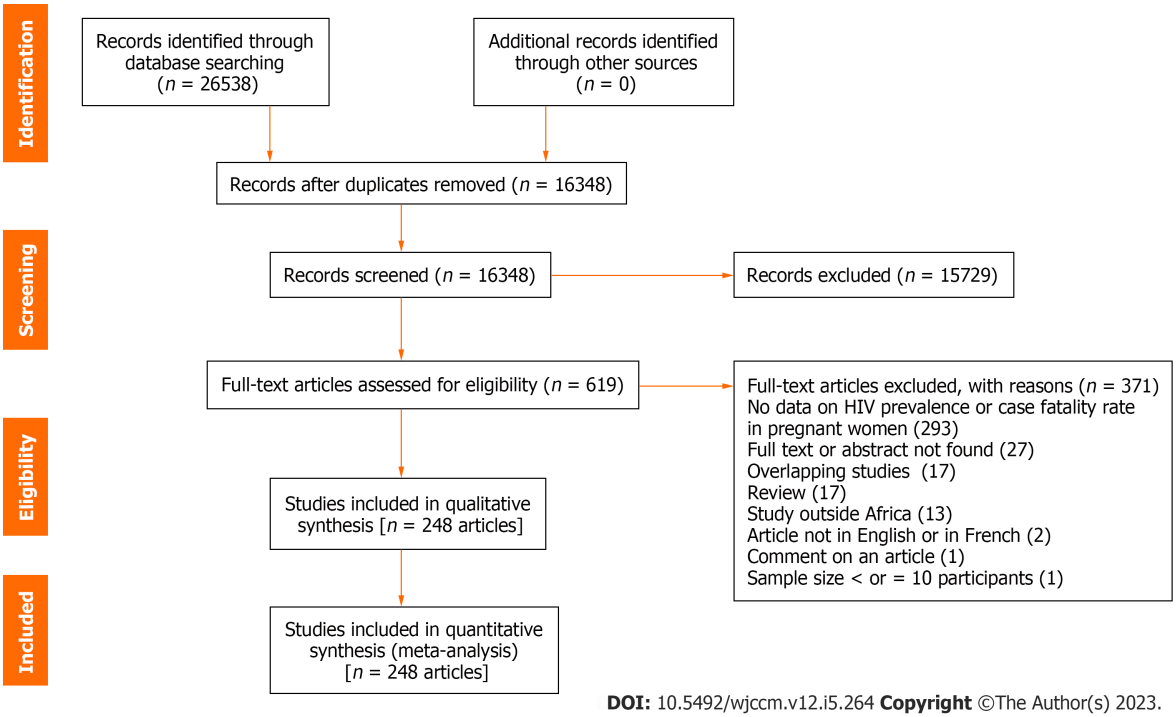

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Figure 1 Study selection.

Metanalysis by United Nation regions

Subgroup analysis was conducted to explore the difference in seroprevalence among different United Nation regions (Figure 2). The results showed statistically significant heterogeneity across subgroups ($P < 0.001$). The seroprevalence of the disease varied across different regions with the highest observed in Southern Africa (29.4%, 95%CI: 26.5-32.4) and the lowest in Northern Africa (0.7%, 95%CI: 0.3-1.3). Eastern Africa had a relatively high seroprevalence (11.7%, 95%CI: 10.2-13.2), while that in Western Africa was relatively low (6.2%, 95%CI: 5.2-7.3). Middle Africa had a moderate seroprevalence (4.8%, 95%CI: 4-5.8). The difference in seroprevalence between United Nation regions was statistically significant ($P < 0.001$).

Meta-analysis of other regional categories

HIV seroprevalence in pregnant women varied among different countries (Table 1). The highest seroprevalence was reported in South Africa (29.9%, 95%CI: 26.7-33.2), followed by Zimbabwe (25.7%, 95%CI: 16.4-36.3) and Malawi (18.7%, 95%CI: 14.2-23.8) (Figure 3). The lowest seroprevalence was reported in Sudan (1.0%, 95%CI: 0.4-1.7) and Senegal (0.7%, 95%CI: 0.5-0.9). The difference was statistically significant ($P < 0.001$). HIV seroprevalence in pregnant women varied significantly among WHO regions ($P < 0.001$) (9.5%, 95%CI: 8.4-10.6 in Africa *vs* 1.4%, 95%CI: 0.6-2.4 in Eastern Mediterranean) (Table 1). HIV seroprevalence during pregnancy was significantly different among World Bank Income Groups ($P < 0.001$) (Table 1). The highest seroprevalence was observed in upper-middle-income countries (24%, 95%CI: 19.9-28.3), followed by low-income countries (8.4%, 95%CI: 6.9-10.1) and lower-middle-income countries (8.1%, 95%CI: 7.2-9.1).

Meta-analysis by HIV characteristics

The HIV-1 seroprevalence was 8.7% (95%CI: 7.5-10) with a 95% prediction interval of 0.5-25.4%, while the HIV-2 seroprevalence was 1.2% (95%CI: 0.7-1.9) with a 95% prediction interval of 0-5.2% (Table 1). HIV-1 seroprevalence was significantly higher than HIV-2 ($P < 0.001$) (Figure 3). Regarding the HIV diagnostic method, the highest seroprevalence was found in the combination of rapid antibody test and indirect ELISA subgroup (15.9%; 95%CI: 1.3-42.1) (Table 1). The lowest seroprevalence was found in the algorithm (rapid antibody test, indirect ELISA, and enzyme immunoassay) subgroup (3.3%; 95%CI: 1.9-4.9). There was a statistically significant difference between subgroups ($P < 0.001$).

Meta-analysis by pregnant women's characteristics

The subgroup analysis by gestational age included 17 studies involving 36935 participants (Table 1). The HIV seroprevalence was highest in the second trimester with 9.6% (95%CI: 5.2-15), followed by the third trimester with 8.7% (95%CI: 5.2-13.1) and the least during the first trimester with a prevalence of 7.3% (95%CI: 3.5-12.2) but without statistical significance ($P = 0.902$). Ten studies were included in the parity subgroup analysis, involving 18015 participants. HIV seroprevalence was 6.7% (95%CI: 4-10) among nulliparous women, 6.5% (95%CI: 4.5-8.8) among multiparous women, and 5% (95%CI: 2.8-7.8) among primiparous women. There was no statistically significant difference between the different categories ($P = 0.690$). The subgroup analysis by gravidity included 17 studies with 53860 participants. HIV seroprevalence was 9.2% (95%CI: 5.5-13.7) among multigravidae and 6.5% (95%CI: 4.2-9.2) among primigravidae. HIV

Table 1 Summary of meta-analysis results for human immunodeficiency virus seroprevalence among pregnant African women from 1984 to 2020

	Prevalence (95%CI, %)	95% prediction interval	N Studies	N Participants	H (95%CI)	I^2 (95%CI)	*P* heterogeneity	*P* difference subtypes
Study design								< 0.001
Cohort	21.6 (15.5-28.4)	(2.6-51.8)	12	95334	19.6 (18.4-21)	99.7 (99.7-99.8)	< 0.001	
Cross-sectional	8.8 (7.7-9.8)	(0-30.6)	236	1276343	20.7 (20.4-21)	99.8 (99.8-99.8)	< 0.001	
Sampling								0.554
Non probabilistic	9.1 (8.1-10.2)	(0.1-29.9)	225	1228039	19.7 (19.5-20)	99.7 (99.7-99.8)	< 0.001	
Probabilistic	10.5 (6.4-15.5)	(0-45.1)	26	146353	24.4 (23.5-25.4)	99.8 (99.8-99.8)	< 0.001	
Timing of samples collection								0.936
Prospectively	9.2 (8.1-10.5)	(0-32.1)	205	942978	19.3 (19-19.6)	99.7 (99.7-99.7)	< 0.001	
Retrospectively	9.2 (6.9-11.8)	(0-31.2)	43	428329	26.6 (25.9-27.3)	99.9 (99.9-99.9)	< 0.001	
Countries								< 0.001
Angola	4.9 (0.6-13.2)	(0-100)	3	3008	7.8 (5.8-10.4)	98.3 (97-99.1)	< 0.001	
Burkina Faso	7.6 (5.6-9.9)	(1.6-17.5)	10	55644	6 (5.1-7.1)	97.2 (96.2-98)	< 0.001	
Cameroon	6.6 (5.4-7.9)	(2.5-12.3)	13	55429	5.5 (4.7-6.4)	96.7 (95.5-97.5)	< 0.001	
Democratic Republic of the Congo	3 (2-4)	(0.5-7.3)	6	21268	3.8 (2.9-5.1)	93.2 (87.9-96.2)	< 0.001	
Ethiopia	5.6 (3.1-8.8)	(0-25.1)	18	25412	9.2 (8.4-10.1)	98.8 (98.6-99)	< 0.001	
Ghana	3.4 (0.4-9)	(0-46.7)	4	4736	6.7 (5.2-8.8)	97.8 (96.3-98.7)	< 0.001	
Ivory Coast	13 (12.1-13.8)	(10.2-16)	9	74677	2.9 (2.2-3.8)	88.3 (80-93.2)	< 0.001	
Kenya	14.4 (10.4-18.8)	(1.8-36)	14	51495	13.2 (12.2-14.3)	99.4 (99.3-99.5)	< 0.001	
Malawi	18.7 (14.2-23.8)	(3.9-41.2)	12	130923	17.6 (16.4-18.9)	99.7 (99.6-99.7)	< 0.001	
Nigeria	6.1 (5-7.3)	(0.4-17.2)	57	84396	6.6 (6.2-7)	97.7 (97.4-98)	< 0.001	
Republic of the Congo	5 (4.1-6)	(2.3-8.7)	7	12841	2.4 (1.7-3.4)	82.8 (66-91.3)	< 0.001	
Rwanda	14.5 (6.9-24.2)	(0-70.4)	4	28796	18.4 (16.1-21)	99.7 (99.6-99.8)	< 0.001	
Senegal	0.7 (0.5-0.9)	(0-4.5)	3	23529	1.6 (1-3.1)	62.9 (0-89.4)	0.068	
South Africa	29.9 (26.7-33.2)	(16.7-45.1)	18	134840	10 (9.2-10.9)	99 (98.8-99.2)	< 0.001	
Sudan	1 (0.4-1.7)	(0-3.2)	4	1296	1.1 (1-2.7)	12.2 (0-86.6)	0.332	
Tanzania	7.3 (5.9-8.8)	(1.9-15.8)	21	157211	10 (9.3-10.9)	99 (98.8-99.2)	< 0.001	
Uganda	11.4 (6.9-16.8)	(0.2-35)	8	50585	14.6 (13.2-16.2)	99.5 (99.4-99.6)	< 0.001	

Zambia	18.6 (14.7-22.8)	(6.3-35.3)	8	326966	20.3 (18.7-22)	99.8 (99.7-99.8)	< 0.001	
Zimbabwe	25.7 (16.4-36.3)	(0.7-68.5)	10	33198	17.6 (16.3-19.1)	99.7 (99.6-99.7)	< 0.001	
WHO Region								< 0.001
Africa	9.5 (8.4-10.6)	(0-31.3)	244	1366377	20.8 (20.5-21.1)	99.8 (99.8-99.8)	< 0.001	
Eastern Mediterranean	1.4 (0.6-2.4)	(0-5.7)	6	7651	2.1 (1.4-3.2)	78.3 (52.3-90.2)	< 0.001	
UN Regions								< 0.001
Eastern Africa	11.7 (10.2-13.2)	(1.2-30.3)	99	813901	20.1 (19.7-20.5)	99.8 (99.7-99.8)	< 0.001	
Middle Africa	4.8 (4-5.8)	(0.9-11.5)	33	101346	6.6 (6-7.1)	97.7 (97.3-98)	< 0.001	
Northern Africa	0.7 (0.3-1.3)	(0-2.8)	5	4328	1.4 (1-2.3)	46.4 (0-80.4)	0.113	
Southern Africa	29.4 (26.5-32.4)	(16.5-44.2)	21	136338	9.3 (8.6-10.1)	98.8 (98.6-99)	< 0.001	
Western Africa	6.2 (5.2-7.3)	(0.2-19.2)	92	317532	11.5 (11.2-11.9)	99.3 (99.2-99.3)	< 0.001	
Sustainable Development Goal regions								< 0.001
Northern Africa and Western Asia	0.7 (0.3-1.3)	(0-2.8)	5	4328	1.4 (1-2.3)	46.4 (0-80.4)	0.113	
Sub-Saharan Africa	9.5 (8.5-10.6)	(0-31.4)	246	1370064	20.7 (20.4-21)	99.8 (99.8-99.8)	< 0.001	
World Bank Income Groups								< 0.001
Low-income countries	8.4 (6.9-10.1)	(0-28.5)	81	712218	23.3 (22.8-23.9)	99.8 (99.8-99.8)	< 0.001	
Lower-middle-income countries	8.1 (7.2-9.1)	(0.5-23.2)	147	521930	12.7 (12.4-13)	99.4 (99.3-99.4)	< 0.001	
Upper-middle-income countries	24 (19.9-28.3)	(6.9-47.2)	22	139297	14.8 (13.9-15.7)	99.5 (99.5-99.6)	< 0.001	
Study period								0.255
(1987-2001)	9.9 (8.1-11.8)	(0.4-29)	62	238301	14.7 (14.2-15.3)	99.5 (99.5-99.6)	< 0.001	
(2001-2016)	8 (6.8-9.4)	(0-27.7)	128	919743	21.7 (21.3-22.1)	99.8 (99.8-99.8)	< 0.001	
(2016-2020)	9.5 (5.9-13.8)	(0-41.9)	30	189325	26.6 (25.8-27.5)	99.9 (99.8-99.9)	< 0.001	
Parity								0.69
Multiparous	6.5 (4.5-8.8)	(0.9-16.1)	10	18015	4.6 (3.8-5.5)	95.2 (92.9-96.8)	< 0.001	
Nulliparous	6.7 (4-10)	(0.1-21.1)	9	14035	5.3 (4.4-6.4)	96.5 (94.9-97.6)	< 0.001	
Primiparous	5 (2.8-7.8)	(0-16.6)	9	8581	4 (3.2-5)	93.8 (90.3-96)	< 0.001	
Gravidity								0.276
Multigravidae	9.2 (5.5-13.7)	(0-35.1)	17	53860	14.2 (13.2-15.2)	99.5 (99.4-99.6)	< 0.001	
Primigravidae	6.5 (4.2-9.2)	(0-21)	16	22946	6.6 (5.9-7.5)	97.7 (97.1-98.2)	< 0.001	
Gestational age								0.902

First trimester	7.3 (3.5-12.2)	(0-32.7)	17	6164	4.1 (3.5-4.8)	94 (91.8-95.6)	< 0.001	
Second trimester	9.6 (5.2-15)	(0-40.7)	18	15874	7.8 (7.1-8.6)	98.4 (98-98.7)	< 0.001	
Third trimester	8.7 (5.2-13.1)	(0-39.4)	27	16897	8.5 (7.8-9.2)	98.6 (98.4-98.8)	< 0.001	
Residence								0.789
Rural	8.1 (5.8-10.6)	(0-29.9)	43	103272	13.5 (12.9-14.1)	99.5 (99.4-99.5)	< 0.001	
Urban	8.5 (7-10.2)	(1.6-20.2)	32	92657	8.5 (7.9-9.1)	98.6 (98.4-98.8)	< 0.001	
Education								0.804
None	5.8 (3.8-8.2)	(0-18)	18	29175	6 (5.3-6.8)	97.2 (96.5-97.8)	< 0.001	
Primary	6.6 (4.1-9.6)	(0-24.6)	21	26835	7.9 (7.2-8.7)	98.4 (98.1-98.7)	< 0.001	
Secondary	7.3 (5.4-9.6)	(0.8-19.1)	20	13337	4.1 (3.5-4.7)	94 (92-95.5)	< 0.001	
Tertiary	6.2 (4.3-8.5)	(0.3-17.6)	18	4744	2.8 (2.3-3.3)	86.8 (80.6-91)	< 0.001	
Type of HIV								< 0.001
HIV-1	8.2 (6.6-10)	(0.2-25.7)	58	279778	15.9 (15.4-16.5)	99.6 (99.6-99.6)	< 0.001	
HIV-2	1.2 (0.7-1.9)	(0-5.2)	16	143453	9.7 (8.8-10.6)	98.9 (98.7-99.1)	< 0.001	
Sample size								0.097
< 100	19.5 (7-36.1)	(0-82.2)	6	425	3.8 (2.9-5.1)	93.2 (87.9-96.2)	< 0.001	
≥ 100	9.1 (8.1-10.2)	(0-30.8)	242	1371252	21 (20.7-21.3)	99.8 (99.8-99.8)	< 0.001	
Risk of bias								0.205
Low risk of bias	8.8 (7.5-10.2)	(0-31)	146	1159206	25.3 (24.9-25.6)	99.8 (99.8-99.8)	< 0.001	
Moderate risk of bias	10 (8.6-11.5)	(0.6-28.5)	102	212471	10.6 (10.3-11)	99.1 (99.1-99.2)	< 0.001	

HIV: Human immunodeficiency virus.

seroprevalence was not significantly higher among multigravidae than among primigravidae (P = 0.276).

The metaregression analysis revealed an association between different factors and HIV seropositivity, with an overall variability of 63.07% observed in our multivariate model (Supplementary Table 5).

DISCUSSION

Participants were recruited in 248 studies between 1984 and 2020 from 39 African countries, with 1374392 participants in total. The overall HIV seroprevalence among pregnant women in Africa was estimated to be 9.3% (95%CI: 8.3-10.3), which suggests that a significant proportion of pregnant women in the region live with HIV. However, it is worth noting that no HIV-positive pregnant women died in any of the included studies. The study also found significant differences in HIV seroprevalence by United Nation region, WHO region, World Bank Income Groups, and individual countries. United Nation regions showed Southern Africa had the highest seroprevalence, followed by Eastern Africa, Western Africa, Middle Africa, and Northern Africa. The WHO region with the greatest seroprevalence was Africa compared to the Eastern Mediterranean. There were significant differences in HIV seroprevalence among World Bank Income Groups, with upper-middle-income countries having the highest seroprevalence, followed by low-income countries, and lower-middle-income countries. The analysis presented data on HIV seroprevalence in different African countries, with South Africa having the highest seroprevalence, followed by Zimbabwe, Malawi, Zambia, and Rwanda. The lowest seroprevalence was observed in Senegal and Sudan. The study found significantly higher HIV-1 seroprevalence (8.2%)

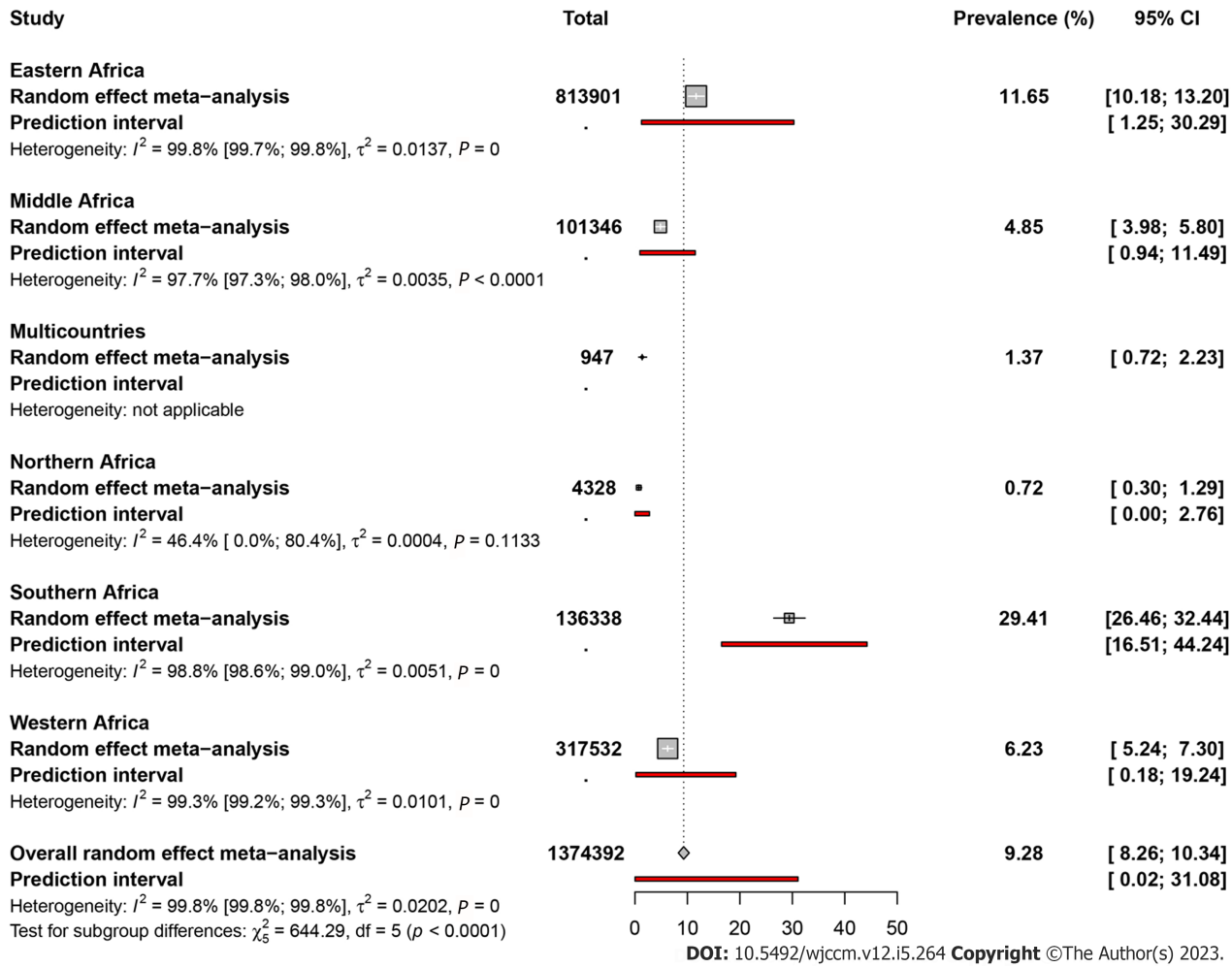

Figure 2 Human immunodeficiency virus seroprevalence among pregnant African women according to United Nation regions from 1984 to 2020.

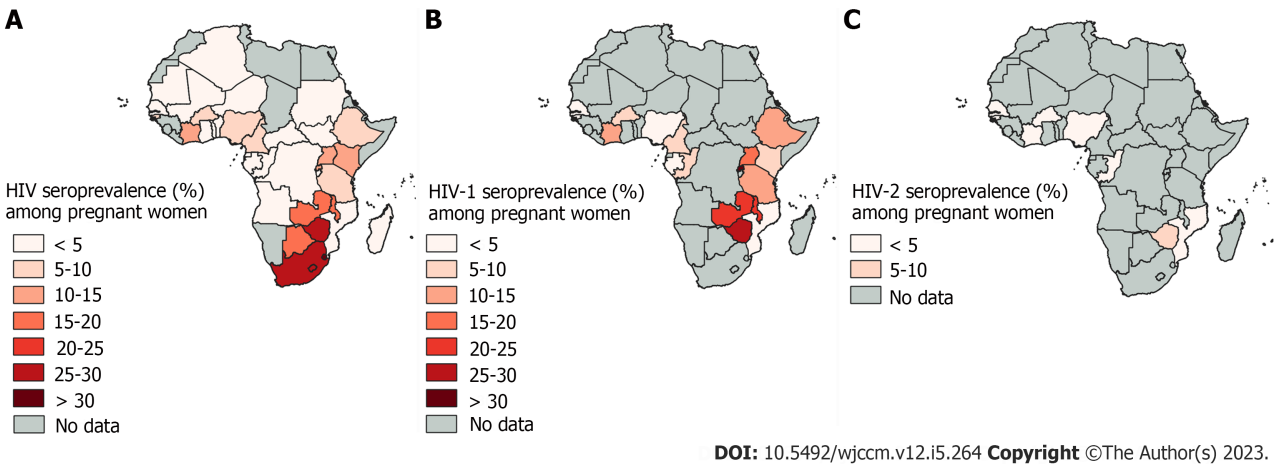

Figure 3 Map of the distribution seroprevalence data among pregnant women in Africa. A: Human immunodeficiency virus; B: Human immunodeficiency virus-1; C: Human immunodeficiency virus-2. The base map was taken from (https://www.naturalearthdata.com/) and modified with Qgis software. HIV: Human immunodeficiency virus.

than HIV-2 (1.2%). No significant differences were observed in seroprevalence based on gestational age, parity, and gravidity.

It is concerning to find that the overall HIV seroprevalence among pregnant women in Africa was estimated to be 9.3% (95%CI: 8.3-10.3), which indicates that the HIV epidemic continues to have a high impact on the continent. Previous studies show pregnant women in Africa are at higher risk of HIV infection[6,7]. There have been previous reports of death in African pregnant and postpartum women, primarily in longitudinal studies[11,13,273]. It is noteworthy that none of the included studies reported the death of HIV-positive pregnant women. As previously reported[274,275], Southern Africa had the highest HIV seroprevalence among pregnant women, followed by Eastern Africa, Western Africa, Middle Africa, and Northern Africa. This highlights the urgent need for continued efforts to prevent HIV transmission and provide effective care and treatment to HIV-positive pregnant women in these regions. The high HIV seroprevalence in Southern Africa is well documented, with countries like South Africa being among the highest HIV seroprevalence in the world[276,277]. This can be attributed to a range of factors, including data availability, poverty, violence against women, cultural restrictions promoting intergenerational sex, unprotected sex, multiple sexual partners, political barriers, recreational drug use, stigma, and discrimination[276,277]. Eastern and Western Africa also have high HIV seroprevalence, with countries like Zimbabwe, Malawi, Zambia, Rwanda, Uganda, and Kenya reporting significant numbers of HIV infections each year[278]. These findings suggest that efforts to prevent HIV transmission and provide care and treatment to HIV-positive pregnant women need to be targeted towards these high-prevalent regions. This may include scaling up prevention interventions such as condom use and pre-exposure prophylaxis (PrEP), as well as increasing access to HIV testing and treatment services[279-281]. In addition, addressing social and economic factors that contribute to HIV transmission, such as poverty, gender inequality, and stigma, is crucial to reducing HIV seroprevalence in these regions.

HIV-1 seroprevalence was significantly higher than HIV-2 seroprevalence, which has implications for HIV prevention and treatment. HIV-1 and HIV-2 are two distinct types of the virus that cause HIV infection, and they differ in their transmission, clinical presentation, and response to treatment[282-284]. HIV-1 is more prevalent globally and is the predominant HIV type in sub-Saharan Africa, where the HIV burden is highest. In contrast, HIV-2 is primarily found in West Africa and is less prevalent globally[282,283]. This has significant implications for prevention efforts, as HIV-1 is more easily transmitted than HIV-2 and associated with faster AIDS progression. Prevention efforts must therefore focus on reducing HIV-1 transmission through strategies such as condom use, pre-exposure PrEP, and promoting HIV testing and treatment for people living with HIV. Antiretroviral therapy is the cornerstone of HIV treatment, and it suppresses both HIV-1 and HIV-2. However, HIV-2 is less responsive to some antiretroviral therapy regimens and may require different treatment strategies[282,283,285]. The high HIV-1 seroprevalence in the study population suggests that healthcare providers should know the HIV-1 predominance and tailor treatment accordingly.

There was no significant difference in seroprevalence based on gestational age, parity, or gravidity, indicating that HIV infection does not discriminate against these demographic characteristics. This finding is consistent with previous research that shows that HIV can affect anyone, regardless of their age, parity, or gravidity[286-288].

This systematic review and meta-analysis of HIV seroprevalence among pregnant women in Africa has some limitations. We acknowledge that not searching the grey literature might introduce a potential limitation to our review. The lack of uniformity in testing methods and cutoffs used in included studies may have affected the results comparability. However, this systematic review and meta-analysis of HIV seroprevalence among pregnant women in Africa has several strengths. The comprehensive search strategy and pre-defined inclusion and exclusion criteria minimized the risk of missing relevant studies and ensured that only appropriate studies were considered. The large sample size and broad time frame of the review increased generalizability. Finally, meta-analysis allowed for the estimation of overall seroprevalence rates and identification of factors associated with HIV seroprevalence among pregnant women in Africa, providing significant insights for clinicians, researchers, and policymakers.

CONCLUSION

This study reports that HIV seroprevalence in pregnant African women was estimated to be 9.3%, highlighting the substantial burden of HIV in Africa. Southern Africa had the highest HIV seroprevalence among pregnant women, followed by Eastern, Western, Middle, and Northern Africa, emphasizing the need for targeted efforts to prevent transmission and provide care and treatment in these regions. HIV-1 seroprevalence was considerably higher than HIV-2, underscoring the need for tailored prevention and treatment strategies.

ARTICLE HIGHLIGHTS

Research background

An extensive literature review was carried out in various databases up until February 2023, using key terms such as Human immunodeficiency virus (HIV), pregnancy, and Africa. Through this literature search, we noted a significant body of evidence detailing HIV infection prevalence among pregnant women in Africa.

Research motivation

Given the continued high incidence and impact of HIV among pregnant women in Africa, there is a critical need to

enhance our understanding of the specific factors that contribute to this high prevalence and the variations in these proportions. There is also an urgent need to examine strategies that could effectively mitigate both horizontal (person-to-person) and vertical (mother-to-child) HIV transmission during pregnancy and breastfeeding.

Research objectives

This research aims to provide a comprehensive understanding of HIV prevalence among pregnant women in Africa by identifying and analyzing the regional and clinical characteristics that contribute to variations in study-specific estimates.

Research methods

This systematic review and meta-analysis, compliant with Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines and registered in PROSPERO, assessed the seroprevalence of HIV serological markers among pregnant women in Africa up to 2023. All types of study designs from any African region were eligible if the sample size was greater than 10 and published in English or French. A literature search was conducted in databases such as Pubmed, Web of Science, African Index Medicus, and African Journal online, with relevant search terms. The quality of the included studies was assessed using the appropriate tool. The DerSimonian and Laird random-effects model was used to determine pooled HIV seroprevalence.

Research results

This systematic review analyzed data from 248 studies investigating HIV seroprevalence in pregnant women across various African countries from 1984 to 2020. The overall HIV seroprevalence was estimated at 9.3% [95% confidence interval (CI): 8.3-10.3]. The highest seroprevalence was found in Southern Africa (29.4%, 95%CI: 26.5-32.4), while Northern Africa had the lowest (0.7%, 95%CI: 0.3-1.3). Among the different types of HIV, HIV-1 seroprevalence was significantly higher than HIV-2 ($P < 0.001$).

Research conclusions

This comprehensive analysis identified a high HIV seroprevalence among pregnant women in Africa at an estimated 9.3%, highlighting the significant burden of HIV in the region.

Research perspectives

Considering the substantial HIV seroprevalence among pregnant women in Africa, this analysis underlines the need for sustained efforts to prevent HIV transmission and provide effective care and treatment for HIV-positive pregnant women, especially in regions with high seroprevalence. Future research should aim to elucidate the factors contributing to high seroprevalence, especially in Southern Africa, and devise effective preventive and therapeutic strategies tailored to the region's needs.

FOOTNOTES

Author contributions: Ebogo-Belobo JT, Kenmoe S, and Njouom R were responsible for conception and design of the study as well as project administration; Ebogo-Belobo JT, Kenmoe S, Mbongue Mikangue CA, Tchatchouang S, Robertine LF, Takuissu GR, Ndzie Ondigui JL, Bowo-Ngandji A, Kenfack-Momo R, Kengne-Ndé C, Mbaga DS, Menkem EZ, Kame-Ngasse GI, Magoudjou-Pekam JN, Kenfack-Zanguim J, Esemu SN, Tagnouokam-Ngoupo PA, Ndip L, and Njouom R were responsible for the data curation and interpretation of results; Kengne-Nde C and Kenmoe S were responsible for statistical analysis; Kenmoe S and Njouom R were responsible for the project supervision; Ebogo-Belobo JT and Kenmoe S wrote the original draft; All authors critically reviewed the first draft and approved the final version of the paper for submission, and have read and approve the final manuscript.

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