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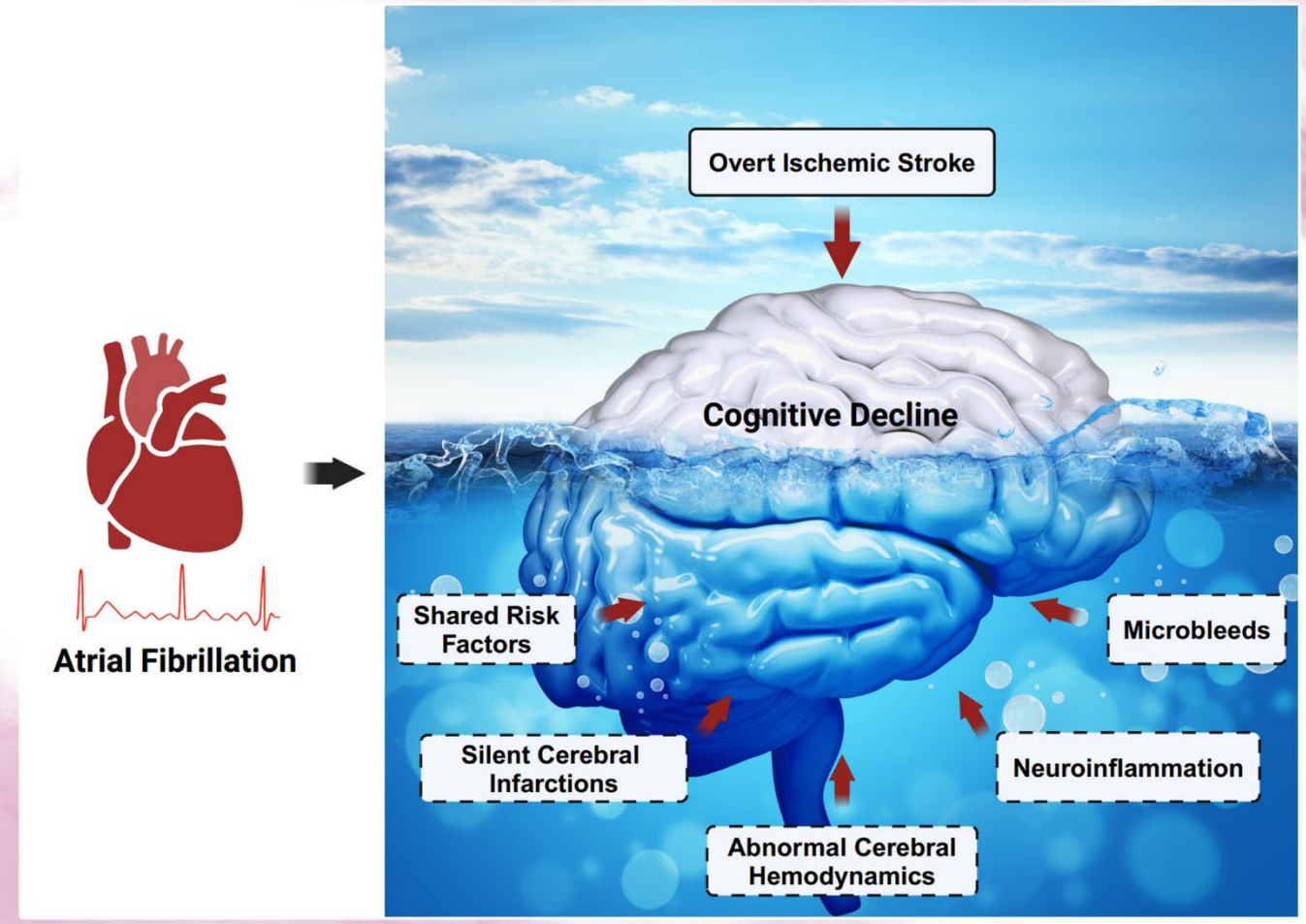

Atrial fibrillation and risk of cognitive impairment and dementia: Relationships, potential mechanisms, and current therapies

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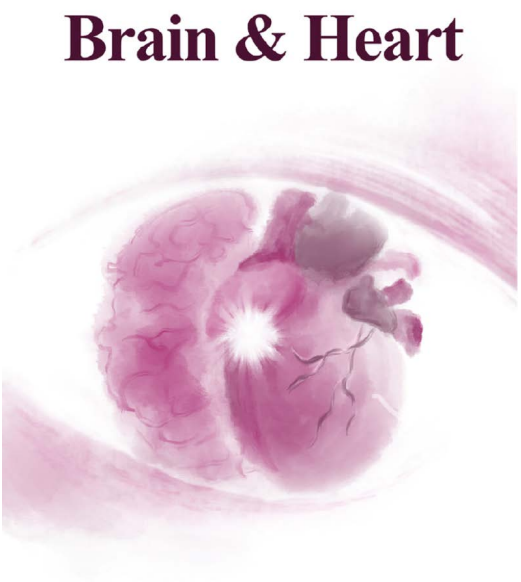

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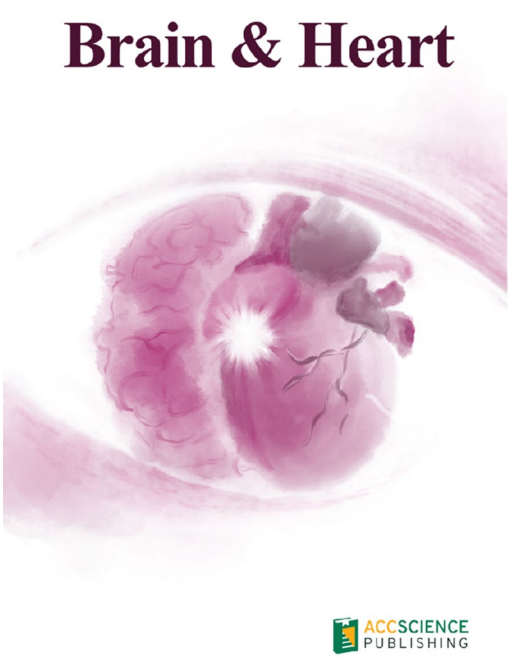

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REVIEW ARTICLE

Atrial fibrillation and risk of cognitive impairment and dementia: Relationships, potential mechanisms, and current therapies

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(This article belongs to the *Special Issue: The Brain Disorders with Left Atrium*)

Abstract

Atrial fibrillation (AF), cognitive impairment, and dementia are significant health concerns. The prevalence and incidence of AF have been increasing and are expected to increase continuously in the future. In recent years, emerging evidence has indicated that AF, cognitive dysfunction, and dementia are associated with one another. Given the global increase in individuals who are at risk for AF, a greater focus is needed on the primary and secondary prevention of cognitive impairment and dementia in high-risk groups. Although earlier studies hypothesized that ischemic stroke is the main cause of cognitive impairment and dementia in patients with AF, recent studies have demonstrated that AF may contribute to cognitive impairment in the absence of stroke through other mechanisms. To date, various pathomechanisms have been proposed to explain the association between AF and cognitive decline, including overt ischemic stroke, silent cerebral infarctions, impaired cerebrovascular reactivity, decreased cerebral blood perfusion, neuroinflammation, microbleeds, and shared risk factors. However, a complete understanding of these mechanisms remains elusive. In addition, whether treatments targeting AF, including anticoagulation and rhythm control strategies, can avert cognitive decline and dementia has great clinical implications. To pave the way for targeted effective interventions for cognitive protection, we provide an overview of the association between AF and cognitive impairment and the potential mechanisms underlying this association. In addition, the effectiveness of AF-related treatment strategies, including anticoagulation, sinus rhythm restoration through elective cardioversion and catheter ablation, for cognitive protection in patients with AF is also discussed in this review.

Keywords: Atrial fibrillation; Cognitive impairment; Dementia; Brain

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1. Introduction

Atrial fibrillation (AF) is the most common type of arrhythmia, affecting approximately 60 million patients worldwide, and is an important risk factor for ischemic stroke and

mortality.[1] Cognitive impairment and dementia are also significant public health issues. The increasing prevalence of AF and dementia due to an aging population presents a significant healthcare challenge.[2,3] Over the past decade, accumulating evidence has suggested that AF is an independent risk factor for cognitive decline and an increased risk of dementia.[4-6] While some previous studies proposed that the association between AF and cognitive dysfunction and dementia is mainly a consequence of ischemic stroke, more recent evidence indicates that the pathomechanisms underlying this association and brain damage caused by AF are not limited to cerebrovascular events. The mechanisms underlying the association between AF and cognitive decline may be multiple and are not completely understood. A better understanding of the relationship between AF and cognitive impairment and the potential mechanisms offers opportunities for high-risk population identification and cognitive impairment prevention. In this review, we aim to provide an overview of the literature, illustrate emerging insights into the association between AF, cognitive decline and dementia, and further discuss potential pathophysiological mechanisms and the treatment effects of different strategies (Figure 1).

2. Association of AF with cognitive impairment and dementia

Accumulating evidence has highlighted the association between AF and the risk of dementia, independent of prior or incident ischemic stroke. The significant association between AF and dementia was first investigated in the Rotterdam Study, in which the authors reported significant positive associations of AF with both dementia and impaired cognitive function.[7,8] Notably, AF appears to be associated with both vascular dementia (VaD) and Alzheimer's disease (AD), independent of clinical stroke. These findings have been further confirmed in an increasing number of longitudinal studies in recent years, in which a positive association between AF and subsequent dementia has been reported.[9-12] A meta-analysis including 11 prospective cohort studies involving 112,876 participants revealed that AF is an independent risk factor for dementia in individuals with normal baseline cognitive function and no acute stroke.[6] A more recent meta-analysis further assessed the relationship between AF and dementia in studies of adults aged <70 years and demonstrated that AF contributed to early-onset dementia.[13] A recent longitudinal cohort study, which used the UK biobank database and included 373,415 participants, also indicated that people with AF had an increased future risk of all-cause dementia, AD, and VaD.[14]

Notably, studies investigating the association between AF and dementia have been based mostly on studies that have evaluated AF in a binary fashion (present or absent). However, the American Heart Association has stated that understanding the prognostic significance of AF burden and its relationship with AF complications is essential

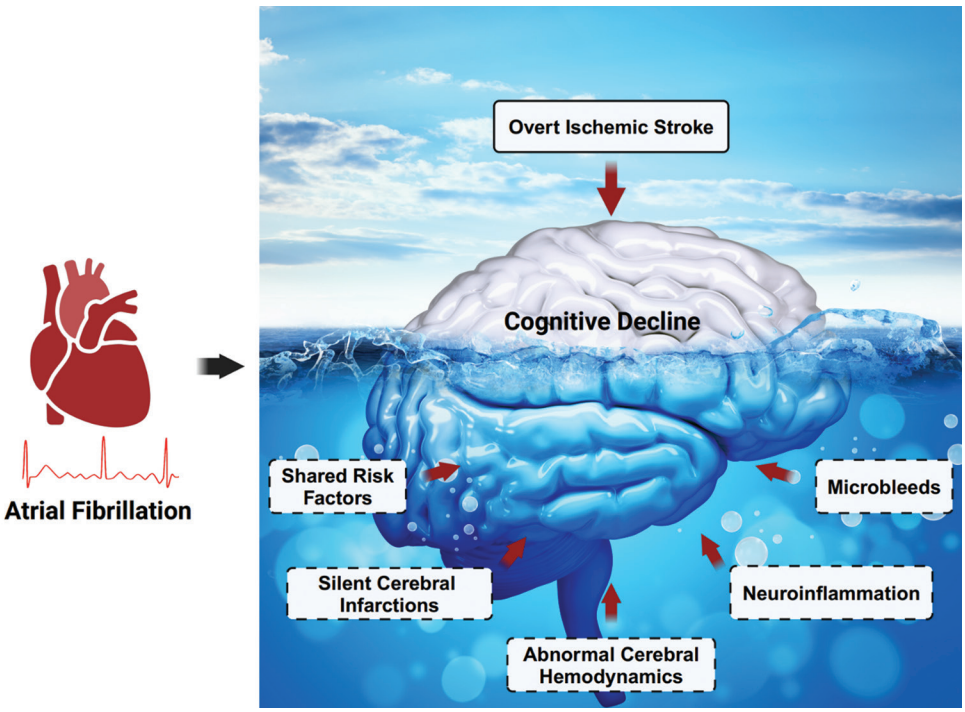

Figure 1. Potential mechanisms between atrial fibrillation and cognitive decline

for identifying high-risk populations and determining the optimal timing of therapeutic intervention.[15] There are relatively few studies exploring the role of AF burden on cognitive function and dementia risk. A recent prospective, population-based cohort study using data from the UK Biobank demonstrated that earlier onset of AF is associated with an increased risk of dementia, indicating that AF burden may play an important role in cognitive decline.[16] A small cross-sectional study based on the database of the Atherosclerosis Risk in Communities (ARIC) study reported that persistent AF was associated with lower cognitive functional scores in elderly individuals, while the association between paroxysmal AF and cognitive decline was not statistically significant.[17] Another cross-sectional study also demonstrated that cognitive function differed across AF types, patients with permanent AF had lower cognitive function scores than patients with paroxysmal or persistent AF.[18] More recently, a prospective study reported that cognitive function in patients with AF was associated with AF burden, which was defined as the percentage of time spent in AF detected by a 14-day ambulatory electrocardiogram.[19] In contrast, another study that used data from more than 3 years of continuous heart rhythm monitoring in AF patients reported no association between AF burden and changes in cognitive function.[20] A likely cause of this null result could be that, in this study, early detection and treatment might have mitigated the accelerated cognitive decline attributed to AF reported in other studies. Overall, the number of studies on the relationships between AF burden and cognitive impairment and dementia are relatively small. The methods used to assess AF burden are not uniform across different studies, and conclusions remain controversial. Therefore, further longitudinal cohort studies are needed to confirm the association of a greater AF burden with greater cognitive decline and determine whether reducing the AF burden can preserve cognitive function in AF patients. In addition, further studies exploring the use of continuous cardiac rhythm monitoring techniques to assess the burden of AF more accurately and its impact on cognitive impairment are needed. The Swiss-AF Burden Study, a substudy of the Swiss-AF (NCT02105844), will assess AF burden (defined as time in AF measured through long-term electrocardiogram monitoring and implantable loop recorders) and cognitive function. This study may provide further insights.

3. Potential mechanisms of cognitive impairment in AF

3.1. Overt ischemic stroke and silent cerebral infarctions

Patients with AF have the propensity to developing intracavitary thrombi with the potential for cerebral embolization. Both clinical and subclinical damage to the brain may exist in AF patients. AF is a significant contributor to ischemic stroke, which is a well-known risk factor for cognitive impairment and dementia.[1,21] Poststroke cognitive impairment is a common and important complication of ischemic stroke, which has been reported to occur in almost half of stroke patients within the 1st year.[22] Therefore, overt ischemic stroke may be an important mechanism for the association between AF and cognitive impairment. However, some findings indicate that overt stroke is not the only mechanism involved. First, several studies have demonstrated that the acceleration of cognitive decline and increased risk of dementia exist in AF patients even in the absence of prior or incident cerebrovascular events.[4,23,24] Second, VaD is known to represent dementia caused by cerebrovascular brain injury. However, AF increases not only VaD but also AD, which is the most common neurodegenerative disease.[4,16] AF also contributes to cognitive decline in patients with AD.[25] These findings indicate that mechanisms other than ischemic stroke may also play important roles in the relationship between AF and cognitive decline. Silent cerebral infarcts (SCIs) may be one of the reasons. In a previous study, among 1390 stroke-free AF patients, 18% had small non-cortical infarcts, and 15% had large non-cortical or cortical infarcts, although 90% of these patients received oral anticoagulation, which seemed to be greater than in the general population.[18] The authors also demonstrated that SCIs were associated with worse cognitive function. Similarly, another cross-sectional study demonstrated that AF was associated with magnetic resonance imaging (MRI) findings of lacunes and SCIs.[26] Another study based on the ARIC study confirmed the longitudinal association of incident AF and SCIs, in which the authors reported that participants who developed AF after the first MRI had greater odds of having increased SCIs after approximately 10 years.[27] In a more recent prospective, multicenter cohort study (Swiss-AF) of patients with AF, 5.5% had a new brain infarct on MRI after 2 years of follow-up.[28] The majority of the infarcts were clinically silent, occurred in patients treated with anticoagulants, and were associated with cognitive decline. In summary, patients with AF may be more likely to suffer from both overt and covert brain infarcts, which seem to explain at least part of the relationship between AF and cognitive decline.

3.2. Abnormal cerebral hemodynamics and associated brain structural changes

In addition to ischemic stroke and SCI, AF has also been linked to reduced brain volume in addition to a decline in cognitive function, independent of stroke, and silent brain infarcts.[29] A large cross-sectional study of non-demented

elderly individuals in the general population revealed that AF was significantly related to reduced volume of total brain, gray, and white matter.[29] Another cross-sectional study revealed that AF is a risk factor for hippocampal atrophy and cognitive impairment, even in the absence of stroke.[30] A longitudinal analysis also confirmed that AF is independently associated with worsening sulcal and ventricular grades.[27] In addition, a more recent study that integrated a comprehensive analysis approach with extensive clinical and MRI data revealed that cognitive impairment in AF patients was accompanied by alterations of brain structure, such as gray matter volume and reduced cortical thickness, increased extracellular free-water content, and widespread differences in white matter integrity.[31] This finding is consistent with several other studies indicating that AF is associated with a larger white matter hyperintensity (WMH) volume and a faster increase in WMH volume,[26,32] which may be an important reason for cognitive decline.[33] These findings indicate that AF may cause changes in brain structure and function in more ways than cerebral emboli. Possible mechanisms connecting AF with decreased brain volume and increased WMH volume may include decreased cerebral perfusion, abnormal cerebral hemodynamics due to beat-to-beat variation, and changes in autoregulation of blood flow. A study evaluating cerebral blood flow through transcranial Doppler demonstrated that in ischemic stroke patients, AF is related to lower cerebral blood flow.[34] Another study that evaluated cerebral blood flow and brain perfusion through MRI reported that persistent AF is associated with decreased blood flow and blood supply of brain tissue.[35] Moreover, there is evidence that patients with AF have lower cerebral perfusion and impaired cerebrovascular reactivity, which are defined as cerebrovascular arterial carbon dioxide reactivity abnormalities.[36] A recent 7-Tesla MRI study further revealed that AF exerts a direct detrimental hemodynamic effect on lenticulostriate arteries.[37] These findings indicate that AF may induce local hemodynamic perturbations that may result in cerebral small vascular disease. In summary, AF may lead to decreased cerebral blood perfusion and abnormal cerebral hemodynamics, which promote structural brain changes and consequently cognitive decline. Studies are needed to confirm these findings and further investigate whether therapeutic strategies aimed at sinus rhythm maintenance may reduce the risk of cognitive impairment by eliminating AF-induced hemodynamic alterations.

3.3. Shared risk factors

AF, cognitive impairment, and dementia share many cardiovascular risk factors, such as advanced age, diabetes, smoking, and hypertension.[38-40] Patients with AF are more prone to having these cardiovascular risk factors and thus have a greater risk of brain damage and cognitive impairment. However, in several longitudinal cohort studies, the association between AF and cognitive impairment was significant even after adjustments for potential shared risk factors.[9-11] Therefore, although the presence of shared risk factors may partly contribute to cognitive decline in patients with AF, they appear to be not enough to completely explain this relationship.

3.4. Microbleeds

Cerebral microbleeds (CMBs), which may be caused by AF itself and the use of anticoagulation therapy in patients with AF, may be another possible link between AF and cognitive impairment. However, evidence concerning the prevalence of CMBs in patients with AF and their causal relationship with cognitive decline remains controversial. A cross-sectional study revealed that patients with AF had a significantly greater prevalence of CMBs,[41] whereas another more recent cross-sectional study demonstrated that AF was associated with a greater prevalence of CMBs only in the frontal lobe.[26] A meta-analysis including 17 studies with 6978 patients reported that the prevalence of CMBs in the AF population was estimated to be 28.3%, which was almost double that reported in the general population.[42] In addition, CMBs were found to be associated with both intracerebral hemorrhage and ischemic stroke events in patients with AF, which may further lead to cognitive impairment. In a multicenter study including 1737 patients with AF (90% taking oral anticoagulant agents), the authors reported no significant association between CMB count and cognitive function in a combined multivariate model including all types of lesion.[18] Other studies, on the other hand, have demonstrated that CMBs are associated with poor cognitive performance.[43,44] Further prospective studies with larger sample sizes are needed.

3.5. Neuroinflammation

The pathogenesis of AF is linked to inflammatory reactions and oxidative stress, which may lead to fibrosis of the atria and contribute to the progression of the disease.[45,46] AF can, in turn, aggravate the inflammatory response.[47] As inflammation is one of the devastating factors affecting vascular endothelia and a predisposing factor of thrombotic microinfarctions,[48] it is plausible that it can further lead to brain damage and cognitive impairment. Studies have reported that increased inflammation and oxidative stress may lead to the progression of brain damage, including small vessel disease[49] and stroke.[50] In addition, an analysis of a small sample using intensive lipid-lowering treatment revealed a significant association between reduced inflammatory markers and delayed cognitive decline in

patients with AF.[48] Further, investigations are warranted to evaluate the underlying mechanisms to facilitate the discovery of novel therapeutic strategies.

4. Treatment strategies for cognitive decline in patients with AF

4.1. Anticoagulation

The influence of anticoagulation on cognitive decline in patients with AF is controversial. The use of anticoagulant agents may reduce the rate of embolic stroke, resulting in a reduced risk of cognitive impairment and dementia, but it may also promote the formation of CMBs, increase the risk of intracerebral hemorrhage, and increase the risk of cognitive decline.[51] A meta-analysis conducted in 2018 included one randomized controlled trial (RCT) and five cohort studies and suggested a protective effect of oral anticoagulant use in reducing dementia risk.[52] Several more recent studies also confirmed this finding.[53,54] However, data regarding the choice of anticoagulant strategies for preventing cognitive decline in patients with AF are limited. The results from the GIRAF trial, a 24-month RCT, revealed no evidence of a beneficial cognitive prevention effect of dabigatran compared with warfarin.[55] In contrast, two other cohort studies demonstrated that non-Vitamin K oral anticoagulant use may result in a lower incidence of dementia than Vitamin K antagonist use does.[56,57] Overall, evidence indicates that oral anticoagulation prevents cognitive decline beyond ischemic stroke, and an optimal anticoagulation regimen is still lacking. In addition, most previous studies were observational, and RCTs are needed to confirm these findings in the future. The BRAIN-AF study (NCT02387229) is a double-blind, prospective RCT that aims to investigate the use of rivaroxaban to prevent neurocognitive impairment in patients with AF and a low risk of stroke.[58] We look forward to the results of this study to shed further light on this topic.

4.2. Sinus rhythm restoration

Thromboembolism prophylaxis with anticoagulation is an effective way to reduce thromboembolic and stroke risks. However, anticoagulation therapy alone may not be enough to protect patients with AF from cognitive decline since cognitive dysfunction involves many other mechanisms, such as abnormal cerebral hemodynamics and decreased cerebral blood perfusion.[59] On the other hand, it is plausible that the restoration of sinus rhythm may prevent these impairments and prevent the occurrence of cognitive decline. A study of 44 patients who underwent elective cardioversion for AF revealed that the restoration and maintenance of sinus rhythm were associated with increased cerebral blood flow and brain perfusion.[60] Another study further demonstrated that sinus rhythm restoration by elective electrical cardioversion may reduce the burden of extreme single-beat hemodynamic events in the cerebral microcirculation.[61] These results revealed the benefits of sinus rhythm restoration through electrical cardioversion on stable hemodynamics and cerebral perfusion. However, a study evaluating changes in neurologic biomarkers and cognitive function before and after electrical cardioversion demonstrated that the restoration of sinus rhythm with electrical cardioversion was not associated with significant changes in cognitive function or neurologic biomarkers.[62] Of note, it is possible that the small sample size and the short follow-up may have contributed to some false negatives. Further studies with larger sample sizes and longer follow-up periods are needed to further evaluate the impact of rhythm restoration by electrical cardioversion on brain function. Catheter ablation, which is another effective strategy for rhythm control, has also been found to have favorable effects on cerebral blood flow and perfusion in several studies.[63-65] A study evaluating both brain activity through near-infrared spectroscopy and cognitive function in AF patients demonstrated that frontal and temporal brain activity improved in more than 50% of persistent AF patients who underwent catheter ablation and maintained sinus rhythm at 3 months after ablation.[66] The authors also reported that improvements in brain activity were associated with improvements in cognitive function. In a previous meta-analysis which included a large sample size of 193,830 patients with AF, we found that rhythm-control strategies, especially catheter ablation, can significantly reduce the risk of all-cause dementia, VaD, and AD.[67] In summary, these findings suggest that rhythm control treatment may protect cognitive function through various pathways and should be considered for AF treatment, even in asymptomatic patients.

5. Conclusion

AF increases the risk of onset of cognitive decline and dementia, independent of ischemic stroke. The mechanisms underlying this association seem to be multifactorial. Available evidence indicates that overt stroke, SCIs, abnormal cerebral hemodynamics, shared risk factors, CMBs, and the inflammatory response are seemingly involved in the relationship between AF and cognitive decline, but these mechanisms are still a matter of intense discussion. There is a great need for patients with AF to receive a comprehensive evaluation and close monitoring of both their heart and brain functions. The early detection and intervention of AF may shed new light on the prevention of cognitive decline and dementia. Future studies, especially RCTs, are needed to determine the optimal treatment strategy for cognitive protection in patients with AF.

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Conflict of interest

The authors declare that they have no competing interests

Author contributions

Conceptualization: Xingquan Zhao
Writing – original draft: Jiahuan Guo
Writing – review & editing: Xingquan Zhao

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

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REVIEW ARTICLE

An overview of the anticoagulation therapy in ischemic stroke associated with non-valvular atrial fibrillation

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Abstract

Atrial fibrillation (AF) significantly contributes to ischemic stroke, which poses a major healthcare challenge due to its significant morbidity and mortality rates. AF increases with age and is a common cause of cardioembolic strokes – a substantial economic and social burden in cerebrovascular disease management. The cornerstone of treatment for AF-related ischemic stroke lies in anticoagulation therapy. Current clinical evidence strongly supports the prolonged administration of warfarin or novel oral anticoagulants (NOACs) in non-valvular AF patients. Considering the practicality and their consistent blood levels in real-world settings, NOACs are opted over traditional therapies by an increasing number of patients; NOACs, such as apixaban and dabigatran showing promising effectiveness and lower bleeding risks compared to warfarin, an increasing number of patients are opting for NOACs over traditional therapies. Recent studies focus on determining the optimal timing for initiating anticoagulation post-stroke, as early intervention potentially reduces recurrence and complications. However, given the diverse clinical presentations of these patients, careful consideration must be given to the timing of anticoagulation initiation and the unique circumstances of special populations, including those with renal impairment, elderly adults, and patients with cerebral microbleeds. This comprehensive review delves into the complexities of anticoagulation management in AF-related ischemic stroke, with a particular focus on the optimal timing of oral anticoagulant initiation and tailored strategies for special patient subgroups. The ultimate goal of this review is to equip healthcare providers with valuable clinical insights and guidance to manage the challenges of AF-related ischemic stroke.

Keywords: Non-valvular atrial fibrillation; Ischemic stroke; Anticoagulation

1. Introduction

Ischemic stroke stands as the most prevalent cerebrovascular disorder, marked by high rates of disability and fatality, posing considerable societal and economic burdens worldwide.[1,2] Atrial fibrillation (AF) is a common and recurrent arrhythmic condition encountered in clinical settings. Its prevalence rises with age, varying from 2% in individuals under 65 years to 9% in those over 65 years, and it can climb to almost 18% in elderly individuals over 85 years.[1,3] A subset of ischemic stroke patients, constituting roughly 15 – 30%, experience cardioembolic events due to AF[4,5] Furthermore, some individuals have coexisting AF and can display electrocardiographic irregularities following an acute ischemic stroke or transient ischemic attack (TIA), with AF being the most prevalent abnormality.[6] The disordered electrical signals and lack of coordinated atrial contraction associated with AF, combined with endothelial dysfunction and other prothrombotic states, often result in thrombus formation in the left atrial appendage. When these thrombi dislodge, the resulting emboli can cause relatively large infarct volumes and more severe neurological deficits, leading to poorer prognoses.[7]

2. Overview of anticoagulation therapy for AF-related ischemic stroke

For the secondary prevention of AF or its associated ischemic stroke, whether due to cardioembolism or intracranial atherosclerosis coupled with AF, a pivotal aspect of treatment lies in the precise selection and timing of anticoagulant medications (Figure 1). Currently, high-level clinical evidence supports long-term anticoagulation therapy for patients with non-valvular AF combined with ischemic stroke.[8-10] Subgroup analysis of the Rivaroxaban Once Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) AF trial indicated that novel oral anticoagulants (NOACs) and warfarin have similar safety and efficacy in preventing stroke in patients with non-valvular AF combined with carotid artery disease.[11] Given that NOACs are easier to maintain a consistent anticoagulant effect and have a lower risk of bleeding compared to warfarin, with fewer drug interactions, they are more favorable for practice.[12]

Since 2010, several NOACs—including apixaban, dabigatran, edoxaban, and rivaroxaban—have gained approval for use in patients with non-valvular AF. Subsequent studies have demonstrated that NOACs exhibit comparable effectiveness to vitamin K antagonists (VKAs) in both primary and secondary stroke prevention while reducing the risk of intracranial hemorrhage compared to VKAs.[13] Between 2010 and 2016, the international prospective The Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD-AF) registry showed that the usage rate of NOACs as baseline treatment for non-valvular AF increased from 3% to 43%.[14] A meta-analysis of phase III randomized controlled trials further highlighted that NOACs, compared to VKAs, reduce thromboembolic events and intracranial hemorrhage for secondary stroke prevention in AF patients with absolute risk reductions of 0.78% and 0.88%, respectively.[15] Therefore, in recent years, numerous clinical trials have focused on investigating the usages of anticoagulants for AF-related ischemic stroke and the timing of their administration, aiding in optimizing clinical guidelines and consensus.

3. Anticoagulation strategies for AF-related ischemic stroke

3.1. Early anticoagulation therapy attempts

For secondary prevention of AF-related ischemic stroke, the critical focus is on optimizing the timing for initiating anticoagulation therapy after an ischemic stroke. In 2016, the European Society of Cardiology suggested starting anticoagulation therapy approximately 3 days after a mild stroke, 6 days after a moderate stroke (or after imaging assessment of hemorrhagic transformation), and 12 days after a severe ischemic stroke (or after imaging assessment of hemorrhagic transformation).[16] The 2018 practical guidelines by the European Heart Rhythm Association reaffirmed this recommendation regarding the use of NOACs in AF patients,[17] and the "1 – 3 – 6 – 12 days" rule continues to be widely adopted in clinical practice. Patients with TIA should resume anticoagulation therapy after 1 day. For mild strokes, National Institute of Health Stroke Scale (NIHSS) (NIHSS <8), anticoagulation should be resumed about 3 days after the acute event. For moderate strokes (NIHSS 8 – 15), anticoagulation should be resumed about 6 days after the acute event. For severe strokes (NIHSS >15), anticoagulation should be resumed about 12 days after the acute event.

In Switzerland, the Novel Oral Anticoagulants in Ischemic Stroke Patients (NOACISP) study compared the outcomes of early initiation (≤7 days) versus delayed initiation (>7 days) of anticoagulation in patients with AF-related stroke. The findings reported an annual risk of stroke recurrence at 7.7%, with a lower corresponding risk in the early initiation group (5.1%) compared to the delayed initiation group (9.3%); the early initiation group also demonstrated a lower risk of intracranial hemorrhage.[18]

The RAF study prospectively included 1,029 patients with AF-related stroke to investigate the impact of various antithrombotic treatments on major clinical endpoint

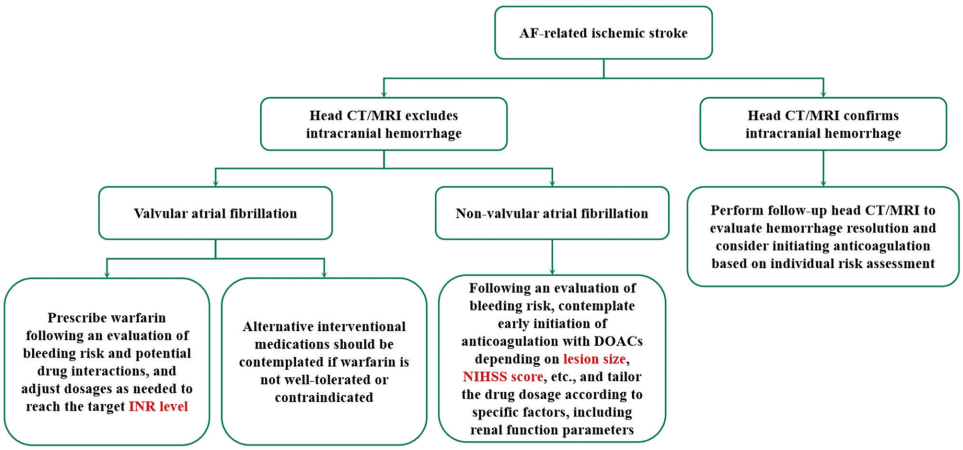

Figure 1. A flowchart for administration of NOACs
Abbreviations: AF: Atrial fibrillation; CT: Computed tomography; MRI: Magnetic resonance imaging; INR: International normalized ratio; DOAC: Direct oral anticoagulant; NIHSS: National Institutes of Health Stroke Scale.

events, including recurrent stroke, TIA, systemic embolic events, and symptomatic intracranial hemorrhage within 90 days.[19] Cox regression analysis demonstrated that initiating anticoagulation therapy within four to 14 days post-acute stroke significantly reduced the risk of ischemic and hemorrhagic events compared to earlier (<4 days) or later (>14 days) initiation.[19]

According to the 2018 American Heart Association/ American Stroke Association guidelines for ischemic stroke management, it is recommended to commence oral anticoagulation therapy between four and 14 days following the stroke onset.[20]

3.2. Design of early anticoagulation timing

Several studies have emerged, focusing on determining the best time to initiate anticoagulation in patients with AF-related ischemic stroke. The SAMURAI-NVAF study from Japan revealed that early initiation (within 4 days post-stroke) of oral anticoagulants in patients with AF-related ischemic stroke might be safe.[21]

A 2021 prospective observational study aimed to compare the outcomes of early (≤5 days post-ischemic stroke) versus late (>5 days post-ischemic stroke) initiation of NOACs.[22] Out of 2,550 patients, 1,362 (53%) underwent early NOAC treatment, while 1,188 (47%) received late NOAC treatment. Among those in the early NOAC initiation group, 23 patients (1.7%) suffered recurrent ischemic stroke, and only 2 patients (0.1%) experienced intracranial hemorrhage. In the late NOAC initiation group, 14 patients (1.2%) experienced recurrent ischemic stroke, and 4 patients (0.3%) had intracranial hemorrhage. The results of this study did not confirm an excessive risk of intracranial hemorrhage with early NOAC initiation, suggesting that early NOAC initiation might be reasonable.[22] The study published by Kimura *et al.*[23] investigated an optimal timing scheme for NOAC initiation based on data derived from two registries.[23] Patients were categorized into TIA and three stroke subgroups based on NIHSS scores: Mild (0 – 7), moderate (8 – 15), and severe (≥16). Among 1,797 patients, those in the early DOAC initiation group (785 patients) had a lower risk of stroke or systemic embolism and ischemic stroke compared to the delayed NOAC initiation group (1,012 patients). The early treatment group is defined as patients within each subgroup who started using NOACs earlier than the median start time. The incidence of major bleeding was comparable between the two groups. In addition, in the validation cohort, the rates of ischemic stroke and intracranial hemorrhage were similar between the two groups. The study indicates that initiating NOACs within the first 1 – 4 days decreases the risk of recurrent stroke or systemic embolism without elevating the risk of major bleeding.[23]

Currently, four major clinical trials are underway to ascertain the optimal timing for anticoagulation in AF-related stroke. Timing of Oral Anticoagulant Therapy in Acute Ischemic Stroke With Atrial Fibrillation (TIMING) (NCT02961348)[24] is an open-label, non-inferiority study, where patients with AF-related ischemic stroke were randomly allocated in a 1:1 ratio to commence a NOACs either early (within ≤4 days) or delayed (between 5 and 10 days) after the stroke onset. The primary outcome assessed was the occurrence of recurrent ischemic stroke, symptomatic intracranial hemorrhage, or all-cause mortality within 90 days. However, the TIMING trial was pre-maturely terminated due to the global coronavirus disease-19 pandemic, resulting in the enrollment of only

about 800 participants, despite the initial aim to recruit 3,000 people. The rate of ischemic stroke among patients in the early initiation group was 3.11%, compared to 4.57% in the late initiation group. Notably, there were no reported cases of symptomatic intracranial hemorrhage in either group.[24] However, the majority of patients in this study had low NIHSS scores, indicating that early anticoagulation is safe for patients with mild stroke. Nevertheless, further evidence is required for patients with more severe strokes, characterized by higher NIHSS scores.

Another study, Early versus Late initiation of direct oral Anticoagulants in post-ischaemic stroke patients with atrial fibrillatioN (ELAN) (NCT03148457), is an open-label, randomized trial in which 2,013 patients with AF and ischemic stroke were assigned to receive either early anticoagulation initiation (within 48 h for mild or moderate stroke, or on day 6 or 7 for severe stroke) or late anticoagulation initiation (on days 3 or 4 for mild stroke, days 6 or 7 for moderate stroke, or days 12, 13, or 14 for severe stroke).[25] The outcome comprises the incidence of recurrent ischemic stroke, systemic embolism, major extracranial hemorrhage, symptomatic intracranial hemorrhage, or vascular death within 30 days after randomization. The participants of the study had a median NIHSS score of 5. Within 30 days, 29 participants (2.9%) in the early treatment group and 41 participants (4.1%) in the late treatment group experienced at least one primary outcome event. A separate *post hoc* analysis of the trial results suggested that the incidence of the primary outcome was relatively lower in the early anticoagulation initiation group across different ischemic stroke infarct sizes.[26] The results and *post hoc* analyses of the ELAN trial confirm the benefits of early anticoagulation and question the principle of "1 - 3 - 6 - 12 day" anticoagulation based on stroke severity although further studies are needed for validation.

OPTIMAS (NCT03759938) is another large-scale randomized trial that was conducted in 100 hospitals in the UK. Between 2019, and 2024, a total of 3,648 recent stroke patients were randomly assigned in a 1:1 ratio to receive anticoagulation either early (within 96 h post-stroke) or late (7 – 14 days post-stroke) after an AF-related ischemic stroke.[27] The primary outcome involved a composite of recurrent ischemic stroke, symptomatic intracranial hemorrhage, unclassifiable stroke, or systemic embolism incidence at 90 days. The safety outcome was defined as any occurrence of symptomatic intracranial hemorrhage, severe extracranial hemorrhage, clinically relevant non-severe extracranial hemorrhage, or any severe hemorrhage within 90 days of randomization. Early versus delayed NOAC initiation showed a 3.3% incidence of the primary endpoint at 90 days in both groups. There were no statistically significant differences in the proportion of symptomatic intracranial hemorrhage in the early NOAC initiation group versus the delayed NOAC initiation group (0.6% vs. 0.7%).[28] The findings of indicate that the early initiation of NOAC treatment for AF-related ischemic stroke patients does not increase the risk of hemorrhage, thereby not supporting existing clinical guidelines to delay the initiation of NOAC treatment.

The ongoing STRAT study (NCT03021928) recruited 1,500 participants, divided into two cohorts: mild to moderate stroke patients (1,000 people) and severe stroke patients (500 people).[29] This is a multicenter, prospective, randomized clinical trial in which participants are randomly assigned to one of four groups based on the timing of anticoagulation initiation. For patients experiencing mild to moderate strokes, anticoagulation therapy is initiated on days 3, 6, 10, or 14. In cases of severe stroke, anticoagulation is commenced on days 6, 10, 14, or 21. The key outcome being measured is the occurrence of ischemic or hemorrhagic events within 30 days following the stroke onset.[29] The results of these trials will provide new insights into the optimal timing of early anticoagulation in AF-related ischemic stroke (Table 1).[24-29]

4. Anticoagulation therapy in special populations with AF-related ischemic stroke

4.1. Patients with renal impairment

In clinical practice, patients with AF-related ischemic stroke exhibit diversity, comprising numerous special groups that are less frequently addressed in clinical trials. NOACs are eliminated through the kidneys; however, patients with a creatinine clearance rate below 30 mL/min were excluded from clinical trials. Previous studies, such as the RE-LY trial, have evaluated changes in glomerular filtration rate (GFR) for up to 30 months.[11,30,31] The results showed that, among AF patients undergoing oral anticoagulation therapy, the decline in renal function was more pronounced in the warfarin group compared to the dabigatran group.[32]

Evidence suggests that the use of oral anticoagulants is an effective method of thromboprophylaxis in patients with mild to moderate renal impairment (creatinine clearance >30 mL/min).[33] In addition, a study utilizing the Danish database included AF patients on oral anticoagulants and followed them for 2 years to assess the risk of stroke or thromboembolism and major bleeding. The study found no notable difference in stroke or thromboembolism risk between the two groups. However, apixaban led to a 21%

Table 1. Summary of RCTs evaluating the optimal timing of direct oral anticoagulation after ischemic stroke in atrial fibrillation patients

	TIMING (NCT02961348)	ELAN (NCT03148457)	OPTIMAS (NCT03759938)	START (NCT03021928)
Participants enrollment	888 patients (3000 planned participants)	2013 patients	3648 patients	1500 planned participants (1000 patients with mild or moderate stroke and 500 with severe stroke)
Intervention	Early initiation (within 4 days after acute ischemic stroke) versus late initiation (5 – 10 days after acute ischemic stroke)	Early initiation (within 48 h of a mild or moderate stroke, or at day 6 or 7 after severe stroke) versus late initiation (at 3 – 4 days after a mild stroke, 6 or 7 days after moderate stroke, or 12, 13, or 14 days after severe stroke)	Early initiation (within 96 h after acute ischemic stroke) versus late initiation (7 – 14 days after acute ischemic stroke)	Early initiation (at 3, 6, 10, or 14 days for mild or moderate stroke; at 6, 10, 14, or 21 days for severe stroke) versus late initiation (at 3, 6, 10, or 14 days for mild or moderate stroke; at 6, 10, 14, or 21 days for severe stroke)
Assessment time	90 days	30 days	90 days	30 days
Primary outcome	Composite of stroke recurrence, symptomatic intracerebral hemorrhage, or all-cause mortality	Composite of major bleeding, stroke recurrence, systemic embolism, or vascular death	Composite of stroke recurrence, intracerebral hemorrhage, systemic embolism	Composite of any CNS hemorrhagic or other major hemorrhagic events and the ischemic events of stroke or systemic embolism
Result	The incidence of ischemic stroke was 3.11% in patients who initiated anticoagulation early, compared with 4.57% in patients who started anticoagulation at a later stage. There were no cases of symptomatic intracranial hemorrhage in either group.	The incidence of major outcome events was 2.9% in the early start group and 4.1% in the late start group. Four subjects experienced symptomatic intracranial hemorrhage within 30 days.	The primary outcome occurred in 59 (3.3%) of 1814 participants in the early DOAC initiation group compared with 59 (3.3%) of 1807 participants in the delayed DOAC initiation group. Symptomatic intracranial hemorrhage occurred in 11 (0.6%) participants of the early DOAC initiation group compared with 12 (0.7%) participants of the delayed DOAC initiation group.	To be published.

Abbreviations: RCT: Randomized controlled trial; CNS: Central nervous system; NOAC: Novel oral anticoagulants.

decrease in major bleeding incidents compared to VKAs. The risk reduction was particularly notable in patients with a GFR of 15 – 30 mL/min/1.73 m^2, where apixaban demonstrated a significant reduction in risk compared to VKAs.[34]

Furthermore, there is an ongoing debate regarding the utilization of reduced doses of NOACs in patients with poor renal function. A study from the COMBINE AF database included over 70,000 AF patients. Among all patients included in the study from the COMBINE AF database, the risks of major bleeding, intracranial hemorrhage, stroke, systemic embolism, and death increased significantly with declining renal function. Further analysis demonstrated that in patients with renal impairment and a creatinine clearance of at least 25 mL/min, standard-dose NOACs exhibited superior safety and efficacy compared to warfarin. For patients with renal impairment, standard-dose NOACs provided a greater relative advantage compared to warfarin or low-dose NOACs. Among those with the worst renal function (creatinine clearance <25 mL/min), using low-dose NOACs instead of standard-dose NOACs was linked to a higher risk of stroke, systemic embolism, and death, without a significant decrease in major bleeding or intracranial hemorrhage events. Therefore, reducing the dose of NOACs in patients with renal impairment may be inadvisable, as it could increase the risk of stroke, systemic embolism, and death without providing any safety benefit in terms of bleeding or intracranial hemorrhage.[35] In conclusion, the impact of renal impairment on anticoagulation therapy may be inconsequential in patients with mild impairment. Nevertheless, for patients with severe renal impairment, the limited evidence suggests that the use of standard doses of NOACs may be a viable option.

4.2. Elderly patients

The clinical evidence supporting the use of NOACs in elderly patients with AF-related ischemic stroke remains limited. However, with the increasing aging population,

the number of such patients is gradually rising.[36,37] These patients are frequently excluded from clinical trials due to the presence of comorbidities or frailty, which can lead to uncertainty in clinical decision-making. The current evidence in this field requires further enhancement.

Studies comparing NOACs and VKAs in elderly AF patients indicate that NOACs significantly reduce the risk of stroke and systemic embolism compared to VKAs, without an increase in the risk of major bleeding events.[38] The available evidence suggests that edoxaban is a safer option than warfarin for the management of bleeding in AF patients aged 75 and above, with this advantage being particularly pronounced in patients aged 80 and above.[39] Elderly Asian patients with AF benefit more from edoxaban, apixaban, and dabigatran in stroke prevention, while these drugs also pose a lower bleeding risk.[40] The ELDERCARE-AF study is a multicenter, phase 3 clinical trial utilizing low-dose edoxaban for the treatment of elderly AF patients. This is the first clinical trial investigating NOAC in a population of individuals aged 80 years and above.[39] The study included 984 patients from 164 hospitals in Japan, with participants randomly assigned in a 1:1 ratio to receive either edoxaban (15 mg once daily) or a placebo. The findings demonstrated that the edoxaban group exhibited a 66% reduction in the risk of stroke or systemic embolism in comparison to the placebo, with a similar incidence of major bleeding events.[41]

Previous research has examined patient data from prospective stroke cohorts. The comparison between NOACs and VKAs treatment outcomes was conducted in AF patients aged 85 and above who had experienced a recent ischemic stroke. The results suggest that NOACs offer a comparable net clinical benefit after adjusting for relevant variables, regardless of whether the patient is older or younger than 85 years.[42]

4.3. Patients with cerebral microbleeds or hemorrhage

The detection rate of cerebral small vessel disease on imaging is also increasing, with cerebral microbleeds (CMBs) serving as a biomarker for intracranial hemorrhage.[43] CMBs are prevalent in elderly AF patients who have experienced acute ischemic stroke.[44] A prospective cohort study (NCT02513316) recruited patients diagnosed with AF and acute ischemic stroke or TIA from 79 hospitals in the UK and one hospital in the Netherlands. These patients underwent treatment with either VKAs or NOACs. The main focus was on the incidence of symptomatic intracranial hemorrhage-monitored up until the final follow-up at 24 months. The results indicated that in AF patients receiving anticoagulation therapy after a recent ischemic stroke or TIA, CMBs were independently associated with the risk of symptomatic intracranial hemorrhage and may serve as a valuable factor in guiding anticoagulation therapy decisions.[45]

A research team from Korea investigated the influence of CMBs, their burden, and their location on the outcomes of AF patients receiving different anticoagulation therapies after ischemic stroke. The primary outcome was the occurrence of major adverse cerebrovascular and cardiovascular events (MACCE), such as stroke, acute myocardial infarction, or vascular death, within 2 years. After accounting for confounding factors, the results showed a significant link between the presence of CMBs and the future risk of MACCE. The risk of MACCE was similar in patients with only one CMB and those without CMBs. However, patients with multiple CMBs (≥2), particularly those with a high burden of CMBs (≥5), exhibited a markedly elevated risk of MACCE. The location of CMBs was not found to significantly impact the incidence of MACCE. For patients treated with warfarin, there was a significant link between CMBs and the risk of MACCE, but this was not seen in those treated with NOACs.[46] Hence, in AF patients who have had an ischemic stroke, the risk of subsequent vascular events may rise with an increase in the number of CMBs. This phenomenon appears to be more pronounced in patients who are taking warfarin rather than NOACs.

In addition, the CMB-NOW study included ischemic stroke patients with non-valvular AF and at least one CMB detected on baseline magnetic resonance imaging.[47] The study discovered that 28.6% of patients in the NOAC cohort and 66.7% in the warfarin cohort showed an elevated number of CMBs.[47] While the sample size was limited, this study tentatively suggested that NOACs might be less likely to worsen CMBs compared to warfarin in the treatment of AF-related ischemic stroke.

The decision to resume anticoagulation following an intracranial hemorrhage presents a significant clinical dilemma, largely due to the heterogeneity and the absence of high-level clinical guidance. This often leads to a high variability in practice and reliance on empirical judgment in decision-making. They suggested that anticoagulation therapy could be recommenced 4 – 8 weeks after the hemorrhage, a principle still followed in current clinical practice.[16]

In summary, CMBs are relatively common in imaging studies of AF patients with ischemic stroke, and their presence is associated with the risk of hemorrhage. While the current evidence for secondary prevention is limited, it supports considering NOACs in patients with CMBs. In cases of intracranial hemorrhage, restarting anticoagulation

may be necessary. However, the optimal timing for this should be individualized, and further clinical evidence is warranted to guide these decisions.

5. Conclusion

AF-related ischemic stroke poses a significant clinical burden. The use of NOACs in non-valvular AF patients is on the rise. There is ongoing debate regarding the timing of anticoagulation and its application in special populations. It is crucial to initiate and maintain long-term anticoagulation therapy as early as possible, following standardized protocols, while carefully managing the risk of bleeding. For special populations, such as the elderly, individuals with renal impairment, and those with cerebral microbleeds, tailoring the anticoagulation approach to the specific clinical context is crucial. This personalized strategy aims to maximize the benefits of stroke prevention while minimizing the risks associated with anticoagulation therapy.

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Conflict of interest

The authors declare they have no competing interests.

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REVIEW ARTICLE

Acute symptomatic perinatal stroke syndromes: A review of risk factors, presentation, evaluation, and outcomes

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Abstract

Perinatal stroke encompasses a diverse group of localized brain lesions that develop during the early stages of brain maturation. While many of these injuries manifest clinically within the first days of life, some may not be noticeable until later, often within the first year of life. These injuries are referred to as presumed perinatal stroke. This review aims to provide a clinical update on the current evidence regarding the epidemiology, risk factors, clinical manifestations, diagnosis, treatment, and complications of the different types of perinatal stroke. Major databases, including PubMed, ScienceDirect, PubMed Central, and Google Scholar, were searched using Medical Subject Headings and regular keywords. The search terms used were "stroke" AND "neonate," "stroke" AND "fetus," "stroke" AND "perinatal," "stroke" AND "perinatal" AND "clinical presentation," "stroke" AND "perinatal" AND "diagnosis," "stroke" AND "perinatal" AND "management," "stroke" AND "perinatal" AND "outcomes." Any form of study on perinatal stroke was included, while literature not written in or translated into English was excluded from the study. Some of the clinical features of perinatal stroke include seizures, irritability, hypotonia, lethargy, or apnea. Cerebral palsy, epilepsy, developmental delay, and mental impairment are some complications that may arise following these lesions.

Keywords: Perinatal; Stroke; Neonate; Fetal; Syndrome

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1. Introduction

Stroke in children is an increasingly significant cause of health, financial, and social burdens for children, their families, and society. The overall incidence of pediatric stroke is recognized as 3 – 25/100,000 children, and due to recent reports on the disease burden, it is considered an orphan disease.[1] Unlike adults, where 80 – 85% of stroke cases are ischemic, ischemic stroke constitutes about 50% of cases in the pediatric population. Similarly, the spectrum of stroke causes also varies considerably between adults and children. Hypertension, diabetes, and atherosclerosis are the main causes of stroke in adults, whereas pediatric stroke is commonly caused by non-atherosclerotic cardiovascular diseases and hematological disorders, with some cases attributed to inherited metabolic disorders, infections, or traumatic conditions.[2] The World Health Organization defined stroke in 1970 as "rapidly developed clinical signs of focal

(or global) disturbance of cerebral function, lasting more than 24 h or leading to death, with no apparent cause other than of vascular origin."[3] In 2013, the American Heart/Stroke Association (AHA/ASA) redefined it as "an episode of acute neurological dysfunction presumed to be caused by ischemia or hemorrhage, persisting ≥24 h or until death."[4] This definition applies to both adult and pediatric stroke. In children, features of acute neurological dysfunction can easily be missed, and therefore, a high index of suspicion is needed.[5]

Stroke in children has been erroneously regarded as uncommon or a rare event. However, it constitutes a significant cause of morbidity and mortality in children. Unlike adults, children with stroke face considerable delays in their access to medical care. In addition, features of acute neurologic deficit are usually subtle and often not recognized in children. Therefore, clinical diagnosis of stroke is often not considered, which may result in significant delays before receiving diagnostic imaging.[6] The median interval of the time delay in the diagnosis of childhood stroke was estimated to be 23 h from symptom onset to diagnosis.[7] This diagnostic delay in the identification and management of pediatric stroke plays a significant role in causing high stroke mortality and disabilities in children. This can be prevented and improved by developing and implementing acute stroke protocols or guidelines and establishing a primary pediatric stroke center with a strong stroke team that will ensure timely delivery of care to pediatric patients with stroke and early application of diagnostic approaches.[8] Pediatric stroke can be classified based on the nature of the stroke etiology, as either ischemic or hemorrhagic, based on the blood vessel involved and the mechanism of injury, as either arterial stroke or venous stroke, consisting of hemorrhagic stroke and cerebral sinovenous thrombosis (CSVT), and based on the timing of the injury, as either perinatal or childhood stroke.[5] It can also be classified based on the onset of clinical features, as either acute symptomatic perinatal stroke or presumed perinatal stroke. Thus, this review aims to provide an overview of acute symptomatic perinatal stroke syndromes.

2. Definition

Perinatal stroke is defined as a stroke occurring from 28 weeks of gestation to the first 7 days of life. However, some scholars consider a stroke that occurs from 14 to 20 weeks of gestation through 28 days after birth as a perinatal stroke, due to some documented evidence of lesions observed before 28 weeks of gestation.[9] The National Institute of Neurologic Disorders and Stroke Common Data Elements defines it as "a group of heterogeneous conditions in which there is a focal disruption of cerebral blood flow secondary to arterial or cerebral venous thrombosis or embolization, between 20 weeks of life through the 28th postnatal day confirmed by neuroimaging or neuropathological studies."[10] Perinatal stroke is a heterogeneous group of localized brain lesions that develop during the early stages of brain maturation. It is estimated that over 5 million individuals are affected worldwide, often resulting in long-term sequelae.[11]

3. Classification

Perinatal stroke is classified into two based on timing; fetal stroke, occurring before birth from 14 weeks of gestation until just before delivery,[12] and neonatal stroke, occurring from birth to 28 days after birth.[5] Based on the onset of clinical manifestation, perinatal stroke is further classified as acute symptomatic perinatal stroke or presumed perinatal stroke.[13] Acute symptomatic perinatal stroke presents with clinical symptoms within days after birth, whereas presumed perinatal stroke presents with a delayed manner, such as early handedness or convulsion occurring approximately 4 – 12 months after delivery.[13] The term "presumed perinatal stroke" describes chronic infarcts diagnosed later in infancy that are presumed to have occurred perinatally. It is typically identified as a remote infarction following neuroimaging in infants presenting with early abnormal handedness or convulsions.[14,15] Acute symptomatic perinatal stroke is the most common perinatal stroke syndrome and is broadly subdivided into three main categories:[13] perinatal arterial ischemic stroke (PAIS), perinatal CSVT (PCSVT), and perinatal hemorrhagic stroke (PHS). Similarly, the presumed perinatal stroke syndromes are also categorized into three:[13] arterial presumed perinatal ischemic stroke, periventricular venous infarction, and presumed PHS, as shown in Figure 1.

3.1. PAIS

PAIS is the most common type of perinatal stroke and the most frequent presentation of all childhood strokes.[13] It is defined as "a focal disruption of cerebral blood flow secondary to arterial or cerebral venous thrombosis or embolization, between 20 weeks of fetal life through the 28th postnatal day, confirmed by neuroimaging."[16] Most perinatal ischemic strokes occur in an arterial distribution, classified as PAIS, although a smaller number have a venous distribution, suggestive of venous infarction.[17]

3.1.1. Epidemiology

Arterial ischemic infarction is the cause of the majority of perinatal strokes, with an approximate incidence of 1 in 3,500 births.[18] The incidence of ischemic stroke is significantly higher in newborns than in older children,

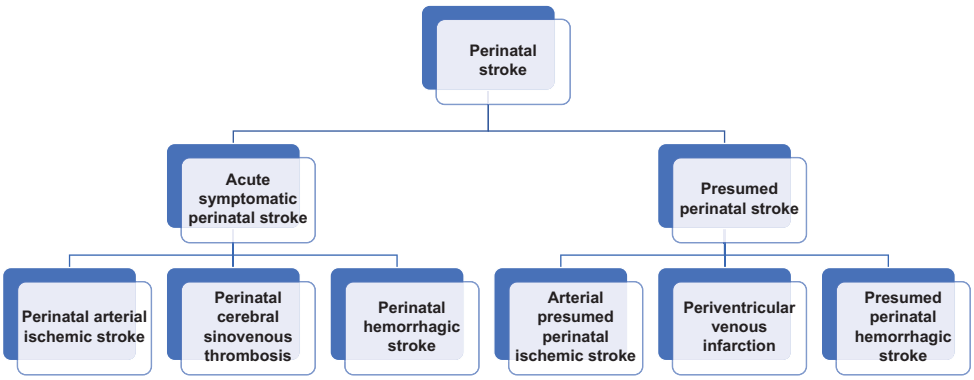

Figure 1. Classification of perinatal stroke syndromes based on the onset of clinical manifestations

with an approximately six-fold increase, accounting for about 80% of perinatal stroke cases, and affecting more males than females.[18,19]

3.1.2. Pathophysiology and risk factors

The main pathophysiologic mechanisms of perinatal ischemic stroke include embolism, from both cardiac or extracardiac origins, and thrombosis secondary to abnormal homeostasis. Several factors could increase the risks of PAIS and are categorized into maternal and neonatal factors (Table 1). Maternal factors include maternal thrombosis, which may be caused by advanced maternal age, dehydration or shock, maternal infection, obesity, a personal or family history of thromboembolic events, surgery (including surgical delivery), and prolonged bed rest.[20] Other maternal factors include chorioamnionitis, oligohydramnios, premature rupture of membranes, primiparity, history of infertility, preeclampsia, vacuum extraction, and coagulopathies that may lead to thrombosis at either the maternal side of the placenta (where maternal uterine spiral arteries supply the fetus) or the fetal side, which may be an important source of emboli that pass through the hepatic and pulmonary circulation through patent foramen ovale to the fetal brain.[5] Another significant maternal factor is placental pathology due to inflammation (chorioamnionitis), infection (SARS-CoV-2 placentitis), or hypoxia (multiple pregnancies).[21] The greater the number of risk factors, the higher the risk of developing PAIS.[22] Neonatal factors encompass deficiencies of coagulation factors, inherited thrombophilia, cardiac disorders such as congenital heart diseases, infections, trauma, and birth asphyxia.[22,23] In addition, congenital brain malformations, such as prosencephaly and genetic mutations, are associated with fetal stroke.[5]

Table 1. Risk factors for perinatal arterial ischemic stroke

Maternal risk factors	Neonatal risk factors
Maternal thrombosis	Deficiency of coagulation factors
Maternal infection including chorioamnionitis	Inherited thrombophilia
Maternal obesity	Birth asphyxia
Personal or family history of thromboembolic events	Congenital brain malformations like prosencephaly
History of infertility	Birth traumas
Surgical procedures: surgical delivery, vacuum extraction	Cardiac disorders like congenital heart diseases
Prolong bed rest	Neonatal infections
Oligohydramnios, primiparity, or PROM	Genetic mutations

Abbreviations: PROM: Premature rupture of membranes.

3.1.3. Clinical presentation

A common feature of perinatal stroke is localized motor seizure, typically involving a single extremity.[5,24] Evidence suggests that seizures occur in up to 94% of neonatal stroke cases, supported by a Canadian study where seizures were the predominant clinical presentation in approximately 88% of neonatal strokes.[19] Unlike neonatal encephalopathy, seizures in perinatal stroke are not commonly accompanied by altered levels of consciousness, feeding difficulties, or abnormal tone. Infants often appear normal between seizures, with only subtle, non-specific systemic signs such as hypotonia, lethargy, or apnea, if present at all.[9] In rare cases of PAIS, encephalopathy may be the predominant clinical feature and is often misdiagnosed for hypoxic-ischemic injury rather than AIS. However, neuroimaging can differentiate the two conditions, with the left-sided cerebral hemisphere infarction identified in 80% of babies with unilateral infarctions.[24] Clinical and sub-clinical seizures may occur during the neonatal period but are often confused with normal infant movements, leading to delayed diagnosis. Consequently, a diagnosis of presumed perinatal stroke is often made later in infancy when the child presents with delayed motor milestones, epilepsy, asymmetric motor function, or early handedness.[24,25]

3.1.4. Diagnosis

Diagnosis of PAIS is primarily based on neuroimaging. Magnetic resonance imaging (MRI) should be the primary method to diagnose perinatal stroke. However, other neuroimaging studies, such as computed tomography (CT), ultrasonography, functional MRI, magnetic resonance angiography (MRA) for detecting occlusion and hypoplastic vessels, and magnetic resonance venography (MRV) for venous thrombosis, can also be used.[5,9] In addition, supportive investigations, such as thrombophilia testing, can be performed. However, recent evidence suggested a lack of clinical benefit from this testing, as levels of protein C, protein S, antithrombin, and factor XI are normally reduced in neonates to 30% of adult levels, reaching adult levels at various stages of childhood, which may be misleading.[5] Other supportive investigations include the use of plain skull films, which may show thinning of the skull bone usually on the affected side, electroencephalogram (EEG) for prognostication, which is usually done in the first 24 h, and cerebral blood flow studies, which may show asymmetric flow velocities, especially in middle cerebral artery infarction.[9] Additional investigations to rule out risk factors can be performed, including maternal testing for coagulation abnormalities, neonatal testing for metabolic and coagulation abnormalities, lumbar puncture, urine toxicology screening, and cardiac imaging.[9] In a study by Server *et al.*,[26] the most common site of injury in neonatal ischemic stroke was the left middle cerebral artery territory, more often involving areas posterior to the central sulcus[26] (Figure 2).

3.1.5. Treatment

Treatment modalities for PAIS include emergency treatment and strategies for secondary and tertiary prevention. Emergency treatment is further subdivided into general supportive measures and hyper-acute stroke therapy. Recommended supportive measures for PAIS include fever control with antipyretics, treatment of dehydration with intravenous fluids, correction of anemia, control of seizures with antiepileptics, and optimization of oxygenation.[5] However, there is no evidence of clinical benefits of supplemental oxygen in non-hypoxic neonates or prophylactic anticonvulsants without clinical or EEG evidence of seizures.[27] Hyperacute emergency treatment involves thrombolytic therapy and mechanical thrombectomy, but current evidence discourages their use in neonates due to the lack of clinical benefit of thrombolytic therapy and the small artery size of neonates, which poses challenges for thrombectomy.[6,28] Treatment for secondary prevention includes the use of antiplatelet therapy with aspirin and anticoagulation using low-molecular-weight heparin or unfractionated heparin. However, these are not commonly used due to the reduced risk of recurrence in neonates with PAIS but are strongly indicated in

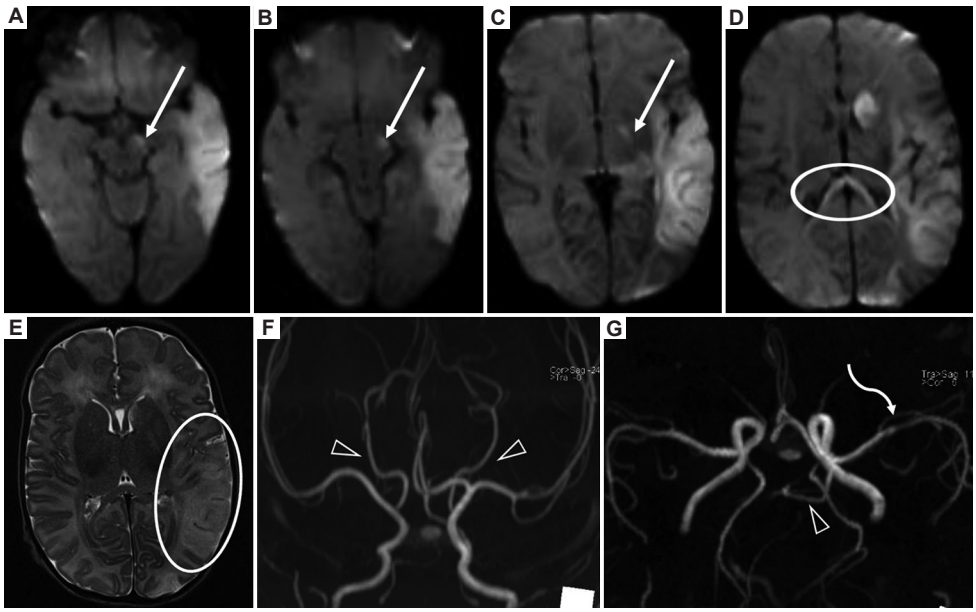

Figure 2. Neonatal arterial ischemic stroke. Acute middle cerebral artery (MCA) infarct of term neonate who presented with the right-sided seizures. Magnetic resonance imaging was performed on day 3. (A-D) Axial diffusion-weighted imaging shows an acute ischemic infarct in the territory of the left MCA. There are signs of early network injury of the splenium of the corpus callosum (circle) as well as restricted diffusion in the left posterior limb of the internal capsule and cerebral peduncle, consistent with acute Wallerian degeneration (arrows in A, B, C). (E) The axial T2-weighted image demonstrates a missing cortex sign (circle). (F and G) Magnetic resonance angiography shows a fetal posterior cerebral artery bilaterally, a persistent trigeminal artery (arrowheads), and a narrowed left M2 segment (curved arrow in G). Image taken from Server *et al.*[26]

neonates with documented evidence of thrombophilia or complex congenital heart disease due to a high rate of recurrence.[21] Recently, stem cell therapies were employed in the treatment of PAIS. A systematic review of preclinical studies by Lehnerer *et al.*[29] found that mesenchymal stem cell therapy shows promise for PAIS, as it caused significant improvement in cognitive performance and sensorimotor function in PAIS-injured animals.[29]

3.1.6. Outcome

PAIS is associated with several complications, such as prolonged neurologic deficits, cerebral palsy, cognitive dysfunction, speech impairment, mental retardation, and epilepsy.[30] However, it is difficult to determine stroke-related complications in neonates with complex congenital heart disease or serious medical comorbidities, as these conditions can lead to abnormal brain development even in the absence of a stroke.[31] Nevertheless, standard motor evaluation and careful assessment of the corticospinal tract on MRI could greatly help determine the chance of cerebral palsy development after PAIS.[32]

3.2. PCSVT

PCSVT is a rare disease associated with serious neurologic sequelae. However, diagnosis is becoming more rapid, driven by increased clinical awareness and improved neuroimaging techniques.[33] CSVT significantly contributes to neonatal morbidity and mortality. Notably, neonates account for 18 – 51% of all reported pediatric CSVT cases, making them the most vulnerable population for this condition.[34] Neonatal CSVT is defined as "a presence of thrombus in one or more of the cerebral veins or sinuses in the first 28 days after birth." The presence of a clot alone does not constitute a stroke; however, venous infarction, which occurs in approximately half of the affected neonates, can lead to stroke.[11]

3.2.1. Epidemiology

The highest lifetime incidence of CSVT occurs during the neonatal period. Due to subtle clinical presentations and diagnostic challenges, the true incidence rates are likely underestimated.[35] PCSVT has a lower incidence rate compared to PAIS, estimated to be between 0.6 and 12/100,000 live births. A slightly higher incidence, up to 4%, is observed in preterm infants, likely due to the routine application of cranial ultrasonography with Doppler in this population.[36] A study by Sorg *et al.*[37] found an incidence of 6.6/100,000 live births for CSVT in both term and preterm infants.[37] CSVT exhibits a male predominance, with varying incidence rates reported across different countries. For example, the Canadian registry reports 47 cases/100,000 live births, while the Dutch registry reports 1 – 12 cases/100,000 live births.[38]

3.2.2. Pathophysiology and risk factors

As the name suggests, the primary pathophysiologic mechanism of CSVT is thrombosis in one or more of the cerebral veins or sinuses. Numerous risk factors have been identified that may contribute to the occurrence of CSVT. Studies report a single risk factor in approximately 48% of cases and multiple risk factors in about 39% of cases.[36] These factors can be maternal, intrapartum, or neonatal (Table 2). The most commonly reported maternal factor is pre-eclampsia, which induces a hypercoagulable state. Other maternal factors include gestational hypertension, chorioamnionitis, and factors leading to fetal distress syndrome.[39] Intrapartum factors include intrapartum asphyxia, meconium aspiration, intubation at birth, and complicated delivery, which is reported in approximately 60% of cases.[36] Neonatal factors include sepsis, meningitis, dehydration, cardiac defects, genetic mutation, congenital thrombophilia, and coagulation disorders.[38] Mechanical compression of the superior sagittal sinus by the occipital bone, which can occur when newborns are placed in a supine position or complicated deliveries with skull molding, has been independently associated with an increased risk of neonatal CSVT. Proper positioning can help reduce this risk.[40]

3.2.3. Clinical presentation

The clinical features of PCSVT are often more subtle than those of PAIS, leading to missed diagnoses. However, it can present with non-specific symptoms, such as irritability, respiratory distress, apnea, poor feeding, seizures, jitteriness, or lethargy.[41,42] Presentation typically occurs at birth or within the 1st week of life, with seizure being the most common manifestation, occurring in approximately 60 – 70% of cases. This may prompt early neuroimaging and, consequently, early detection.[39] In some cases, CSVT is discovered

Table 2. Risk factors for perinatal cerebral sinovenous thrombosis

Maternal risk factors	Intrapartum risk factors	Neonatal risk factors
Pre-eclampsia	Intrapartum asphyxia	Sepsis
Gestational hypertension	Meconium aspiration	Meningitis
Chorioamnionitis	Complicated delivery	Dehydration
Hypercoagulable state	Intubation at birth	Cardiac defects
		Genetic mutation
		Congenital thrombophilia
		Coagulation disorders

incidentally in critically ill neonates, such as those with bacterial meningitis or in asymptomatic, extremely low birth weight neonates.[39] In addition, neonates with CSVT may only be identified later in the neonatal period when they present with delayed seizures or features of encephalopathy; however, these presentations can also be non-specific and difficult to recognize.[39]

3.2.4. Diagnosis

The goal standard for diagnosing PCSVT is neuroimaging, which aims to detect thrombi or lack of flow in the cerebral venous system and to identify any accompanying parenchymal lesions, which are present in approximately 60 – 80% of cases.[26,43] MRV, either alone or in combination with MRI, is the goal standard neuroimaging modality for diagnosing PCSVT. However, other neuroimaging modalities, such as MRI (which can detect additional white matter lesions due to periventricular congestion), cranial ultrasonography, or CT venography, can also be used for diagnosis.[26,44] Due to periodic flow gaps in the venous systems of neonates, meticulous interpretation of neuroimaging features is necessary. Therefore, contrast-enhanced MRV is needed, especially in the acute phase, and interpretation should be made in conjunction with other diagnostic findings and the patient's clinical presentation.[39] Figure 3 illustrates contrast-enhanced imaging detecting thrombosis in the cerebral venous system with associated cortical lesions. The International Study on Cerebral Vein and Dural Sinus Thrombosis identified the following distribution of CSVT locations: transverse sinus (86%), superior sagittal sinus (62%), straight sinus (18%), cortical veins (17%), jugular veins (12%), and vein of Galen along with internal brain veins (11%). Therefore, careful attention should be paid during neuroimaging studies and interpretation.[38] Other supportive investigations include the use of color flow Doppler (although it has low sensitivity) to detect the absence or reduction of venous flow, EEG in neonates with symptomatic seizures to detect the location of the seizures, cardiac ultrasonography to detect cardiac anomalies, and laboratory tests for coagulation status.[36]

3.2.5. Treatment

The primary aim of CSVT treatment is to address any underlying cause that may have led to the development

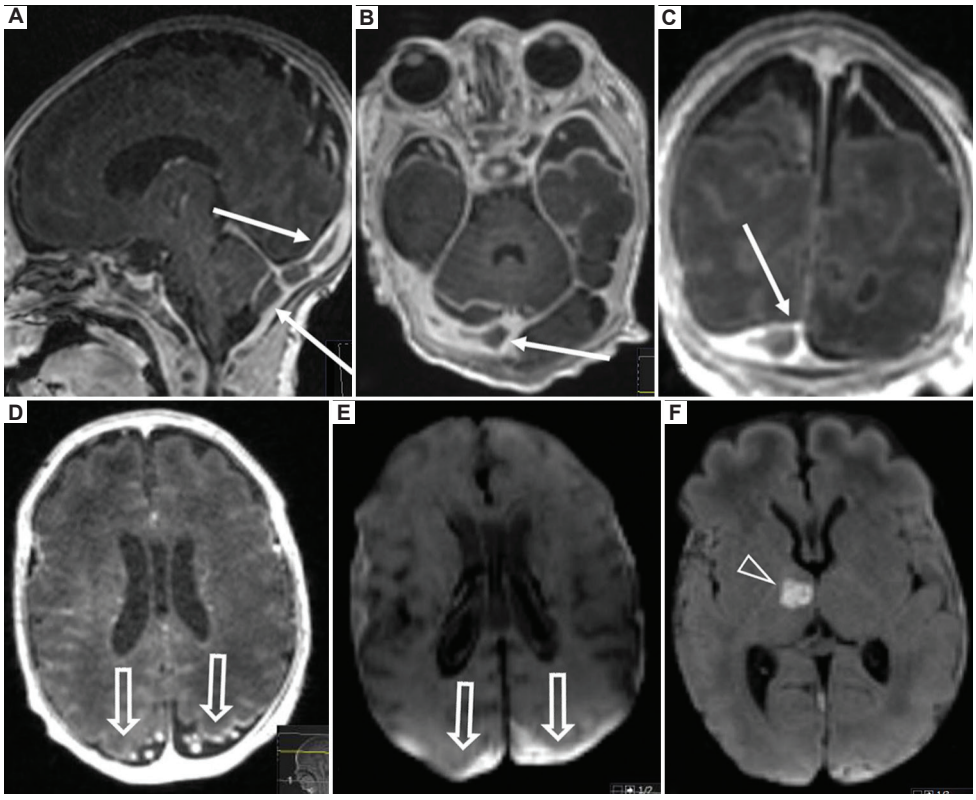

Figure 3. Neonatal cerebral sinovenous thrombosis and neonatal meningitis (*Escherichia coli*) in a 19-day-old neonate. (A-C) Sagittal, axial, and coronal postcontrast T1-weighted images show a clot within the superior sagittal venous sinus and in the right transverse venous sinus (arrows). (D and E) Axial contrast-enhanced T1-weighted image shows subdural empyema (open arrows in D), and diffusion-weighted imaging shows reduced diffusion within the subdural fluid, confirming purulent material (open arrows in E). (F) Diffusion-weighted imaging shows a hyperintense signal in the right thalamus, consistent with infarction (arrowhead). Image taken from Server *et al.*[26]

of the thrombus, including correction of dehydration and anemia, treatment of infections like sepsis or meningitis, and early management of congenital heart disease.[19] At present, there is no documented evidence of clinical benefit from thrombolytic therapy or endovascular therapy in the hyperacute treatment of neonatal CSVT.[5] Other supportive, non-invasive therapy involves adjusting newborns' pillows (when placed in a supine position) to decompress the occipital bone, which increases blood flow in the sigmoid and superior sagittal sinuses.[5] The use of anticoagulation in neonates with CSVT has been a subject of great debate. However, anticoagulation appears to be safe even in the presence of thalamic hemorrhage, may prevent the progression of the initial thrombus and enhance recanalization, and has been recommended by the American Chest Physicians and British Committee for Standards in Hematology guidelines.[36]

3.2.6. Outcome

The commonly reported complication is neurological sequelae, which tend to be more severe in neonates with venous infarction and seizures at the time of diagnosis.[19] Other complications include intracranial hemorrhage, neurodevelopmental impairment (more common in neonates with large venous infarction), cognitive and behavioral disorders, cerebral palsy, and epilepsy.[42,45] The presence of a parenchymal infarct, bilateral involvement, and neurological comorbidities indicate a poor prognosis and neonates with deep venous thrombosis and thalamic hemorrhage are at increased risk of developing late-onset epilepsy.[39]

3.3. PHS

PHS involves bleeding into the brain of a fetus or newborn due to the rupture of a blood vessel. It can lead to serious morbidity and mortality with lifelong disability.[46] Presentation of hemorrhagic stroke in term neonates is not uncommon, but research in this area is limited, with variable terminologies posing serious challenges in its proper understanding. PHS can be defined as blood accumulation in a localized area within the brain parenchyma, supported by neuroimaging autopsy findings, with features of encephalopathy such as altered consciousness level, convulsions, or neurological disability within the first 28 days of life.[46] This definition particularly describes the word neonates and excludes intraventricular hemorrhages common in infants born prematurely, where hemorrhages in the germinal matrix are often seen.[47] Neonatal hemorrhage in the newborn is often classified based on the brain area affected. For example, hemorrhages in the ventricles or choroid plexus are termed intraventricular hemorrhages, hemorrhages due to internal cerebral vein occlusion are called thalamo-ventricular hemorrhages, and hemorrhage in the parenchyma of a cerebral lobe is referred to as lobar cerebral hemorrhages, while others include cerebellar, subarachnoid, epidural, and subdural hemorrhages.[48] Nonetheless, isolated subarachnoid, epidural, or subdural hemorrhages that are typically caused by trauma do not constitute neonatal hemorrhagic stroke.[46] In general, neonatal hemorrhage is classified into primary idiopathic hemorrhage and hemorrhagic transformation of arterial or venous infarcts, with profound difficulty in differentiating between the two. Any secondary hemorrhagic transformation of infarction within a well-recognized large artery infarct zone should be classified as hemorrhagic AIS, but on the other hand, any hemorrhage related to deep vein occlusion, internal cerebral, or basal vein tributaries should be classified with CSVT.[48]

3.3.1. Epidemiology

The prevalence of PHS, comprising hemorrhagic transformation of ischemic injury and presumed PHS, is 16/100,000 as compared to the previously reported prevalence of 6.2/100,000.[46,49] Data regarding PHS are limited; however, a recent population-based study determined that the birth prevalence of primary PHS in term or near-term neonates is 10.5/100,000.[46,49] This data excludes other types of neonatal hemorrhages, such as isolated subdural or subarachnoid hemorrhage, as well as germinal matrix bleeding in preterm newborns.[50] When considering both primary idiopathic hemorrhage and hemorrhagic transformation of arterial or venous infarcts, the overall incidence of PHS is approximately 1 in 6,300 live births, with idiopathic PHS estimated at 1/9,500 live births.[11]

3.3.2. Pathophysiology and risk factors

Acute or prolonged spontaneous bleeding underlies the pathophysiologic mechanism of PHS. Unlike other perinatal stroke, PHS has some definitive causes, especially in term neonates. These include inherited or acquired coagulopathies like hemophilia, or hemorrhagic disease of newborns, thrombocytopenia, trauma, and, rarely, structural vascular lesions like arteriovenous fistula.[5] Nevertheless, in the majority of cases, no definitive causes of NHS are identified, but many risk factors have been reported. These recognized factors include emergency cesarean delivery, fetal distress, male gender, and post-maturity.[49,51] Other risk factors include genetic mutation and family history suggestive of an autosomal dominant syndrome, such as hereditary hemorrhagic telangiectasia, porencephaly, glaucoma, or cataracts.[52,53]

3.3.3. Clinical presentation

Clinical features usually occur early in the neonatal period and tend to be acute. Localized and systemic non-specific features form the hallmark of the clinical manifestation. These include unexplained apnea, encephalopathy, feeding difficulties, fever, convulsions, irritability, bulging fontanel, or excessive growth of the cranial vault.[46,54,55] In some cases, asymptomatic cases of PHS, which occur in about 15% of near-term or term neonates, are incidentally identified through routine neuroimaging investigation.[56]

3.3.4. Diagnosis

The diagnostic method of choice for detecting hemorrhages in neonates is MRI. Similarly, susceptibility-weighted imaging, a blood-sensitive MRI sequence, and gradient echo remain the best diagnostic techniques for hemorrhagic stroke in neonates. When performed in conjunction with parenchymal sequences (T1 and T2), these techniques can help determine the timing of the bleeding event.[5,26] Vessel imaging, such as MRA, MRV, and diffusion-weighted imaging should be used to identify possible etiologies.[5,26] As shown in Figure 4, an MRA identified occlusion of the right internal carotid artery/middle cerebral artery segments, indicating a possible etiology. However, for immediate and quick diagnosis of PHS, cranial ultrasound and CT should be used. Specific patterns and sites of hemorrhage need to be carefully identified, such as hemorrhages within the ventricles or thalami.[57] Other supportive investigations comprise a full blood count with differentials, including platelets measurement and clotting profile for partial thromboplastin time and an international normalized ratio for assessment of coagulation.[54]

3.3.5. Treatment

The management of PHS is primarily supportive and typically requires a multidisciplinary approach involving a neonatologist, hematologist, neurologist, and neurosurgeon with expertise in neonatal neurointensive care and seizure monitoring.[39] An urgent hematological work-up is necessary to ensure adequate hemoglobin levels, and normal platelet count, and to rule out coagulation factor deficiencies. Markedly low hemoglobin or extremely low platelet count may require urgent transfusion with blood products. In cases of coagulation factor deficiencies, high-dose Vitamin K can be used for treatment.[5,39] In the event of secondary hemorrhage, acute surgical decompressive craniectomy or hematoma evacuation may be considered to avoid damage to surrounding brain

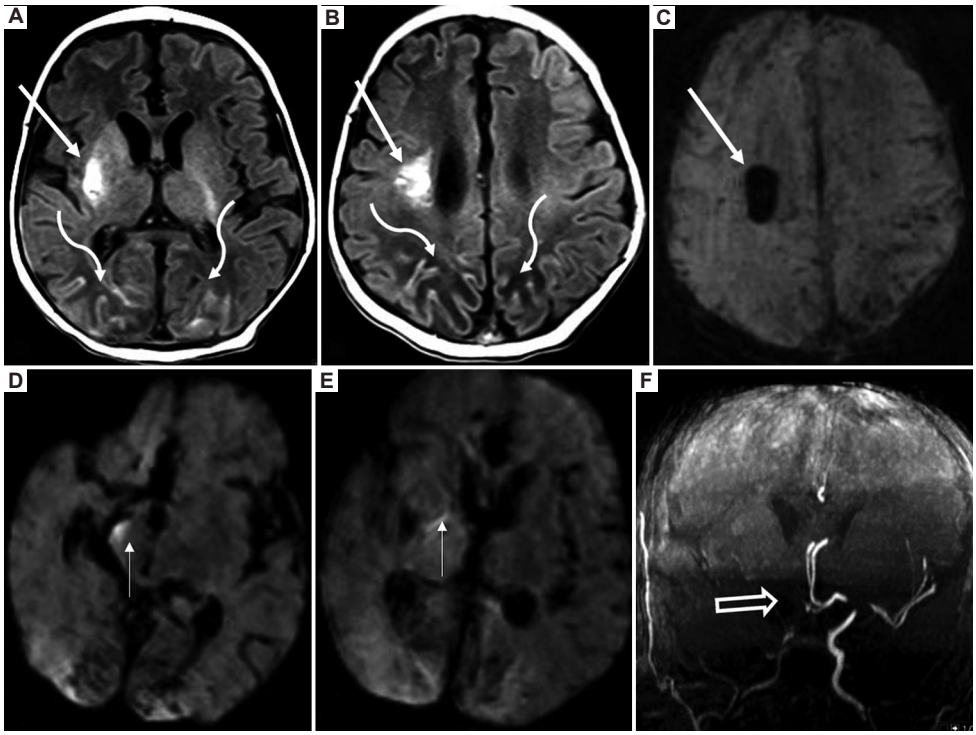

Figure 4. Neonatal hemorrhagic stroke. Hemorrhagic infarct, hypoxic-ischemic encephalopathy, and Apgar scores <5 at 10 min with therapeutic hypothermia. Brain magnetic resonance imaging was performed on day 13. (A-C) Hemorrhagic stroke as seen on axial T1-weighted images (A and B), susceptibility-weighted imaging (C) (arrows), and cortical laminar necrosis bioccipital and biparietal (curved arrows). (D and E) Diffusion-weighted imaging shows Wallerian degeneration of the corticospinal tract (thin arrows). (F) The magnetic resonance angiography demonstrates occlusion of the right internal carotid artery/middle cerebral artery segments (open arrow). Image taken from Server *et al.*[26]

Table 3. Comparison between the three different types of acute symptomatic perinatal stroke syndromes

Factors	PAIS	PCSVT	PHS
Incidence	1 in 3,500 newborns	0.6 – 12/100,000 live births	1 in 6,300 live births
Predominant clinical features	Focal motor seizure, rarely encephalopathy	Seizures	Acute seizures, unexplained apnea, encephalopathy, raised fontanel, or a cranial vault overgrowth.
Goal standard diagnostic technique	MRI	MRV alone or in combination with MRI	Blood-sensitive MRI sequences
Treatment	Mainly supportive; thrombolytic therapy not recommended; anticoagulation not recommended unless in cases of thrombophilia or complex congenital heart disease.	Mainly supportive, thrombolytic therapy is not recommended, anticoagulation is recommended.	Mainly supportive, an acute surgical evacuation of hematoma in some cases.
Complications	Long-term neurologic deficits	Long-term neurologic sequelae.	Rare when occurs in isolation.

Abbreviations: MRI: Magnetic resonance imaging; MRV: Magnetic resonance venography; PAIS: Perinatal arterial ischemic stroke; PCSVT: Perinatal cerebral sinovenous thrombosis; PHS: Perinatal hemorrhagic stroke.

structures. If performed carefully, this procedure can significantly reduce raised intracranial pressure associated with the hematoma.[39] Acute surgical evacuation of the hematoma may be necessary for massive or infratentorial hemorrhages that threaten to compress brain stem structures, cause herniation, or lead to acute obstructive hydrocephalus.[46,54] Imaging after the resorption of blood products, typically around 3 months, is recommended to identify potential underlying pathologies, such as brain tumors or arteriovenous malformations.[58] In addition, continuous monitoring of head circumference is necessary to detect hydrocephalus, which may result from the intraventricular extension of the hemorrhage and could require ventricular drainage or later shunting if indicated.[11]

3.3.6. Outcome

PHS has a better long-term outcome compared to other subtypes of perinatal strokes. However, if it is accompanied by other comorbidities such as PAIS, hypoxic-ischemic encephalopathy, and long-term life-threatening conditions, like hemophilia, the prognosis is typically poor.[59,60] Other complications may include epilepsy, hydrocephalus, motor impairment, and cognitive and behavioral dysfunctions.[46,61] Table 3 compares and summarizes the three different types of acute symptomatic perinatal stroke syndromes.

4. Conclusion

This general overview of the different types of perinatal strokes is intended to help clinicians better identify and manage different stroke types during the perinatal period. The review extensively discussed the epidemiological profile, risk factors, clinical presentation, treatment, and potential complications of different types of perinatal strokes. Stroke is a preventable disease; however, primary prevention in perinatal stroke is almost impossible, except when diagnosed early *in utero*. In addition, due to a very low risk of recurrence, secondary prevention is rarely achievable. Tertiary prevention entails various rehabilitative therapies. Finally, the following recommendations from the AHA/ASA[5] regarding perinatal stroke should be considered in clinical practice: (i) routine administration of Vitamin K to newborns, (ii) thrombolytic agents or embolectomy should be avoided in neonates with arterial occlusion, (iii) anticoagulation is recommended for neonates at risk of stroke recurrence due to severe thrombophilia or cerebral embolism from cardiac disease, (iv) surgical evacuation of an intracranial hematoma should only be considered in neonates if there is significantly high intracranial pressure, and (v) ventricular drainage and, if necessary, subsequent shunting may be required for progressive hydrocephalus caused by intraventricular hemorrhage.

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Consent for publication

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Availability of data

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REVIEW ARTICLE

Evaluation and management of recurrent pericarditis in special populations: A contemporary review

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Abstract

About 15 – 30% of patients develop recurrent episodes of pericarditis following an acute pericarditis attack. In developed countries, most cases of pericarditis are of idiopathic etiology. First-line therapy typically includes non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine, with corticosteroids being the traditional second-line agents. Anti-interleukin-1 (IL-1) agents are a novel treatment option increasingly utilized due to their high efficacy as an alternative second-line therapy or for resistant cases, while pericardiectomy remains the last resort. Special populations with recurrent pericarditis (RP), including patients at the extremes of age or during pregnancy, have been understudied. In some cases, pericarditis may develop secondary to infections (including viral infections, such as coronavirus disease 2019, bacterial infections, such as tuberculosis, and fungal infections), autoimmune diseases (such as systemic lupus erythematosus, rheumatoid arthritis, vasculitis, and inflammatory bowel disease), post-cardiac injury syndromes, cancer, and other rare conditions. Non-idiopathic etiologies are associated with a higher risk of RP, chronic constrictive pericarditis, and cardiac tamponade. The general treatment algorithm may not be applicable to these special populations due to patient-related or etiological factors. For example, NSAIDs or corticosteroids are often contraindicated in older patients due to comorbidities. Bacterial or fungal purulent pericarditis requires aggressive treatment of infection followed by pericardial fluid drainage, with corticosteroids and anti-IL-1 agents contraindicated in these cases. Therefore, management often requires a multidisciplinary approach and must take place at a specialized pericardial center to optimize patient outcomes. In this review, we present current evidence on the evaluation and management of RP in the aforementioned special populations.

Keywords: Pericarditis; Recurrent pericarditis; Echocardiography; Cardiac magnetic resonance; Special populations; Anti-inflammatories; Anti-interleukin-1 agents

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1. Introduction

Pericarditis, the inflammation of the pericardium, is the most common form of pericardial disease and accounts for up to 5% of chest pain-related emergency room

visits.[1] The incidence rates of pericarditis vary widely depending on geographic location but are estimated to be 27.7 cases per 100,000 patients in the Western World.[2] Pericarditis is sub-classified temporally as follows: (i) Acute pericarditis (AP), when the episode lasts for <4 – 6 weeks; (ii) incessant, when the episode lasts from more than 4 – 6 weeks up to 3 months; (iii) recurrent pericarditis (RP), when there are two or more episodes of pericarditis following a 4 – 6-week symptom-free interval between episodes; and (iv) chronic, when the episode lasts longer than 3 months.[3,4] Myopericarditis and perimyocarditis refer to the concomitant presence of pericarditis and myocarditis, with the former or latter predominating, respectively.

Most cases of RP are idiopathic and are postulated to involve autoinflammatory responses of the innate immune system, mainly driven by cytokines, such as interleukin-1 (IL-1), or autoimmune responses of the adaptive immune system, involving autoantibodies or autoreactive T lymphocytes. Despite advances in the understanding of RP, its presentation and management in special populations, such as patients at the extremes of age and pregnant individuals, remain understudied, highlighting the need for further research. Although rare, immune dysregulation due to coronavirus disease 2019 (COVID-19) is increasingly recognized as a cause of pericarditis, occurring during acute infection, as a post-infectious sequela, and, in some cases, following vaccination. The two main phenotypes of RP are autoinflammatory and autoimmune. The autoinflammatory phenotype of idiopathic RP is often linked to innate immune dysregulation. In contrast, autoimmune mechanisms, involving adaptive immune dysregulation, are seen in systemic autoimmune diseases such as systemic lupus erythematosus or rheumatoid arthritis, or post-cardiac injury syndromes (PCISs), where autoantibodies target pericardial antigens. Other etiologies include bacterial infections (e.g., tuberculosis [TB], a leading cause in developing countries), neoplasms, metabolic conditions, and drug-related factors.[5]

This review will discuss RP in special populations that have been understudied, including patients at the extremes of age, pregnant individuals, and the previously mentioned non-idiopathic cases. A PubMed search of relevant studies published until December 01, 2024, was performed for this review. Medical subject headings (terms) used were "pericarditis" and "pericardium."

2. Clinical evaluation

The initial workup for RP involves obtaining a detailed medical history, with an emphasis on identifying the nature of chest pain, the time course, potential etiologies, and risk factors. Physical examination may reveal pericardial rubs or signs of systemic disease.[6] To diagnose pericarditis, at least two of the following four criteria must be met: (i) Chest pain consistent with pericarditis, (ii) pericardial friction rub, (iii) electrocardiogram (ECG) showing diffuse ST-segment elevation or PR-segment depression, and (iv) new or worsening pericardial effusion.[4] Other supportive evidence for pericarditis includes elevated inflammatory markers, such as erythrocyte sedimentation rate, C-reactive protein, and/or leukocytosis, as well as imaging evidence of inflammation, such as cardiac magnetic resonance (CMR).[7]

Multimodality imaging offers a comprehensive assessment of pericarditis, utilizing a stepwise approach.[3] Transthoracic echocardiography (TTE) remains the first-line imaging modality to assess for pericardial effusion, thickening, and constriction, along with cardiac chamber size, function, and valvular abnormalities.[8] It is readily accessible, portable, low-cost, and has high temporal resolution, making it effective for assessing abnormal physiology. TTE is important in evaluating the size, location, and characteristics (clear or organized) of pericardial effusion (Figure 1A), detecting cardiac tamponade physiology, and guiding pericardiocentesis.[6] TTE can also be used to detect constrictive physiology, allowing for early treatment with anti-inflammatory medications to prevent chronic, irreversible constriction that may require pericardiectomy. However, TTE has limited use in tissue characterization due to its inability to directly assess pericardial inflammation, which may result in normal findings, even during pericarditis recurrences.[3]

CMR is indicated when the diagnosis remains uncertain despite clinical evaluation, ECG, laboratory tests, and echocardiography, as well as for evaluating RP and complicated AP that is unresponsive to therapy.[3,9] CMR can aid in diagnosis, grade pericarditis severity, prognosticate risk, guide therapy, assess response to treatment, evaluate for constriction, and characterize pericardial effusions and masses. The late gadolinium enhancement sequence with fat suppression (to differentiate epicardial fat) is used to assess pericardial inflammation and grade its severity and potential persistence, from the acute phase to the chronic phase, until recovery or burnout. On the other hand, the T2 short tau inversion sequence is used to detect pericardial edema, which is typically present during acute flare-ups but resolves in the chronic or recovery phase (Figure 1B-D). The black-blood spin echo sequence depicts pericardial anatomy and helps identify thickening in pericarditis. Free-breathing bright-blood sequences and tagging sequences can help identify constrictive physiology. Like echocardiography, CMR

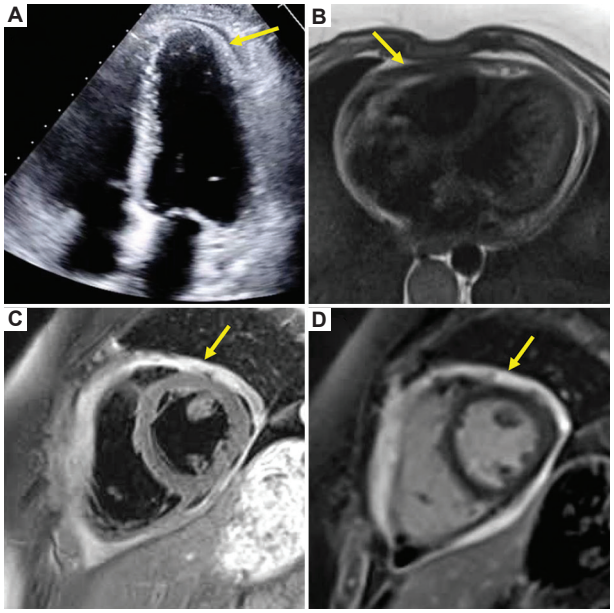

Figure 1. Multi-modality cardiac imaging evaluation of recurrent pericarditis. (A) Transthoracic echocardiography, apical four-chamber view, showing a small apical pericardial effusion (yellow arrow) with pericardial thickening. (B) Cardiac magnetic resonance black-blood spin echo sequence, axial imaging, indicating significant pericardial thickening (yellow arrow). (C) Cardiac magnetic resonance T2-short tau inversion recovery sequence, short axis at the mid-ventricle, showing increased signal of pericardial edema (yellow arrow). (D) Cardiac magnetic resonance late gadolinium enhancement sequence, showing severe circumferential enhancement of pericardial inflammation (yellow arrow). Image created by the authors.

can assess cardiac chamber size, function, and valvular abnormalities.[10] Important drawbacks of CMR include its cost, limited availability, lack of portability, the possibility of claustrophobia, incompatibility with certain devices, and the potential for artifacts caused by arrhythmias or suboptimal breath-holding.[6]

Cardiac computerized tomography (CT) is sometimes used for pericardial assessment, particularly when CMR is contraindicated, or TTE views are suboptimal.[3] It offers rapid scan acquisition within minutes and superior spatial resolution—though lower temporal resolution—compared to TTE. CT is the most effective imaging technique for assessing pericardial calcifications in patients with constrictive pericarditis. CT can also be used to evaluate pericardial effusion (though size is often overestimated compared to TTE), thickening, and the characterization of pericardial effusions and masses. It is also occasionally used for contrast enhancement in pericarditis, although it provides a lower yield compared to CMR.[4,11] In addition, retrospective-gated four-dimensional contrast CT can be employed to determine chamber size, function, and signs of constriction, similar to the bright-blood cine imaging on CMR. CT is also useful for pre-operative planning for procedures such as pericardiectomy by visualizing thoracic and aortic anatomy. Moreover, positron emission tomography/CT can be especially useful in identifying active pericardial inflammation.[3] The disadvantages of CT include radiation exposure and the use of iodinated contrast, making it less suitable for patients with chronic kidney disease or contrast allergies.[6]

3. RP in special populations

3.1. General management guidelines

First-line therapies for RP have not changed significantly in recent years. Initial treatment for RP includes colchicine for 6 months (compared to 3 months for 1st-time AP), in conjunction with non-steroidal anti-inflammatory drugs (NSAIDs) or high-dose aspirin (ASA).[12] After clinical improvement, ASA or NSAIDs, are gradually tapered over weeks or months. Common doses include 750 – 1000 mg of ASA taken 3 – 4 times daily and 600 – 800 mg of ibuprofen taken 3 times daily.[4] Corticosteroids, starting with prednisone (0.25 – 0.50 mg/kg/day), have traditionally been considered a second-line option for RP, typically used after multiple recurrences or lack of response to first-line therapies.[4,13] In patients with RP, exercise restriction is recommended to reduce the risk of recurrent or refractory symptoms by minimizing tachycardia and shear stress on the pericardium.[14]

A better understanding of the role of NOD-, LRR-, and pyrin domain-containing protein 3 inflammasome activation in the pathogenesis of RP has revolutionized its management. The development of several anti-IL-1 agents has provided an alternative to corticosteroids for treating medically refractory RP. These agents have demonstrated high efficacy in colchicine-resistant or corticosteroid-dependent inflammatory RP, with fewer side effects compared to corticosteroids.[15-17] Anakinra, an IL-1α and IL-1β antagonist, is typically administered subcutaneously at a dose of 100 mg/day, usually for at least 6 – 12 months, before being slowly tapered to prevent recurrences.[18] The United States Food and Drug Administration (FDA) has approved rilonacept, which inhibits both IL-1α and IL-1β, typically given with a loading dose of 320 mg, followed by 160 mg weekly for 12 – 24 months.[19] Other anti-IL-1 agents, such as goflikicept and canakinumab, have shown promise, although further trials are needed for canakinumab.[20] Cannabidiol is also being investigated for its potential anti-inflammatory effects in RP.[21] Pericardiectomy remains a last resort for medically refractory cases and is preferably performed at an experienced surgical center. This procedure involves cardiopulmonary bypass and complete, rather than partial, resection.[6]

The dosage and/or administration of treatments for RP may vary depending on whether the patient belongs to a special population. Key management considerations are summarized in Table 1.

3.2. Pediatric population

AP is rare in children, accounting for approximately 0.13% of emergency room visits by patients under 19 years old with chest pain and no history of cardiac disease.[22] In the

Table 1. Pericarditis management in special populations

Parameter	Clinical features	Colchicine	Aspirin and NSAIDs	Corticosteroids	Anti-IL-1 agents	Special considerations
Dosages	• Not applicable	• 0.6 mg twice daily for patients ≥70 kg and 0.6 mg once a day for those <70 kg, >70 years, intolerant to higher doses or with impaired renal function (eGFR 35 – 49 mL/min)	• Aspirin 750 – 1000 mg every 8 h • Ibuprofen 600 – 800 mg every 8 h • Indomethacin 25 – 50 mg every 8 h	• Prednisone 0.2 – 0.5 mg/kg daily	• Anakinra 1 – 2 mg/kg daily (maximum 100 mg/day) • Rilonacept: loading dose 320 mg (4.4 mg/kg up to 320 mg for 12 – 17-year-olds)	• Not applicable
Duration	• Not applicable	• Three months for the first event, 6 months or longer for recurrence or chronic pericarditis	• Use for 1 – 2 weeks at top dose, then taper over weeks to months	• Months, starting at a moderate dose with a slow mean	• Year(s), may be indefinite	• Not applicable
Children (<18 years)	• Fever, elevated inflammatory markers, pericardial effusion, and recurrences are more common • Higher percentage of pericarditis due to genetic and autoinflammatory causes	• Approved for children ≥4 years of age	• Avoid aspirin (risk of Reye syndrome) • Ibuprofen and indomethacin are safe	• Avoid due to adverse side effects (behavioral issues, growth defects, etc.).	• Anakinra is approved for use in children ≥2 years of age, and rilonacept for ≥12 years of age	• Consider proceeding directly to anti-IL-1 agents as second-line therapy for pericarditis refractory to colchicine and NSAIDs
Older adults (>65 years)	• Dyspnea, pleural involvement, and cardiac tamponade are more common • Chest pain, fever, and leukocytosis are less frequent	• Colchicine dosage and/or frequency may need to be decreased if there is renal impairment or intolerable GI side effects	• Cautious use due to comorbidities	• Contraindicated in renal impairment	• Safe	• NSAIDs and steroids are generally contraindicated due to comorbidities; proceed to anti-IL-1 agents
Pregnant	• Presentation similar to non-pregnant patients • Use of gadolinium contrast and CT are to be avoided	• Safe	• Discontinue after 20 weeks gestation	• Safe at low doses (prednisone <2.5 mg/day)	• Anakinra and canakinumab are safe • No data on rilonacept	• Colchicine/NSAIDs/steroids/anakinra are safe during breastfeeding
COVID-19	• Can present with acute infection, long COVID, or after COVID-vaccine • More common in young males • High prevalence of myopericarditis	• Safe	• Safe	• Safe	• Safe	• Proceed with usual treatment algorithm

(Cont'd...)

Table 1. ***(Continued)***

Parameter	Clinical features	Colchicine	Aspirin and NSAIDs	Corticosteroids	Anti-IL-1 agents	Special considerations
Purulent pericarditis	• Chest pain, pericardial friction rub, and ECG abnormalities are often absent • Presents with fever and pericardial effusion	• Not available	• Not available	• Contraindicated	• Contraindicated	• Aggressive antibiotic therapy and pericardial drainage
TB-associated pericarditis	• Insidious onset with heart failure and systemic symptoms • HIV co-infection common • Confirmation of diagnosis requires high levels of adenosine deaminase or gamma interferon and the presence of TB bacilli in the pericardial fluid obtained through pericardiocentesis or in pericardial tissue obtained through pericardial biopsy	• Minimal data	• Minimal data	• Safe to patients without HIV	• Contraindicated	• Treat infection with standard four-drug therapy (isoniazid, rifampicin, ethambutol, and pyrazinamide) • Pericardiocentesis and pericardiectomy in cases of cardiac tamponade or constrictive pericarditis, respectively
Autoimmune pericarditis	• Symptoms of early heart involvement are difficult to detect; consider workups for autoimmune disease if there is a family history	• Safe	• Safe	• Safe	• Safe	• Treatment of underlying disease is the mainstay • NSAIDs/colchicine/anti-IL-1 agents can be used for persistent symptoms • Azathioprine and intravenous immunoglobulins may be considered
PCIS pericarditis	• Presents days to weeks after the cardiac event, with symptoms such as pleuritic chest pain, shortness of breath, low-grade fever, and pericardial effusion • May be complicated by underlying condition	• Safe	• Safe	• Safe	• Safe	• Perioperative colchicine can be used for prevention • Proceed with usual treatment algorithm • Consider pericardiocentesis in severe cases
Cancer-related pericarditis	• Pericardial effusions are the most common presentation • Pericardiocentesis is needed to differentiate benign and malignant effusions	• Can be used	• Can be used	• Initial therapy for pericarditis from immune checkpoint inhibitors	• Not studied	• If pericarditis is due to cytotoxic agents, discontinue/modify treatment • Consider pericardiocentesis or pericardial window in severe cases

(Cont'd...)

Table 1. ***(Continued)***

Parameter	Clinical features	Colchicine	Aspirin and NSAIDs	Corticosteroids	Anti-IL-1 agents	Special considerations
Pericarditis with renal disease	• Presents as usual, but typical ST-wave elevations on ECG may be absent	• Contraindicated	• Can be used if symptoms persist despite renal replacement therapy intensification	• Can be used if symptoms persist despite renal replacement therapy intensification.	• No reports on anakinra and rilonacept Canakinumab is safe to use in ESRD and has cardiovascular benefits	• Dialysis initiation or intensification is the first-line treatment • Avoid anticoagulation
Drug-related pericarditis	• Can present as acute pericarditis or pericardial effusion, or rarely, constrictive pericarditis	• Case-by-case basis	• Case-by-case basis	• Case-by-case basis	• Case-by-case basis	• Stop the offending drug • Treatment approaches vary on a case-by-case basis • Pericardiocentesis in cases of large symptomatic effusion or pericardiectomy in constrictive pericarditis
Cholesterol pericarditis	• Present as chronic effusions	• Can be used	• Can be used	• Not known	• Not known	• Pericardiocentesis in cases of large symptomatic effusions or pericardiectomy

Abbreviations: COVID-19: Coronavirus disease 2019; CT: Computed tomography; ECG: Electrocardiogram; eGFR: Estimated glomerular filtration rate; ESRD: End-stage renal disease; GI: Gastrointestinal; HIV: Human immunodeficiency viruses; IL-1: Interleukin-1; NSAIDs: Non-steroidal anti-inflammatory drugs; PCIS: Post-cardiac injury syndromes; TB: Tuberculosis.

pediatric population, AP is less common compared to adults, but RP is more frequent, occurring in approximately 35% of cases following an initial episode of pediatric AP.[23] Risk factors for pediatric RP include an erythrocyte sedimentation rate ≥50 mm/h, C-reactive protein ≥125 mg/L, absence of myocarditis, non-idiopathic causes, and corticosteroid use instead of NSAID therapy.[24] Most cases are idiopathic (70%), with infections, autoimmune conditions, drug-induced factors, and post-cardiac injury etiologies contributing to the remaining cases.[25] Compared to adults, children with RP more frequently present with fevers, elevated inflammatory markers, and pericardial effusion.[26] The overall prognosis is generally favorable, with no reported deaths. However, recurrences are common, though milder, and are associated with complications such as cardiac tamponade (13%), pericardial constriction (3%), and myocardial involvement.[27]

Data suggest that typical management strategies for RP in adults are also appropriate for children, with a few exceptions. First-line therapy with colchicine (approved for children ≥4 years of age) in combination with NSAIDs appears to be safe and effective in pediatric patients. While NSAIDs such as ibuprofen and indomethacin pose minimal concern, high-dosage ASA should be minimized due to the potential risk of Reye syndrome.[28] Corticosteroids should be used with caution in pediatric patients, as they may be associated with a range of adverse events (AEs), including behavioral issues and growth defects.[29] In such cases, proceeding directly to anti-IL-1 agents may be more effective. An observational study by Imazio *et al.*[27] involving 110 pediatric patients (median age 13 years) reported 528 recurrences during a 60-month follow-up. Colchicine therapy reduced the incidence of RP from 3.74 to 1.37 recurrences per year ($p < 0.05$). Corticosteroid-treated patients experienced more recurrences (the standardized risk of recurrence per 100 person-years was 93.2 for those treated with corticosteroids compared to 45.2 for those without), along with more side effects and disease-related hospitalizations (all $p < 0.05$). Anakinra therapy ($n = 12$) resulted in a reduction in the number of recurrences from 4.29 per year before treatment to 0.14 per year after ($p < 0.05$). In another study of 51 pediatric patients by Caorsi *et al.*,[30] anakinra administration reduced recurrence with an absolute risk reduction from 3.05 to 0.28 ($p < 0.0001$). In a third study of 15 patients (12 of whom were children), the monthly relapse rate decreased from 0.46 to 0.01 ($p < 0.001$) with anakinra treatment during a median follow-up period of 39 months.[31] A few patients

exhibited minor skin reactions to anakinra administration, but there were no severe AEs. These studies suggest that IL-1 inhibition can be used effectively in children with refractory RP. While anakinra is not FDA-approved for RP, rilonacept is approved for patients ≥12 years.

3.3. Older adults (65 years and older)

RP in older adults may present with a clinical pattern different from that observed in younger patients, often featuring more frequent dyspnea and pleural involvement, while chest pain, fever, and leukocytosis occur less frequently. These differences can make the diagnosis more challenging. In addition, the incidence of cardiac tamponade necessitating pericardiocentesis is more frequent. However, there is no difference in terms of constrictive pericarditis or mortality.[32]

Management of RP in older adults can be complicated by the presence of multiple comorbidities such as congestive heart failure, diabetes mellitus, atrial fibrillation (often requiring anticoagulation), and chronic renal insufficiency, conditions in which NSAIDs and steroids are contraindicated. In addition, older adults may be taking multiple medications, increasing the risk of drug interactions, as well as susceptibility to gastrointestinal side effects, renal impairment, and infections. Colchicine dosages may need to be adjusted to a half-dose once daily or administered on alternate days in patients with renal impairment.[33] Anti-IL-1 agents can be used not only as rescue therapy but also for patients who have contraindications to NSAIDs and/or steroids. Massaro *et al.*[33] followed 26 elderly patients with RP, of whom 10 were treated with anakinra. At the 3-month follow-up, eight out of 10 patients achieved remission. One patient died of acute heart failure, and another voluntarily discontinued anakinra treatment. Anti-IL-1 agents may be particularly beneficial in older adults with comorbidities, as they can be used safely in patients with concurrent renal failure, heart failure, ischemic heart disease, fluid overload, recent surgery, anticoagulation, or gastrointestinal hemorrhages.[32]

3.4. Pregnant women

Pregnancy does not appear to impact the epidemiology or etiology of RP. Based on available studies, pericarditis occurs with similar frequency in pregnant patients as in age-matched controls.[34] The diagnostic evaluation of a pregnant woman with suspected pericarditis is similar to that of a non-pregnant patient. TTE remains the initial diagnostic test, and CMR without contrast is safe to use during pregnancy. However, the prolonged duration of CMR can be uncomfortable in late pregnancy. The left lateral decubitus position can be used in late pregnancy to relieve compression of the inferior vena cava. Gadolinium contrast agents should be avoided, especially in the first trimester, as they have been classified as FDA pregnancy category C. The use of cardiac CT should be minimized due to the potential risk of ionizing radiation to the developing fetus.[35]

Present evidence on the management of pericarditis in pregnancy is limited, with no formal guideline recommendations. A 2019 study by Brucato *et al.*[36] analyzed 21 pregnancies in 14 women with RP. Seventeen live births were reported, along with three early spontaneous abortions and one fetal death at 19 weeks. Birth weight was significantly lower with higher doses of corticosteroids (2,806 vs. 3,323 g with median daily prednisone doses of 10.0 mg vs. 2.5 mg, respectively; $p = 0.048$). Eight recurrences occurred during pregnancy, and five recurred within 1 year after delivery. Based on their results, the authors recommend avoiding NSAIDs in pregnancies beyond 20 weeks, while colchicine, low-dose ASA, and low-dose steroids may be safely continued throughout pregnancy. Another study involving 14 pregnancies in 12 women with both AP and RP confirmed the relative safety of colchicine during pregnancy.[37] Both NSAIDs and colchicine are compatible with breastfeeding.[38] Guidelines indicate that lower doses of corticosteroids are generally considered safe for breastfeeding as well.[38] The recent availability of anti-IL-1 agents makes them particularly interesting for use during pregnancy. A retrospective analysis by Youngstein *et al.*[39] evaluated eight maternal exposures to canakinumab and 23 to anakinra. Seven of the eight pregnancies involving canakinumab resulted in healthy, live births. The single miscarriage occurred at 6 weeks in a 26-year-old woman with Cogan syndrome, who also had a prior miscarriage while on anakinra. Of the 23 pregnancies with maternal anakinra exposure, 21 resulted in healthy live births, with one case each of ectopic neurohypophysis and renal agenesis. Notably, the mother whose baby was born with renal agenesis had corticosteroid-refractory disease. Following birth, 10 babies who were breastfed by mothers on anakinra exhibited no abnormalities. Although there are limited data on rilonacept exposure during human pregnancies, animal studies have demonstrated that rilonacept may increase the risk of stillbirth and lumbar rib anomalies.[40]

3.5. COVID and post-COVID vaccination

AP is a rare complication associated with acute COVID-19 infection, post-COVID-19 syndrome, and COVID-19 vaccines. New-onset pericarditis occurs in approximately 1.5% of patients with COVID-19 infection and is linked to adverse cardiovascular events, with around 62% of cases involving myopericarditis.[41,42] The prevalence of AP in post-COVID-19 syndrome is reported to be lower, with

a rate of about 0.019% among 40,462 patients previously diagnosed with COVID-19, according to a Mayo Clinic study.[43] Rates of pericarditis or myopericarditis following COVID-19 vaccination are much lower, primarily affecting adolescent and young male patients.[44] Reported rates after the original messenger RNA (mRNA) vaccine were 2.38 per million doses for pericarditis and 0.74 per million doses for myopericarditis. These rates were reduced to 0.6 per million and 0.13 per million, respectively, with the newer mRNA bivalent vaccines. In general, the median time to the onset of myocarditis or pericarditis was 3 days (interquartile range: 1 – 19) for the original COVID-19 mRNA vaccination and 7 days (interquartile range: 2 – 32) for the bivalent vaccination.[44]

There are no randomized controlled trials specifically for the treatment of COVID-19-related pericarditis. Standard treatment typically includes ASA or NSAIDs and colchicine, with steroids or anti-IL-1 agents considered for refractory cases.[41] In a case report, a 43-year-old man who presented with RP a year after primary COVID-19 infection experienced resolution of symptoms after standard treatment of colchicine and NSAID.[45] In patients with RP on rilonacept, full vaccination reduced the incidence of COVID-19-related events and did not increase the risk of RP. Continuing rilonacept treatment in patients contracting COVID-19 did not worsen disease severity, whereas interrupting the treatment resulted in increased recurrences. Therefore, rilonacept for RP can be continued during COVID-19 vaccination or active infection.[46] AP following COVID-19 vaccination appears to be mostly self-limited. A single tertiary-center analysis by Collini *et al.*[47] examined 24 patients with a median time to pericarditis of 7.0 ± 4.9 days after vaccination. Patients were treated with conventional therapy of colchicine and NSAIDs, and only five (21%) developed recurrence. Although the study did not include a long-term follow-up, all patients appeared to have favorable short-term outcomes following standard treatment cascade (i.e., corticosteroids to IL-1 blockade in cases unresponsive to colchicine and NSAIDs). Other case studies on post-vaccination RP have reported resolution following the same treatment hierarchy; notably, pericardiectomy was necessary in only one case.[48,49]

3.6. TB

TB is the leading cause of pericarditis in the developing world, contributing to 40 – 70% of pericardial effusion cases and 38 – 83% of constrictive pericarditis cases. However, it is much less common in the Western world, where idiopathic cases of pericarditis predominate.[50] Approximately 1 – 2% of patients with pulmonary TB develop TB pericarditis, which carries a high 6-month mortality rate of 17 – 40%. Most cases of TB pericarditis are associated with human immunodeficiency virus infection.[50] There are four stages of TB pericarditis: (i) The dry stage, where patients present with AP symptoms; (ii) the effusive stage, in which patients exhibit heart failure symptoms due to large pericardial effusion and or cardiac tamponade; (iii) the fibrosis stage; and (iv) the chronic calcific constrictive pericarditis stage.[51]

The most common manifestation of TB pericarditis is pericardial effusion, occurring in approximately 79.5% of cases. This effusion is typically loculated, but it can develop into tamponade in about 10% of patients.[51] Before the widespread use of anti-TB therapy and pericardial drainage, constrictive pericarditis occurred in 30 – 60% of patients; however, more recent studies report rates of 5 – 25%.[50,51] RP may be caused by an excessive immune response to the bacilli, known as immune reconstitution inflammatory syndrome.[52] *Mycobacterium tuberculosis* can reach the heart through direct expansion from an adjacent site, hematogenous dissemination, or retrograde lymphatic expansion.[50] Typical symptoms and signs of AP, such as chest pain and pericardial rub, are uncommon. Patients mainly present with an insidious onset of systemic symptoms and heart failure.[51] The limited availability of imaging modalities, such as CMR and CT, can delay the diagnosis. Confirmation of TB pericarditis requires high levels of adenosine deaminase or gamma interferon, as well as the detection of TB bacilli in the pericardial fluid obtained through pericardiocentesis or in pericardial tissue obtained through biopsy. Patients and physicians may hesitate to perform these tests due to their invasive nature and associated risks, potentially increasing the risk of recurrence if the condition remains undiagnosed during the initial presentation.[50]

The management of TB pericarditis differs greatly from that of idiopathic pericarditis, as treatment is primarily focused on treating the infection. The standard four-drug regimen includes isoniazid (300 mg daily), rifampicin (600 mg daily), ethambutol (15 – 25 mg/kg daily), and pyrazinamide (15 – 30 mg/kg per day) for 2 months, followed by continued rifampicin and pyrazinamide for another 6 months, with modifications as needed for multidrug-resistant TB.[50] Corticosteroids have shown efficacy in preventing progression to constrictive pericarditis in TB pericarditis.[53] The recommended prednisone dose is 1 mg/kg/day for 4 weeks, followed by 0.5 mg/kg/day for 4 weeks, 0.25 mg/kg/day for 2 weeks, and finally 0.125 mg/kg/day for 2 weeks.[53] Colchicine is not effective in TB pericarditis, and IL-1 agents are contraindicated. In cases of cardiac tamponade, emergency drainage is required. Although open surgical drainage reduces the need for repeat pericardiocentesis, it does not decrease mortality; therefore,

percutaneous pericardiocentesis is preferred. In cases of constrictive pericarditis, pericardiectomy may be performed after 6 – 8 weeks of anti-TB therapy.[50]

3.7. RP in systemic autoimmune and autoinflammatory disorders

Autoimmune diseases are a group of disorders characterized by abnormal reactivity to self-antigens, resulting from a decrease in immunologic tolerance. These diseases affect multiple organ systems, including the pericardium, and account for 22% of non-idiopathic pericarditis cases.[54] Examples of these autoimmune diseases are systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, adult-onset Still's disease, systemic sclerosis, sarcoidosis, dermatomyositis, polymyositis, mixed connective tissue disease, Sjögren's disease, sarcoidosis, rheumatic fever, and vasculitis.[54] Autoinflammatory diseases associated with RP include tumor necrosis factor receptor-1 associated periodic syndrome, familial Mediterranean fever, mevalonate-kinase deficiency, and nucleotide-binding oligomerization domain 2-associated autoinflammatory syndrome.[3,54] Many of these autoimmune diseases, such as lupus, follow a relapsing-remitting pattern, where risk factors such as infection or poor treatment adherence lead to recurrent flares, thereby triggering RP.[55] Symptoms of early heart involvement in autoimmune diseases can be easily missed due to the insidious onset of the condition. When heart involvement becomes symptomatic, the damage is frequently severe and typically irreversible.[56] This often leads to a more advanced stage of pericarditis at the time of diagnosis and increases the likelihood of recurrence. Therefore, a workup for autoimmune diseases should be considered for unexplained episodes of RP in the appropriate clinical context, particularly if the RP is associated with other end-organ involvement or a family history of autoimmune disorders.

The mainstay of treatment of RP in these settings is targeting the underlying autoimmune systemic process with agents such as methotrexate, sulfasalazine, hydroxychloroquine, mycophenolate mofetil, tumor necrosis factor inhibitors, and glucocorticoids, under the supervision of a rheumatologist. NSAIDs and colchicine can be used alongside therapy for the underlying systemic disease. Recurrences have been observed in about 20 – 30% of pericarditis cases associated with autoimmune disease. In these patients, immunosuppressive agents such as azathioprine, intravenous immunoglobulin, and agents targeting IL-1 blockade (anakinra and rilonacept) have been used.[57,58]

3.8. PCIS

PCIS refers to a spectrum of inflammatory responses that occur following injury or trauma to the heart.[59] The prevalence of PCIS is increasing, as it can occur after pericardiotomy associated with cardiac surgery (1 – 15%) or other cardiac procedures such as pacemaker/defibrillator implantation (1 – 5%), catheter ablation for arrhythmia, or percutaneous coronary interventions (0.5%). PCIS can also be associated with myocardial infarction (<1 – 3%), radiation, or trauma (0.5 – 5%). It is believed to be immune-mediated, resulting from an autoimmune response to cardiac antigens released during injury.[59] PCIS typically presents days to weeks after the cardiac event, with symptoms, such as pleuritic chest pain, shortness of breath, low-grade fever, and pericardial effusion. Diagnosis can be complicated by the underlying pathological condition that triggered PCIS.[59]

PCIS is generally treated with conventional treatment hierarchies utilized for pericarditis.[60] First-line treatments include ASA or NSAIDs combined with colchicine. Post-pericardiotomy pericarditis can be prevented by perioperative use of colchicine (odds ratio [OR]: 0.38, 95% confidence interval [CI]: 0.22 – 0.65), but not by methylprednisolone (OR: 1.13, 95% CI: 0.57 – 2.25) or aspirin (OR: 1.00, 95% CI: 0.16 – 6.11).[61,62] In severe cases, pericardiocentesis may be required to drain fluid buildup around the heart.[59,60] IL-1 targeted therapy is effective in corticosteroid-dependent and colchicine-resistant cases, as demonstrated in the International Registry of Anakinra for pericarditis study. This study demonstrated a six-fold reduction in recurrence rates, from 2.33 to 0.39 episodes per patient per year, including 28 patients with PCIS (13% of 224).[63] The Rilonacept Inhibition of IL-1 Alpha and Beta for RP trial, in which 15% of patients had PCIS, demonstrated that rilonacept rapidly resolved RP symptoms and reduced the risk of recurrences (Figure 2).[16] In accordance with the most recent consensus guidelines, anti-IL-1 agents are now considered second-line therapy – rather than corticosteroids – in cases of PCIS.[3]

3.9. Cancer-related RP

Cancer-related pericarditis accounts for approximately 5% of all pericarditis cases.[64] It can develop due to direct infiltration from adjacent structures, hematogenous dissemination of cancer cells, or as part of a paraneoplastic syndrome.[64] It may also be associated with cancer treatments such as radiotherapy, immunotherapy with checkpoint inhibitors, chemotherapy with anthracyclines, cyclophosphamide, bleomycin, and cytarabine, and targeted therapies, such as tyrosine kinase inhibitors.[64] Pericardial effusion is the most frequent manifestation, with 5 – 15% of cancer patients having a malignant pericardial effusion and 7% experiencing a non-malignant pericardial effusion. Any type of cancer can metastasize to the pericardium, resulting in an effusion, with the most common cancers

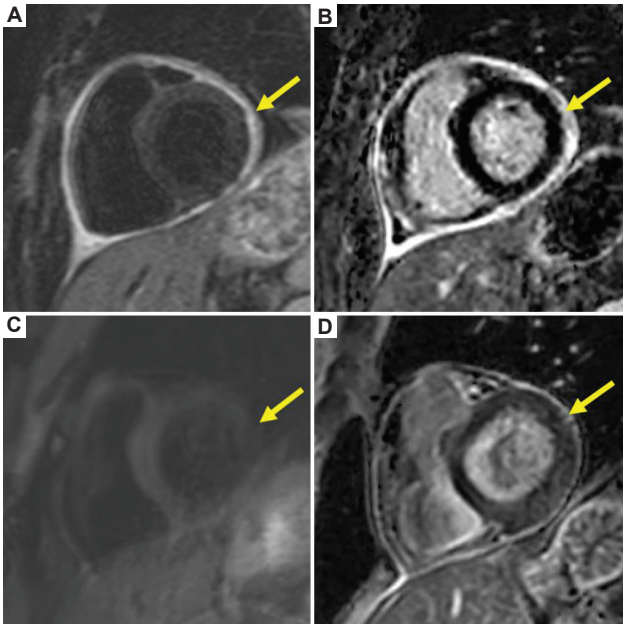

Figure 2. Serial cardiac magnetic resonance imaging of recurrent pericarditis from post-cardiac injury syndrome, before and after treatment with the anti-interleukin 1 agent rilonacept. Before treatment, an increased signal on the T2-short tau inversion recovery sequence indicated edema (A, yellow arrow), and severe circumferential enhancement on the late gadolinium enhancement sequence suggested pericardial inflammation (B, yellow arrow). After 12 months of treatment, no signal was observed on the T2-short tau inversion recovery sequence (C, yellow arrow), and minimal enhancement on the late gadolinium enhancement sequence (D, yellow arrow), corresponding to clinical and biomarker improvement and remission of pericarditis. Image created by the authors.

being breast, lung, and Hodgkin lymphoma. Mesothelioma is the most common primary malignant neoplasm, while other primary cancers include sarcomas and lymphomas.[65] The onset of post-radiotherapy pericarditis varies from months to up to a decade and can also involve other cardiac structures. The risk of pericarditis increases from 5% to more than 50% as the cumulative radiation dose rises from 40 to 50 Gray. Radiation-induced pericarditis also depends on the extent of the heart area exposed to radiation, with a higher incidence of pericarditis if more than 30% of the heart area receives 50 Gray or more.[66]

The symptoms of cancer-related RP are similar to those of other forms of pericarditis, including pleuritic chest pain, pericardial friction rub, and ECG changes, such as widespread ST-segment elevation. In cases of significant pericardial effusion, patients may present with signs of cardiac tamponade, including hypotension, jugular venous distension, and muffled heart sounds. The diagnostic workup is similar to that used for RP of any other cause. TTE is useful for detecting pericardial effusion and assessing its hemodynamic impact. In patients with known malignancies, pericardiocentesis can be performed to obtain the pericardial fluid for analysis, which helps determine whether the effusion is malignant or treatment-related.

There is limited evidence to guide the management of cancer-related pericarditis and treatment recommendations are extrapolated from observational studies, indirect evidence from patients without cancer, and expert opinion. NSAIDs and colchicine are first-line treatments to manage acute inflammation and reduce recurrence rates. Pericarditis induced by cytotoxic agents typically resolves after discontinuation of the agent, followed by the initiation of standard therapy. For patients with severe immune checkpoint inhibitor-associated pericarditis and effusion, initial treatment consists of steroids (methylprednisolone 1 mg/kg/day or prednisone 1 – 2 mg/kg/day) plus colchicine.[67]

The safety of anti-IL-1 agents has not been assessed in the setting of malignancy. The randomized trials of both anakinra and rilonacept in pericarditis excluded patients with a history of cancer in the past 5 years.[15,16] Mild to moderate pericardial effusion may be conservatively monitored with regular TTE. Large pericardial effusions may benefit from therapeutic pericardiocentesis or pericardial window placement to relieve symptoms and prevent recurrence. Malignant effusions may be treated with intrapericardial instillation of agents, such as bleomycin. In such cases, the potential risks and benefits of interrupting cancer treatment should be evaluated by a multidisciplinary cardio-oncology team. The prognosis for patients with cancer-related RP is closely tied to the underlying malignancy. In patients with metastatic disease, RP may signal advanced cancer and, therefore, a poor prognosis. However, in cases where the pericarditis is related to cancer therapy, discontinuation or modification of treatment can improve outcomes.[68]

3.10. Pericarditis in kidney disease

Pericarditis is a recognized complication that can occur across various stages of kidney diseases, including acute kidney injury, chronic kidney disease, and end-stage renal disease (ESRD).[69] The spectrum of pericardial involvement in renal disease consists of acute fibrinous pericarditis, pericardial effusion, cardiac tamponade, and constrictive pericarditis. ESRD-related pericarditis is typically categorized into uremic pericarditis, which develops either before or within 8 weeks of initiating renal replacement therapy, and dialysis-associated pericarditis, which occurs after dialysis has stabilized.[70] The incidence of uremic pericarditis is estimated to range from 1.4% to 29% per patient-year, while dialysis-associated pericarditis occurs at a rate of 0.8 – 6% per patient-year.[69] In a case

series, the incidence was found to be 12.1% in patients undergoing hemodialysis and 3.4% in those undergoing peritoneal dialysis.[69] While the exact pathophysiology of ESRD-related pericarditis remains unknown, uremic pericarditis is thought to result from the buildup of toxic metabolites, although no specific metabolite has been identified. Expected culprits, such as blood urea nitrogen or serum creatinine levels, appear to be similar in ESRD patients with and without pericarditis.[69]

There is ongoing debate regarding whether dialysis-associated pericarditis has a different etiology from uremic pericarditis. Lundin[71] hypothesized that both manifestations share the same underlying cause, with dialysis-associated pericarditis occurring due to inadequate dialysis regimens. Pericarditis has also been reported after renal transplantation, potentially due to uremia, infectious agents such as cytomegalovirus and herpes simplex virus, or immunosuppressive drugs like sirolimus.[72] In a single center study, 82 patients (14%) developed new pericardial effusion after renal transplantation, with a mean time to development of pericardial effusion of 4 years. The need for a pericardial window for pericardial effusions was greater in the late-effusion group (30.4% in those with onset ≥4 years after renal transplant) compared to the early group (13% in those with onset <4 years).[72]

The diagnostic workup for ESRD-related pericarditis is similar to that of pericarditis from other etiologies, involving a combination of multimodality imaging and laboratory tests. Notably, ESRD-related pericarditis does not typically exhibit ST wave elevations on ECG, which are a hallmark of other forms of pericarditis.[4] Initiation or intensification of renal replacement therapy is generally considered the first-line therapy. Rutsky and Rostand[73] reported that 87% of ESRD cases with pericarditis onset within 2 weeks of dialysis initiation, and 53% of cases with pericarditis onset after 2 weeks, resolved with dialysis alone. When patients do not respond to dialysis initiation or intensification, NSAIDs and corticosteroids may be considered, while colchicine is contraindicated.[4] For patients with residual kidney function, NSAIDs should only be used at the lowest effective dose for the shortest duration possible.[74] The effects of novel anti-IL-1 agents, such as anakinra and rilonacept, on ESRD-related pericarditis remain unreported. Although pericarditis was not specifically analyzed, Ridker *et al.*[75] found that canakinumab had cardiovascular benefits with no renal AEs in patients with chronic renal disease, suggesting its potential for use in ESRD-related pericarditis. Notably, European guidelines recommend avoiding anticoagulation in patients with uremic pericarditis who develop atrial fibrillation.[4]

3.11. Drug-related pericarditis

Drug-related pericarditis and associated pericardial effusions are rarely described, with the majority of pertinent literature consisting of case reports. Pericarditis has been reported in association with anti-infective agents (such as minocycline and interferon), chemotherapeutic agents (discussed previously under cancer-related pericarditis), clozapine (an antipsychotic used to treat schizophrenia), bromocriptine, various anticoagulants (including apixaban, dabigatran, rivaroxaban, and streptokinase), antihypertensive drugs (such as hydralazine, minoxidil, and methyldopa), and anti-inflammatory drugs (such as sulfasalazine and adalimumab).[76] The potential for cardiotoxicity should be considered when prescribing medications to patients, especially those with prior cardiovascular complications. In addition, although anticoagulants are traditionally considered a risk factor for cardiac tamponade in the context of RP, multiple cohort studies have shown no such association.[4]

There are limited data on the management of drug-related pericarditis. Patients with large pericardial effusions or constrictive pericarditis require symptomatic management, which may include pericardiocentesis or pericardiectomy.[76] There are no reports on the use of NSAIDs/colchicine or anti-IL-1 agents in the management of drug-induced pericarditis. The primary interest should be identifying the culprit agent and discontinuing it. Such efforts require close interdisciplinary collaborations between the cardiology team and other care teams to ensure the patient's best interests are prioritized.[77]

3.12. Cholesterol pericarditis

Cholesterol pericarditis is a rare form of pericarditis characterized by cholesterol-rich chronic pericardial effusions.[78] Most cases are idiopathic, although a few cases have been reported in association with rheumatoid arthritis, hypothyroidism, and TB.[79] The pericardial fluid typically has a "gold paint" appearance due to cholesterol crystals, and pericardial fluid analysis reveals cholesterol levels >70 mg/dL, with cholesterol crystals and foam macrophages visible under microscopy. Treatment generally consists of pericardial fluid drainage followed by colchicine and ibuprofen. In recalcitrant cases, pericardiectomy may be necessary.[78,79]

3.13. Infectious pericarditis

In addition to TB, the most common cause of infectious pericarditis, other infectious etiologies include bacterial (e.g., *Staphylococcus*, *Streptococcus*, *Pneumococcus*, *Hemophilus*, *Neisseria*, *Mycoplasma*, *Chlamydia*, *Legionella*, *Leptospira*, *Listeria*, *Coxiella*, *Borrelia burgdorferi*), viral

agents (e.g., coxsackieviruses, echoviruses, adenoviruses, parvovirus B-1, herpesviruses, human immunodeficiency virus, COVID-19), fungal organisms (e.g., *Candida*, histoplasmosis, coccidioidomycosis), and protozoa (e.g., *Toxoplasma*).[3] Purulent pericarditis is characterized by the presence of purulent fluid in the pericardial space (either macroscopically or microscopically). It is rare in the present era of antibiotics and can be fatal if left untreated. *Pneumococcus* is the most frequently associated with contagious spread from an intrathoracic site, while *Staphylococcus aureus* is more commonly isolated in cases of hematogenous spread.[80] Treatment involves draining the pericardial space and administering broad-spectrum antibiotic therapy. Initial empiric therapy may include vancomycin combined with ceftriaxone or imipenem, meropenem, or piperacillin/tazobactam, along with fluconazole in immunocompromised patients. Treatment should be adjusted according to the results of the microbiological study. Antibiotic therapy should continue for at least 28 days, or until signs and symptoms of infection resolve. Mortality in patients who are promptly diagnosed and appropriately treated is 40%, generally due to cardiac tamponade, septic shock, or constriction.[80]

3.14. Rarer causes of pericarditis

Pericarditis has also been rarely reported in conditions such as amyloidosis, gout, polycystic kidney disease, chylopericardium, cholesterol pericarditis, pulmonary arterial hypertension, and pectus excavatum.[3] Awareness of these associations and rarer etiologies of pericarditis is crucial for appropriate clinical assessments. Identifying these causes allows for targeted therapies that address both the pericarditis manifestations and the underlying medical condition.

4. Conclusion

RP is a serious condition that requires careful evaluation and stepwise therapies, which can vary widely depending on the status of the patient and the disease etiology. The integration of multimodal imaging techniques, including echocardiography, CMR, and CT, has enabled early detection and characterization of pericardial inflammation, fibrosis, and hemodynamic complications. These imaging modalities facilitate precise diagnosis and help guide therapeutic decision-making, particularly in cases where clinical assessment alone is inconclusive. Each case of pericarditis should be approached individually, with a tailored treatment plan that considers the underlying pathophysiology, potential drug interactions, and a patient-specific risk-benefit assessment. While some etiologies, such as PCIS, respond well to standard treatment protocols, others may require modifications. For instance, in ESRD, colchicine is contraindicated, and NSAIDs should be used at the lowest effective dose, whereas in autoimmune, malignant, or TB pericarditis, addressing the underlying disease is paramount. The advent of anti-IL-1 agents has expanded the treatment options for pericarditis, including in special populations such as pediatric and elderly patients, where conventional therapies may pose risks. However, further clinical trials and broader inclusion of special populations are needed to determine the optimal duration and long-term safety of these agents. A multidisciplinary approach is critical in managing these patients, combining available evidence with an individualized treatment approach.

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ACCSCIENCE PUBLISHING

Brain & Heart

ORIGINAL RESEARCH ARTICLE

The influence of COVID-19 on clinical characteristics and prognosis of traumatic brain injury after rehabilitation treatment: An epidemiological comparative study

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Abstract

The impact of traumatic brain injury (TBI) on health and epidemiological patterns during the COVID-19 pandemic in China remains poorly understood. This retrospective study aimed to examine the influence of COVID-19 on the epidemiological characteristics, prognosis, and rehabilitation outcomes of TBI patients. Medical records from three hospitals in Wuhan, China, were analyzed between January 2018 and December 2023 to examine TBI patients based on the International Classification of Diseases, 10th Edition. A total of 306 TBI patients were included in this study, divided into two groups: 186 patients without COVID-19 (Group 1) and 120 patients with COVID-19 (Group 2). The mean age was 39.47 ± 18 years in Group 1 and 40.95 ± 16.6 years in Group 2. Most patients were male. Road traffic accidents represent the leading cause of TBI in both groups, although it is more prevalent in Group 1 (73.7%) than in Group 2 (55.8%). There were no significant differences in injury severity or initial Glasgow Coma Scale scores between the groups. However, Group 2 showed significantly poorer recovery outcomes, as indicated by lower Functional Independence Measure and Barthel Index scores at discharge. In addition, post-surgical infection rates were higher in Group 2 (18.42%) compared to Group 1 (4.25%). This study highlights the need for further evaluation of the impact of COVID-19 on TBI epidemiology and recovery outcomes to guide improvements in health-care practices.

Keywords: Traumatic brain injury; Rehabilitation; COVID-19; Comparative study

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1. Introduction

Traumatic brain injury (TBI) is a serious condition with significant consequences for patients' lives.[1] The complexity of TBI is notably greater than other diseases due to its diverse range of causes, mechanisms of injury (MOI), treatment approaches, and prognosis. A survey conducted in the early 1980s by Wang *et al.*[2] across six Chinese cities reported an incidence rate of 55.4 – 64.1 TBI cases per 100,000 individuals and a mortality rate of 6.3 – 9.7/100,000 individuals.[3] However, falls and road traffic accidents

(RTAs) remain the primary causes of TBI.[4] The rapid aging of populations in developed countries has rendered numerous concepts and management strategies outdated.[5] At present, patients undergoing rehabilitation often show increased rates of multiple chronic conditions, particularly in older individuals. This trend necessitates changes in management approaches. Rehabilitation treatment methods are crucial in reducing disability and enhancing long-term recovery outcomes.

The COVID-19 pandemic has resulted in the loss of over 6 million lives since its outbreak in Wuhan in January 2020, with confirmed cases exceeding 6.5 million globally.[6] The pandemic has caused widespread disruptions in health-care systems, affecting patient care and altering referral behaviors, as well as neurosurgical and neurorehabilitation treatment.[7] These disruptions are primarily the consequence of ineffective measures implemented to detect, contain, and prevent the spread of COVID-19.[8-12]

Studies examining TBI incidence, surgical practices, and rehabilitation treatments have reported changes in disease manifestation during the early and critical stages of the COVID-19 pandemic. Several countries reported a significant decline in TBI cases due to lockdowns, movement restrictions, remote work, and school closures. However, these measures also increased cases of low-energy falls and alcohol-related violence.[13-17] In addition, mild TBI cases may have been underreported, as many individuals avoided medical treatment due to fears of contracting COVID-19.[13,15]

However, the literature indicates a preference for conservative management approaches for TBI, particularly among older individuals with mild TBI resulting from low-energy falls.[17] Some studies showed minimal differences in neurotrauma management practices, with similar rates of neurosurgical consultations, surgeries, and transfers to rehabilitation treatments both before and after the onset of the COVID-19 pandemic. Moreover, a significant decrease in the overall incidence of head trauma has been observed.[18,19]

Globally, the COVID-19 pandemic has caused significant disruptions in rehabilitation treatments, including expedited discharges, reduced hospital stays, minimized disability management, and the closure of rehabilitation units. The COVID-19 pandemic had a substantial impact on the distribution of rehabilitation treatments worldwide.[8-13]

In China, rehabilitation treatments underwent significant changes during the COVID-19 pandemic, including the adoption of virtual or telerehabilitation, modified protocols for infection control, and a focus on maintaining or improving physical abilities. The specific adaptations varied across regions, depending on the severity of the pandemic and the availability of health-care resources. However, there is a lack of literature on the impact of the COVID-19 pandemic on TBI rehabilitation. Specifically, the effect of COVID-19 on TBI rehabilitation in China remains largely unknown and warrants further investigation.

This study aims to assess the impact of the COVID-19 pandemic on the epidemiological characteristics of TBI and rehabilitation treatment outcomes. We compared two groups: TBI patients without COVID-19 (Group 1) and TBI patients with COVID-19 (Group 2). By analyzing data from both pre-pandemic and pandemic periods, we sought to understand how COVID-19 affected rehabilitation outcomes and the epidemiology of TBI. In addition, the study aimed to identify the factors influencing TBI prognosis and the levels of independence achieved following rehabilitation treatment.

2. Materials and methods

2.1. Data sources

During both the pre- and post-COVID-19 periods, there was no specific area-based registration system for TBI in Wuhan. However, this study analyzed medical records of patients admitted to and discharged from the rehabilitation department at the Affiliated Xianning Medical College Hospital ($n = 306$). Records from January 2018 to December 2023 were examined, focusing on two distinct time periods: the "non-COVID-19" period (2018, 2019, and 2023) (Group 1) and the "COVID-19" period (2020 – 2022) (Group 2). Xianning Hospital, a Grade 3A general hospital, is renowned for its health-care services. With a capacity of over 7,000 beds, it serves patients from across China. Its rehabilitation department ranks sixth nationally and serves as Hubei Province's Rehabilitation Quality Control Center. The department is equipped with advanced technology and staffed by professionals specializing in the latest TBI treatment techniques. The study included patients diagnosed with TBI based on the International Classification of Diseases, 10th Edition criteria.[20]

2.2. Inclusion and exclusion criteria

Patients with TBI who were transferred to the rehabilitation unit following treatment between January 2018 and December 2023 were included in the study. They received care during both the non-COVID-19 and COVID-19 periods. Patients with incomplete records, unclear diagnoses, or those who suffered fatal injuries without hospital admission were excluded from the study. In addition, patients were excluded if they had

mild head injuries that did not meet TBI criteria, severe comorbidities, or severe COVID-19 complications such as pneumonia, acute respiratory distress syndrome (ARDS), myocarditis, arrhythmias, seizures, neuropathy, renal and gastrointestinal complications. Other exclusion criteria included psychiatric disorders, substance abuse, delayed medical care for TBI, critical language or communication issues, or logistical reasons that prevented participation in rehabilitation or follow-up.

2.3. Study variables and definitions

Data were collected while ensuring patient privacy and were used to create case records that included the demographic and clinical characteristics of TBI patients during the non-COVID-19 (2018, 2019, and 2023) and COVID-19 (2020 – 2022) periods. Demographic variables included age, gender, and MOI, whereas clinical characteristics included TBI grade, initial Glasgow Coma Scale (GCS), Glasgow Outcome Scale (GOS), loss of consciousness (LOC), American Society of Anesthesiologists Physical Status (ASA-PS) classification, Functional Independence Measure (FIM), Rancho Los Amigos Scale (RLAS), and Barthel Index (BI) scores.

Functional capability assessments were conducted at both admission and discharge. These included the total FIM score, which measures functional independence across six areas of function, categorized under the motor and cognitive subsets. The RLAS was used to track cognitive and behavioral improvement, whereas the BI score was used to measure functional independence in daily activities.

Patients were divided into six age groups: 0 – 19, 20 – 29, 30 – 39, 40 – 49, 50 – 59, and ≥60 years. The MOI was classified into falls and RTAs. Falls were further categorized into low falls (<1 m) and high falls (≥1 m). TBI was graded as mild (Grade I), moderate (Grade II), or severe (Grade III). GCS was classified into mild (13 – 15), moderate (9 – 12), and severe (3 – 8) categories. The GOS classified patients into five groups: good recovery, moderate disability, severe disability, vegetative state, and death. LOC was categorized by duration: 0 – 30 min, 31 min – 24 h, and more than 24 h. The ASA-PS classification system assessed overall health and systemic diseases, with Grade 1 representing healthy patients, and Grade 4 indicating severe systemic disease posing a life threat.[21]

The total FIM score, which assesses motor and cognitive functions, ranged from 18 to 126, with a higher score indicating greater independence. The RLAS score ranged from 0 to 10, measuring recovery stages from deep coma to purposeful and independent functioning. The BI score ranged from 0 to 100, with a higher score reflecting greater independence.

2.4. Statistical analysis

Data analysis was performed using Microsoft Excel (version 16.0) and IBM SPSS Statistics (version 29.0; IBM Corporation, USA). Descriptive and summary statistics, such as mean, standard deviation (SD), median, and interquartile range (IQR), were calculated. Pearson's Chi-square test was used for nominal data comparison, while the Mann–Whitney U test was used for ordinal data due to its non-normal distribution. T-tests or one-way ANOVA were used for comparative analysis between groups. Statistical difference was considered significant at $p \leq 0.05$.

2.5. Ethical approval

This study was reviewed and approved by the Ethics Committee of the Affiliated Xianning Medical College Hospital (Ethics No. IRP20230214) in adherence to the Declaration of Helsinki. All methods were conducted in compliance with applicable guidelines and regulations. The Ethics Committee waived the requirement for informed consent for this study.

3. Results

The study initially included 362 TBI patients from 2018 to 2023. However, 56 patients were excluded for various reasons, including eight with fatal injuries that did not result in hospital admission, 17 with mild head injuries not meeting TBI criteria, five with severe comorbidities, six with unclear diagnoses, 13 with incomplete medical records, and seven with COVID-19 complications such as myocarditis, ARDS, and pneumonia. After exclusions, 306 TBI patients were analyzed: 186 in Group 1 (TBI patients without COVID-19; 2018, 2019, and 2023) and 120 in Group 2 (TBI patients with COVID-19; 2020 – 2022).

3.1. Demographic characteristics of TBI patients between 2018 and 2023

The study population consisted of 306 TBI cases, with 186 in Group 1 and 120 in Group 2. In Group 1, 125 cases were male (67.2%), and 61 cases were female (32.8%). In Group 2, 68 cases were male (57.5%), and 51 cases were female (42.5%). There was a statistically significant difference in gender distribution between the groups (p = 0.046). The mean age was 39.47 ± 18.06 years in Group 1 and 40.95 ± 16.6 years in Group 2, with the 40 – 49 age group being the largest proportion. RTAs were the most common MOI in both groups (p = 0.022) (Table 1).

3.2. Clinical characteristics of TBI patients between 2018 and 2023

Regarding TBI grades, Grade I was the most common, found in 69.4% (n = 129) of Group 1 and 68.3% (n = 82) of

Table 1. Comparison of demographic characteristics between TBI without COVID-19 (Group 1) and TBI with COVID-19 (Group 2) based on the mechanism of TBI, and other injuries

Characteristics	Group 1 (*n*=186)	Group 2 (*n*=120)	*p*-value
Age			0.116
(mean±SD)	39.47±18	40.95±16.6	
Median (IQR)	42.00 (22)	42.00 (26)	
0 – 19 (%)	25 (13.4)	18 (15)	
20 – 29 (%)	29 (15.6)	18 (15)	
30 – 39 (%)	29 (15.6)	23 (19.1)	
40 – 49 (%)	62 (33.3)	33 (27.5)	
50 – 59 (%)	25 (13.4)	17 (14.2)	
≥60 (%)	16 (8.6)	11 (9.2)	
Gender (%)			0.041
Male	125 (67.2)	68 (56.7)	
Female	61 (32.8)	52 (43.3)	
Mechanism of TBI (%)			0.022
RTAs	137 (73.7)	69 (57.5)	
Assault	8 (4.3)	10 (8.3)	
Falls ≤1 m	33 (17.7)	34 (28.4)	
Falls >1 m	6 (3.2)	4 (3.3)	
*Others (sport and machinery injuries)	2 (1.1)	3 (2.5)	

Abbreviations: IQR: Interquartile range; RTAs: Road traffic accidents; SD: Standard deviation; TBI: Traumatic brain injury.

Group 2. Most of the initial GCS scores were classified as mild (13–15), with 66.1% (*n* = 123) of Group 1 and 67.5% (*n* = 81) of Group 2 falling into this category. Furthermore, regarding the GOS classification, a good recovery level was observed in 48.9% (*n* = 91) of Group 1 and 47.5% (*n* = 57) of Group 2. More than 50% of the patients in both groups fell into the category of LOC for <30 min. Conservative treatment was the most common method used. Approximately half of Group 1 (*n* = 100; 53.8%) and Group 2 (*n* = 68; 56.6%) were classified as ASA I on the initial ASA-PS scale. The next most common classifications were ASA-PS III and ASA-PS IV. The mean ± SD of the admission total FIM score for Group 1 was 61.27 ± 6.4, whereas Group 2 had a lower score of 59.34 ± 4.4. Similarly, the discharge total FIM score showed improvement in both TBI patients, with 87.43 ± 3.7 for Group 1 and 86.23 ± 3.5 for Group 2 (Table 2).

There was no significant difference in the admission RLAS scores between the TBI groups. However, a significant difference was observed in the discharge RLAS score. Group 1 had a score of 8.25 ± 0.9, whereas Group 2 had a lower score of 7.32 ± 0.8. Similarly, the admission BI score for Group 1 was 54.28 ± 6.7, whereas Group 2 had a lower score of 47.76 ± 4.1. There was a significant improvement in the discharge BI scores for both TBI groups, with Group 1 showing 71.67 ± 8.9 and Group 2 showing 63.86 ± 5.2.

3.3. Severity of injury, age, and gender

The injury severity varied between different age groups (Figure 1A). In Group 1, the first peak of TBI Grade III occurred in patients aged ≥60 years, accounting for 42.1% of cases. In addition, the 40 – 49 age group had the highest percentage of TBI Grade I cases, comprising 26.9% of the cases in Group 2. Furthermore, the 40 – 49 age group had the next highest percentage of injury severity, with 40.3% of TBI Grade I cases in Group 1 and 40% of TBI Grade III cases in Group 2.

There were notable gender differences between the two groups. In Group 1, males had a higher percentage of TBI Grade I and II compared to females. However, in TBI Grade III, females represented a higher percentage (52.6%) compared to males (47.4%). Similarly, in Group 2, males were more represented in TBI Grade I and II, whereas females comprised a higher percentage of TBI Grade III cases (53.3%) compared to males (46.7%) (Figure 1B).

3.4. Mechanism of TBI, age, gender, and LOC time

The results of comparative analyses of the mechanism of TBI, age, gender, and LOC time between the two groups are illustrated in Figure 2. In Group 1, the 40 – 49 age group had the highest incidence of injuries, with assault being the most prevalent cause (50%), followed by RTAs, falls ≤1 m, and falls >1 m. Similarly, in Group 2, RTAs (35.2%) were the primary cause of injury, followed by falls ≤1 m, assault, and falls >1 m (Figure 2A). In Group 1, males represented most injuries, accounting for 100% of falls >1 m, 69.7% of falls ≤1 m, and 66.4% of RTAs. In Group 2, RTAs were the most prevalent cause of injury, with females accounting for 68% of cases involving falls ≤1 m. For other injury causes in Group 2, males were the more prevalent (Figure 2B).

RTAs were the most common cause of LOC lasting from 0 to 30 min (62.8%) in Group 1. In addition, falls ≤1 m were the most prevalent cause of LOC lasting > 24 h (66.7%). Conversely, in Group 2, falls ≤1 m were the primary cause of LOC lasting from 0 to 30 min (73.7%), whereas assault was the most prevalent cause of LOC lasting > 24 h (30%) (Figure 2C).

3.5. Comparison of admission and discharge rehabilitation outcomes by age and gender among both groups

In Group 1, the initial GCS score grades showed a statistically significant difference (*p* = 0.002), with most

Table 2. Comparison of clinical characteristics between TBI without COVID-19 (Group 1) and TBI with COVID-19 (Group 2) based on GOS classification

Characteristics	Group 1 (*n*=186)	Group 2 (*n*=120)	*p*-value
TBI grade (%)			0.521
Grade I	129 (69.4)	82 (68.3)	
Grade II	38 (20.4)	26 (21.6)	
Grade III	19 (10.2)	12 (10)	
Initial GCS score (%)			0.785
Mild (13–15)	123 (66.1)	81 (67.5)	
Moderate (9–12)	53 (28.5)	32 (26.6)	
Severe (3–8)	10 (5.4)	7 (8.8)	
GOS (%)			0.049
Good recovery	91 (48.9)	57 (47.5)	
Moderate disability	65 (34.9)	40 (33.3)	
Severe disability	27 (14.5)	23 (19.1)	
Vegetative state	3 (1.6)	8 (6.3)	
Death	0 (0.0)	1 (0.8)	
LOC time (%)			0.137
0–30 min	106 (57.0)	71 (59.2)	
31 min–24 h	37 (19.9)	31 (25.8)	
>24 h	43 (23.1)	18 (15)	
Treatment type (%)			0.121
Conservative	94 (50.5)	72 (60)	
Neurological Surgery	49 (26.3)	28 (23.3)	
Puncture	43 (23.1)	20 (16.7)	
Initial ASA-PS score (%)			0.173
ASA-PS I	100 (53.8)	68 (56.6)	
ASA-PS II	57 (30.6)	42 (35)	
ASA-PS III	22 (11.8)	10 (8.3)	
ASA-PS IV	5 (2.7)	0 (0.0)	
Unknown	2 (1.1)	0 (0.0)	
Admission total FIM (mean±SD) Median (IQR)	64.21±6.7 63.00 (9)	61.27±6.4 60.00 (4)	<0.001
Admission motor FIM (mean±SD) Median (IQR)	37.94±3 39.00 (23)	36.76±2.2 37.00 (5)	<0.001
Admission cognitive FIM (mean±SD) Median (IQR)	19.11±3 19.00 (4)	18.65±3.1 20.00 (24)	<0.001
Discharge total FIM (mean±SD) Median (IQR)	87.43±3.7 87.00 (4)	86.23±3.5 85.50 (23)	<0.001
Discharge Motor FIM (mean±SD) Median (IQR)	70.74±4 28.00 (3)	68.32±3.2 24.00 (4)	<0.001
Discharge cognitive FIM (mean±SD) Median (IQR)	27.12±2.3 28.00 (3)	23.87±2.9 23.00 (4)	<0.001
Admission RLAS (mean±SD)	5.58±1.030	5.02±1.092	<0.001
Discharge RLAS (mean±SD)	8.25±0.9	7.32±0.8	0.031
Admission BI score (mean±SD) Median (IQR)	54.28±6.7 55.50 (12)	47.76±4.1 48.00 (6)	<0.001

(Cont'd...)

Table 2. ***(Continued)***

Characteristics	Group 1 (*n*=186)	Group 2 (*n*=120)	*p*-value
Discharge BI score (mean±SD)	71.67±8.9	63.86±5.2	<0.001
Median (IQR)	69.00 (16)	65.00 (11)	
Type of injury (%)			<0.05
Single	32 (47.05)	23 (45.09)	
Multilabel	36 (52.94)	28 (54.9)	

Abbreviations: ASA-PS: American Society of Anesthesiologists physical status; BI: Barthel index; FIM: Functional independence measure; GCS: Glasgow coma scale; GOS: Glasgow outcome scale; IQR: Interquartile range; LOC: Loss of consciousness; RLAS: Rancho Los Amigos scale; SD: Standard deviation; TBI: Traumatic brain injury.

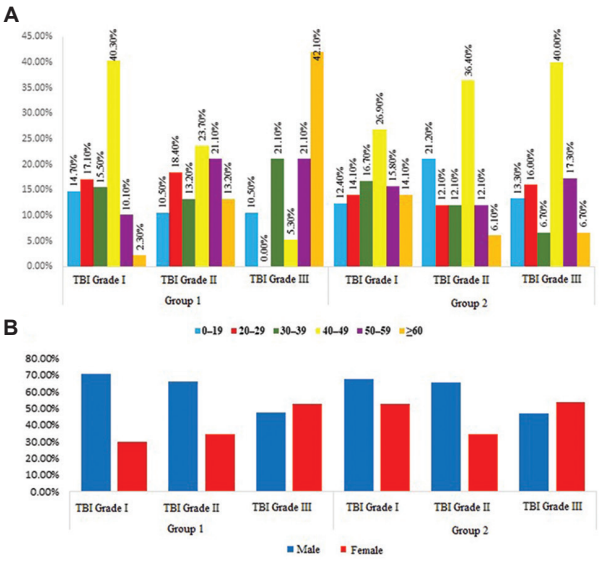

Figure 1. (A) Comparison of injury severity between TBI without COVID-19 (Group 1) and TBI with COVID-19 (Group 2) across various age groups. (B) Comparison of injury severity by gender.
Abbreviation: TBI: Traumatic brain injury.

mild cases (GCS, 13 – 15) occurring in the 0 – 19 age group (92%), followed by the 40 – 49 (71%), 20 – 29 (65.5%), 30 – 39 (65.5%), 50 – 59 (52%), and ≥60 (31.3%) age groups in descending order. In Group 2, the majority of mild cases were found in the ≥60 age group (78.6%), followed by the 50 – 59 (75%), 20 – 29 (72.2%), 0 – 19 (66.4%), 40 – 49 (61.5%), and 30 – 39 (44.4%) age groups in descending order. Regarding the GOS classification, both groups showed statistically significant differences ($p < 0.001$ for Group 1 and $p = 0.031$ for Group 2). In Group 1, the age group with the highest rate of good recovery was the 0 – 19 years, with 92% of patients achieving a good prognosis, followed by the 20 – 29 (72.4%), 30 – 39 (58.6%), 40 – 49 (40.3%), ≥60 (12.5%), and 50 – 59 (12%) in descending order. In Group 2, the age group with the highest rate of good recovery was the ≥60 years, with 78.6% of patients reaching a good recovery level, followed by the 50 – 59 (50%), 0 – 19 (42.9%), 20 – 29 (38.9%), 40 – 49 (33.3%), and 30 – 39 (27.8%) in descending order.

There was a significant difference in the admission total FIM scores among Group 1, with the 30 – 39 age group exhibiting a significantly higher score of 66 ± 7 compared to other age groups. Similarly, in Group 2, the 30 – 39 age group showed a significantly higher admission total FIM score of 65 ± 5 compared to other age groups. Meanwhile, the discharge total FIM score across the six different age groups in Group 1 (87.5%) was higher than in Group 2 (86%). For the admission BI score, the 30 – 39 age group in Group 1 showed a higher score of 54 ± 6 compared to the same age group in Group 2 (51 ± 4). Upon discharge, Group 1 showed higher BI scores in the 0 – 19 age group (71 ± 10), followed by the 40 – 49 (69 ± 8), ≥60 (69 ± 8), 30 – 39 (69 ± 9), 20 – 29 (68 ± 8), and 50 – 59 (68 ± 7) age groups in descending order. Similarly, in Group 2, the 0 – 19 age group had the highest score of 67 ± 4, followed by the ≥60 (66 ± 6), 20 – 29 (66 ± 23), 50 – 59 (65 ± 4), 30 – 39 (65 ± 23), and 40 – 49 (64 ± 23) age groups in descending order (Table 3).

Table 4 presents the comparison of rehabilitation outcomes based on gender. In Group 1, males had a higher initial GCS score in the mild range (13 – 15) compared to females, and had a higher rate of good recovery. However, there was a similarity between males and females in terms of total FIM and BI scores at both admission and discharge, indicating comparable levels of functional independence (Table 4). In Group 2, no significant differences were observed in the analysis of initial GCS score ($p = 0.23$) or admission total FIM scores ($p = 0.32$) between genders. Similarly, no significant differences were found in the analysis of GOS classification, discharge total FIM scores, or both admission and discharge BI scores, indicating similar rehabilitation outcomes between genders in these measures.

3.6. Descriptive of surgical variables among TBI patients without COVID-19 (Group 1) and with COVID-19 (Group 2)

Table 5 presents the results of the frequency and percentage of surgery types and complications of initial neurosurgical treatment. Group 1 underwent craniotomies in 25 cases

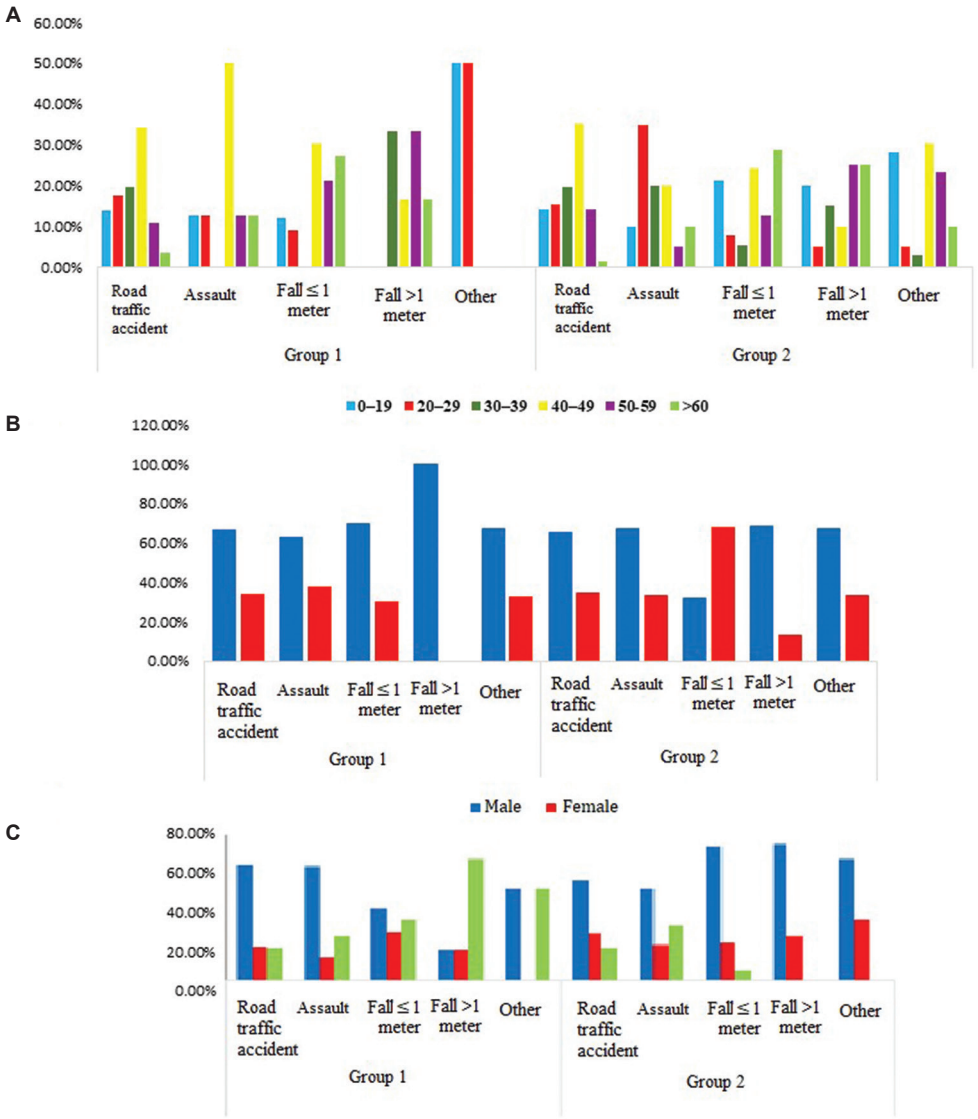

Figure 2. Comparison of TBI mechanisms between TBI without COVID-19 (group 1) and TBI with COVID-19 (group 2) based on (A) age, (B) gender, (C) LOC time.
Abbreviations: LOC: Loss of consciousness; TBI: Traumatic brain injury.

(53.19%), whereas Group 2 had 19 cases (50%) (Table 5). This was followed by craniectomy (Group 1, 11 cases, 23.4% and Group 2, 10 cases, 26.3%), decompressive hemicraniectomy (Group 1, 7 cases, 14.9% and Group 2, 6 cases, 15.8%), burr hole (Group 1, 3 cases, 6.4% and Group 2, 2 cases, 5.3%), and ventriculostomy (Group 1, 1 case, 2.1% and Group 2, 1 case, 2.6%) in descending order. Notably, the incidence of infection complications after initial neurosurgery was higher in Group 2 (18.42%) than in Group 1 (4.25%).

4. Discussion

In December 2019, an outbreak of a novel respiratory disease of unidentified origin emerged. The COVID-19 pandemic influenced the occurrence of TBI, affecting both its frequency and prevalence. In addition, the health-care system faced significant challenges, with a large number of patients requiring intensive care, which strained facilities providing treatment for TBI patients. Social distancing measures aimed at curbing virus transmission further led to a reduction in healthcare worker schedules at many health-care centers.[22-24] This study intends to investigate the impact of the COVID-19 pandemic on the epidemiology of TBI and analyze its effect on TBI prognosis after rehabilitation treatment.

The results revealed disparities in age distribution, gender composition, and MOI between the two groups.

Table 3. Comparison of admission and discharge rehabilitation outcomes by age between TBI without COVID-19 (Group 1) and TBI with COVID-19 (Group 2)

Group	Group 1 (*n*=186)							Group 2 (*n*=120)						
Variables	Age							Age						
	0 – 19	20 – 29	30 – 39	40 – 49	50 – 59	≥60	*p*-value	0 – 19	20 – 29	30 – 39	40 – 49	50 – 59	≥60	*p*-value
Initial GCS scores														
Mild (13–15%)	23 (92.0)	19 (65.5)	19 (65.5)	44 (71.0)	13 (52.0)	5 (31.3)	0.002	11 (66.4)	13 (72.2)	8 (44.4)	24 (61.5)	12 (75.0)	11 (78.6)	0.23
Moderate (9–12%)	2 (8.0)	10 (34.5)	8 (27.6)	16 (25.8)	10 (40.0)	7 (43.8)		6 (33.6)	5 (27.8)	10 (55.6)	11 (33.4)	3 (18.8)	2 (14.3)	
Severe (3–8%)	0 (0.0)	0 (0.0)	2 (6.9)	2 (3.2)	2 (8.0)	4 (25.0)		0 (0.0)	0 (0.0)	0 (0.0)	2 (5.1)	1 (6.3)	1 (7.1)	
GOS (%)														
Good recovery	23 (92.0)	21 (72.4)	17 (58.6)	25 (40.3)	3 (12.0)	2 (12.5)	<0.001	9 (42.9)	7 (38.9)	5 (27.8)	13 (33.3)	8 (50.0)	11 (78.6)	0.031
Moderate disability	2 (8.0)	7 (24.1)	6 (20.7)	32 (51.6)	12 (48.0)	6 (37.5)		3 (14.3)	7 (38.9)	8 (44.4)	20 (51.3)	2 (12.5)	1 (7.1)	
Severe disability	0 (0.0)	1 (3.4)	5 (17.2)	5 (8.1)	8 (32.0)	8 (50.0)		5 (23.8)	4 (22.2)	4 (22.2	6 (15.4)	3 (18.8)	1 (7.1)	
Vegetative state	0 (0.0)	0 (0.0)	1 (3.4)	0 (0.0)	2 (8.0)	0 (0.0)		3 (14.3)	0 (0.0)	1 (5.6)	0 (0.0)	3 (18.8)	1 (7.1)	
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		1 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Admission total FIM, mean (SD)	61 (6)	62 (6)	66 (7)	62 (6)	60 (23)	61 (6)	0.211	60 (4)	60 (23)	65 (5)	63 (6)	62 (4)	59 (3)	0.32
Discharge total FIM, mean (SD)	89 (4)	86 (4)	86 (23)	86 (4)	89 (3)	89 (4)	0.472	88 (3)	82 (4)	86 (23)	87 (3)	87 (4)	86 (3)	0.651
Admission BI score, mean (SD)	52 (6)	52 (7)	54 (6)	52 (7)	50 (6)	50 (6)	0.715	49 (4)	49 (23)	51 (4)	48 (4)	48 (23)	49 (4)	0.426
Discharge BI score, mean (SD)	71 (10)	68 (8)	69 (9)	69 (8)	68 (7)	69 (8)	0.797	67 (4)	66 (23)	65 (23)	64 (23)	65 (4)	66 (6)	0.760

Abbreviations: BI: Barthel index; FIM: Functional independence measure; GCS: Glasgow coma scale; GOS: Glasgow outcome scale; SD: Standard deviation.

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Table 4. Comparison of admission and discharge rehabilitation outcomes among genders between TBI without COVID-19 (Group 1) and TBI with COVID-19 (Group 2)

Group	Group 1 (*n*=186)			Group 2 (*n*=120)		
Variables	Gender		*p*-value	Gender		*p*-value
	Male	Female		Male	Female	
Initial GCS scores (%)			0.098			0.031
Mild (13–15)	89 (71.2)	34 (55.7)		38 (55.9)	35 (67.3)	
Moderate (9–12)	31 (24.8)	22 (36.1)		26 (38.2)	10 (19.2)	
Severe (3–8)	5 (4.0)	5 (8.2)		4 (5.9)	7 (13.5)	
GOS (%)			0.417			0.317
Good recovery	64 (51.2)	27 (44.3)		24 (36.1)	25 (48.1)	
Moderate disability	42 (33.6)	23 (37.7)		23 (34.7)	15 (28.8)	
Severe disability	61 (2.8)	11 (18.0)		17 (23.6)	7 (13.5)	
Vegetative state	3 (2.4)	0 (0.0)		3 (4.2)	5 (9.6)	
Death	0 (0.0)	0 (0.0)		1 (1.4)	0 (0.0)	
Admission total FIM, mean (22)	63 (7)	60 (23)	0.086	62 (23)	60 (3)	0.046
Discharge total FIM, mean (22)	87 (4)	89 (4)	0.079	87 (3)	87 (4)	0.654
Admission BI score, mean (22)	52 (6)	51 (7)	0.390	50 (4)	52 (4)	0.765
Discharge BI score, mean (22)	69 (8)	69 (8)	0.294	65 (4)	65 (23)	0.728

Abbreviations: BI: Barthel index; FIM: Functional independence measure; GCS: Glasgow coma scale; GOS: Glasgow outcome scale; SD: Standard deviation.

Table 5. Descriptive of surgical variables among TBI patients without COVID-19 (group 1) and with COVID-19 (group 2)

Variables	Category	Group 1 *n* (%)	Group 2 *n* (%)
Surgery	No	21 (30.88)	13 (25.49)
	Yes	47 (69.11)	38 (74.5)
Surgery type	Craniotomy	25 (53.19)	19 (50)
	Craniectomy	11 (23.4)	10 (26.31)
	Decompressive hemicraniectomy	7 (14.89)	6 (15.78)
	Burr hole	3 (6.38)	2 (5.26)
	Ventriculostomy	1 (2.12)	1 (2.63)
Complications of initial neurosurgical treatment	Infection	2 (4.25)	7 (18.42)
	Hemorrhage	1 (2.12)	2 (5.26)
	Cerebral Edema	3 (6.38)	2 (5.26)
	Neurological deficits	4 (8.51)	1 (2.63)
	Hydrocephalus	2 (4.25)	1 (2.63)
	Vascular complications	3 (6.38)	2 (5.26)

Abbreviation: TBI: Traumatic brain injury.

In Group 1, the mean age was younger compared to Group 2, consistent with a previous study conducted in Turkey reporting mean ages of 38 ± 17.53 years for the control group and 41 ± 19.18 years for the COVID-19 group.[25] Both groups had a higher percentage of male patients, with a 2:1 male-to-female ratio in Group 1. However, the percentage of females in Group 2 was higher than in Group 1, consistent with previous studies reporting male predominance in TBI.[26-29] This observation may be attributed to males engaging more frequently in occupations and activities with a higher risk of traumatic events.

The predominant MOI in both groups was RTAs, with 137 (73.7%) cases in Group 1 and 71 (56.3%) cases in Group 2. These findings correlate with previous studies that have identified RTAs as the primary cause of TBI on a global scale.[30] Notably, the incidence of TBI resulting from falls ≤1 m was higher in Group 2 compared to Group 1, with 38 (30.2%) cases and 33 (17.7%) cases, respectively. The COVID-19 pandemic likely contributed to an increase in fall events, driven by decreased physical activity, social isolation, and mental health issues.[31,32] In addition, COVID-19 patients may experience fatigue, respiratory symptoms, or neurological impairments, making them particularly susceptible to falls. These factors, combined with the need for medical care and COVID-19-related symptoms, contribute to the higher incidence of fall-related TBI in COVID-19 patients compared to those without contracting the virus.[28]

The results of this study showed significant differences in clinical characteristics between the two groups, which

align with a previous study.[27] Group 2 exhibited higher initial injury severity in terms of GCS scores, TBI grades, and ASA-PS scores compared to Group 1, although these differences were not statistically significant. Interestingly, TBI severity was higher in females, although no specific reasons were identified. Variability in MOI may contribute, as females may be more susceptible to certain types of accidents or engage in activities with a higher risk of severe head trauma. For instance, females are more likely to experience TBI due to fall incidents or partner violence.[27] Consistent with our findings, it has been well recognized that the risk of TBI resulting from falls at ground level increases with age.[33]

In Group 2, a higher percentage of males experienced falls from >1 m, whereas falls ≤1 m were more common in Group 1. This difference can be attributed to the increased time of individuals spent staying at home and the reduction in outdoor activities during the pandemic. With limited opportunities for outdoor activities, individuals may have engaged in more indoor activities, leading to a higher risk of falls from greater heights. In addition, falls >1 m in Group 1 and RTAs in Group 2 were both linked to a duration of LOC >24 h. These findings suggest that falls from significant heights and RTAs are more likely to result in prolonged unconsciousness.[34] The severity of these incidents and the force involved may contribute to the extended duration of LOC in these cases.

This study found that older individuals in Group 1 exhibited higher injury severity compared to those in Group 2. Specifically, individuals aged 40 – 49 exhibited higher injury severity, consistent with findings from a previous study.[27] COVID-19 can significantly affect respiratory, cardiovascular, and systemic health, leading to a decline in overall health status and an increase in the ASA-PS scores. The common respiratory symptoms, pneumonia, and ARDS observed in COVID-19 patients can have a detrimental effect on physical health.[35] Moreover, this study illustrates that rehabilitation plays a significant role in promoting recovery of functional, cognitive, and behavioral abilities in TBI patients.[36] Overall, both groups showed substantial enhancements in total FIM scores, including motor and cognitive subsets, from admission to discharge.[27,37]

Significant differences were observed in the motor FIM, cognitive FIM, and BI scores at discharge, with Group 2 showing poorer outcomes. These differences may be attributed to institutional responses to the pandemic, leading to changes in rehabilitation practices. Such changes could have included the truncation of rehabilitation goals to decrease the length of hospital stays, limited opportunities for walking practice, inability to train for community integration, and the discontinuation of therapeutic weekend passes.

There were no significant differences in these outcomes based on age, except for the GOS among the TBI groups. Regarding gender, significant differences were found in the admission total FIM scores in Group 2. While males are more commonly affected by TBI worldwide, some studies suggest that females may experience poorer outcomes.[38,39] However, this study did not find any significant negative correlation between gender or age and functional outcomes in rehabilitation. In addition, the MOI showed significant differences in the admission BI score in Group 1 and the discharge BI score in Group 2. Rehabilitation approaches can vary depending on the MOI, allowing for tailored interventions to address specific impairments associated with each mechanism. For example, falls may require balance training, while RTAs may necessitate gait retraining. These differences in rehabilitation strategies can influence functional outcomes and contribute to variations in BI scores.

Recovery among TBI individuals can differ based on the MOI. Certain injuries may lead to faster or more extensive recovery, resulting in higher BI scores, which indicate better functional improvements. In contrast, other injuries may result in enduring or long-lasting limitations that hinder functional independence. Furthermore, the surgical management of TBI during the COVID-19 pandemic offers critical insights. Patients with concurrent COVID-19 experience higher infection rates, underscoring the complexities involved in their care. This increased susceptibility is largely due to immune compromise caused by the virus, which heightens the risk of post-operative infections, including surgical site infections. These findings emphasize the necessity for tailored post-operative care and stringent infection control strategies to mitigate risks. Moreover, further research is essential to explore the underlying causal relationships and improve clinical outcomes for these vulnerable populations. This will ensure that healthcare providers can effectively address the dual challenges posed by both TBI and COVID-19.

This study has several limitations. First, the data were collected from three different hospitals, representing only a small portion of all TBI patients, which makes it challenging to determine the precise prevalence and management of TBI patients in China. Second, conducting the study in a single hospital may introduce potential selection bias and reduce the generalizability of the results to a broader population. Third, while these hospitals provide valuable insights into TBI management in China, their characteristics may not be representative of all hospitals nationwide. Fourth, as a retrospective study

relying on the review of previous medical records, some data loss was inevitable due to incomplete or missing records. In addition, the duration of comorbidities before TBI is not possible to be evaluated. Therefore, further extensive research is needed to replicate these findings and evaluate the actual effect of COVID-19 on TBI outcomes, which is crucial for providing more informed guidance to the rehabilitation field and health-care systems.

5. Conclusion

This study provides valuable insights into the demographics and clinical characteristics of TBI patients with and without COVID-19 in Wuhan, China. Notable differences were observed in age, gender, and MOI between the two groups. Group 2 exhibited higher initial injury severity and a greater incidence of fall-related TBI. Furthermore, rehabilitation outcomes in Group 2 were poorer, particularly in motor and cognitive function recovery. Further research is necessary to better understand the impact of COVID-19 on TBI and to enhance rehabilitation procedures. This study underscores the importance of investigating the effects of the COVID-19 pandemic on TBI epidemiology and recovery outcomes to effectively guide improvements in healthcare practices.

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Conflict of interest

The authors declare they have no competing interests.

Author contributions

Conceptualization: Ruba Altahla, Jamal Alshorman
Formal analysis: Ruba Altahla
Investigation: Jamal Alshorman
Methodology: Ruba Altahla
Writing – original draft: Ruba Altahla, Jamal Alshorman
Writing – review & editing: Ruba Altahla, Jamal Alshorman

Ethics approval and consent to participate

The ethics committee of the Second Affiliated Hospital, Clinical Medical College, Hubei University of Science and Technology granted approval for this study (approval ID: 20230214) and certify that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Moreover, the Ethics Committee of Affiliated Tongji Medical College Hospital has waived the requirement to obtain informed consent for this study.

Consent for publication

Not applicable.

Availability of data

The supporting data for the findings of this study can be obtained by contacting the corresponding author upon making a reasonable request.

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ACCSCIENCE PUBLISHING

Brain & Heart

ORIGINAL RESEARCH ARTICLE

Cardiac adverse events post-vaccination

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Abstract

Some vaccine recipients experience cardiac adverse events (AEs) following immunization (AEFIs), which include background events and vaccine-associated AEs for certain vaccines. A small subset of AEs experienced by vaccine recipients is documented in the United States Vaccine AE Reporting System (VAERS). This study retrospectively analyzed VAERS to identify associations for cardiac AEFIs. The analysis considered factors such as vaccine type, vaccine source, vaccine recipient gender, and infant age. Multiple patterns of cardiac AEFI associations were detected: (i) bradycardia and cardiac arrest for infants under 1 year of age, (ii) arrhythmia for COVID-19 and human papillomavirus vaccines, (iii) atrial fibrillation for COVID-19, influenza, and respiratory syncytial virus vaccines, (iv) myocarditis and pericarditis for anthrax, COVID-19, smallpox, and typhoid vaccines, and (v) chest discomfort, chest pain, palpitations, and tachycardia for multiple vaccines. Gender differences were observed for both myocarditis and palpitation AEFIs. Significant differences in bradycardia and cardiac arrest AEFI normalized frequencies were observed for the same infant vaccines from different manufacturers, suggesting possible manufacturing contaminants as potential causative components. In conclusion, delaying specific vaccines until infants are 1 year old, selecting alternative vaccine options, or reducing or eliminating causative components could reduce infant bradycardia and cardiac arrest AEFIs. Mathematical age relationships could model both male and female myocarditis AEs for COVID-19 vaccines, potentially applicable to other vaccines, suggesting shared etiologies. In addition, several vaccines were associated with correlated cardiac AEFI signals for chest discomfort, chest pain, palpitations, and tachycardia. The etiologies of these AEFIs could be attributed to elevated histamine levels.

Keywords: Arrhythmia; Atrial fibrillation; Bradycardia; Cardia arrest; Myocarditis; Palpitations; Pericarditis; Tachycardia

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1. Introduction

Cardiac adverse events (AEs) following immunization, known as AEs following immunization (AEFIs), can include serious AEs (SAEs). These cardiac AEFIs and SAEs may represent either background occurrences in the population or immunization-associated events. Passive collections of AEs post-immunization in databases, such as the United States Vaccine AEs Reporting System (VAERS) database[1] provide population samples of AEFIs. Elevated safety signals for AEFIs can be detected when the frequency of AEs for one or more vaccines exceeds the expected population background

occurrence rate. This background occurrence rate can often be estimated from other vaccines within the dataset. This article focuses on identifying cardiac AEFIs that occur at frequencies higher than the expected population background occurrence rates.

Cardiac AEFIs have been reported following immunizations in both adults and children. In adults, these events have been associated with multiple vaccines,[2-4] with numerous recent reports on COVID-19 vaccines.[5-18] COVID-19 vaccines have been associated with arrhythmia,[5-8] atrial fibrillation,[9-11] chest pain,[7,12-15] myocarditis,[5,7,16-18] palpitations,[7,15] pericarditis,[5,12] and tachycardia.[15] A study of 301 adolescents receiving the BNT162b2 mRNA COVID-19 vaccine found that the most common cardiovascular AEs were tachycardia (7.64%), palpitation (4.32%), and chest pain (4.32%), with cardiovascular AEs occurring in 29.24% of the adolescents.[15] Most of these cardiac AEFIs have been reported in teenagers and adults, although children can also experience them. For preterm infants, cases of bradycardia (low heart rate) have been reported in vaccines such as diphtheria/tetanus/whole-cell pertussis,[19] diphtheria-tetanus-acellular pertussis (DTAP)-*Haemophilus influenzae* type b (Hib),[19,20] diphtheria-tetanus-pertussis-inactivated polio (DTP-IPV-Hib),[21] and DTAP-Hib-meningococcal serogroup C conjugate.[22] Bradycardia also occurs in extremely low birth weight (ELBW) infants immediately after immunization[23] and preterm infants.[24] At present, vaccine dosages are not adjusted for the lower body weight of these infants. The etiology of cardiac AEFIs in both adults and children remains unknown.

In this study, the VAERS database was retrospectively analyzed to identify cardiac AEFI associations.[1] Multiple cardiac AEFI association safety signals were observed. First, bradycardia AEFIs and cardiac arrest SAEs were observed for infants <1 year of age associated with various vaccines. Second, myocarditis and pericarditis association signals were observed for multiple vaccines. The normalized frequencies of myocarditis AEs were consistent with unique log-scale age relationships for both males and females. Third, arrhythmia AEFI signals were observed for COVID-19 and human papillomavirus (HPV) vaccines and atrial fibrillation AEFI signals for COVID-19, influenza, and respiratory syncytial virus (RSV) vaccines. Fourth, chest discomfort, chest pain, palpitations, and tachycardia AEFI signals were observed for multiple vaccines. Options to reduce bradycardia and cardiac arrest AEFIs in infants include adjusting vaccine dosage levels based on the child's body weight, delaying immunization until 1 year of age for certain vaccines, using alternative vaccine options, reducing or eliminating causative components (e.g., aluminum adjuvant or possibly endotoxins) from associated vaccines, and avoiding concomitant vaccination combinations, including live attenuated vaccines.

2. Materials and methods

2.1. Materials

Focusing on cardiac AEs, the VAERS database[1] was retrospectively examined for AEs designated by the following Medical Dictionary for Regulatory Activities (MedDRA) codes:[25] Arrhythmia, Atrial fibrillation, Bradycardia, Cardiac arrest, Chest discomfort, Chest pain, Myocarditis, Palpitations, Pericarditis, and Tachycardia. MedDRA® the MedDRA terminology is an international medical terminology developed by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. The downloaded VAERS data included all AEs reported from 1990 to June 26, 2024.

2.2. Retrospective analysis of the vaccine AE reporting system database

The Ruby program vaers_slice4.rb[26] was used for the retrospective analysis of the VAERS data files, including VAERS DATA, VAERS symptoms, and VAERS vaccine, spanning 1990-2024, and the Non-Domestic data file. The vaers_reports.py program tallied vaccine AEs by vaccine, day of onset, age, and concomitant vaccines. The vaers_slice4.rb program accepted a list of one or more MedDRA codes (used by VAERS) as input.

Vaccines indicated as "foreign," "no brand name," or "unknown" were excluded from the figures to avoid potential sampling biases associated with AE reports. Vaccines with only one AE were also excluded to avoid elevated normalized frequencies possibly associated with population sampling in the VAERS reports. However, an exception was made for palpitation-normalized frequencies in males to facilitate comparisons with female-normalized frequencies (all these exceptions have lower male-normalized frequencies than the corresponding female-normalized frequencies).

2.3. AEFIS formula

For the AE (X), vaccine (V), cardiac AEFI-associated AEs (C), background population rate (B), and population (P), the total expected AEs can be modeled using Equation 1.

$$AEs(X,V|P) = (B_{X,V} + C_{X,V}) \times P \quad (1)$$

When there are no cardiac AEFI-associated AEs (C = 0), this simplifies to Equation 2.

$$AEs(X,V|P) = B_{X,V} \times P \quad (2)$$

For each AE in VAERS, normalized AE frequencies per 100,000 VAERS reports for all AEs can be calculated with Equation 3.

$$\text{AE(X,V) normalized frequency} = \frac{AE(X,V)}{\sum_i AE(i,V)} \times P_{100,000} \quad (3)$$

A candidate cardiac AEFI safety signal is detected when AE (X, V_i) is significantly different from AE (X, V_j), implying that the difference arises from the $C_{X,V}$ terms, as the $B_{X,V}$ should be essentially equivalent when comparing Equation 1 for two vaccines (V_i and V_j).

2.4. Statistical analysis

Microsoft Excel was used to calculate Pearson correlations and prepare figures. Pearson correlations were performed for 119 vaccines with a median normalized frequency greater than zero for the MedDRA terms examined (Table S1). Chi-square calculations were performed using an online Chi-square 2 × 2 calculator.[27]

3. Results

3.1. Arrhythmia AEs

Arrhythmia is a condition characterized by an irregular heartbeat, which can manifest as irregular, rapid, or slow heartbeat. The normalized frequencies for arrhythmia AEs are illustrated in Figure 1. Nine vaccines have arrhythmia normalized frequencies >200/100,000 VAERS reports (more than one in 500 reports) and four with normalized frequencies >500/100,000 VAERS reports (more than one in 200 reports) (Figure 1). The COVID-19 Pfizer-BioNTech vaccine has the highest normalized frequency of 1,442/100,000 (1 in 69) vaccine AE reports with symptoms reported to VAERS. The COVID-19 Janssen, Moderna, and Novavax vaccines have normalized frequencies ranging from 2.8 to 3.8 times lower than the Pfizer-BioNTech vaccine (Figure 1). The HPV Cervarix vaccine has a normalized arrhythmia frequency of 572/100,000. Arrhythmia AEFI has been previously reported for both HPV[28,29] and COVID-19[5-8] vaccines. Six vaccines with more than 5,000 VAERS reports have normalized frequencies of <20/100,000 VAERS reports (meningococcal conjugate [Menactra], influenza [seasonal] [FluMist], Hib [PedvaxHIB], meningococcal B [Bexsero], DTAP + hepatitis [Hep] B + IPV [Pediarix], and rotavirus [Rotarix]). This suggests that the background population rate for arrhythmia ($B_{arrhythmia}$) may be <20/100,000 VAERS reports.

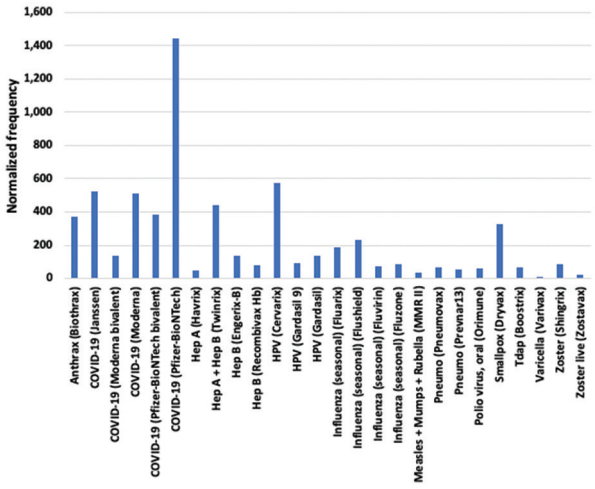

Figure 1. Arrhythmia adverse events normalized frequencies from the Vaccine Adverse Events Reporting System. Data shown for vaccines with 10 or more adverse events.
Abbreviations: Hep: Hepatitis; HPV: Human papillomavirus; Pneumo: Pneumococcal; TDAP: Diphtheria, tetanus, and pertussis.

3.2. Atrial fibrillation AEs

Atrial fibrillation is a condition characterized by an irregular and rapid heartbeat. The normalized frequencies of atrial fibrillation AEs are illustrated in Figure 2. Twelve vaccines have atrial fibrillation normalized frequencies

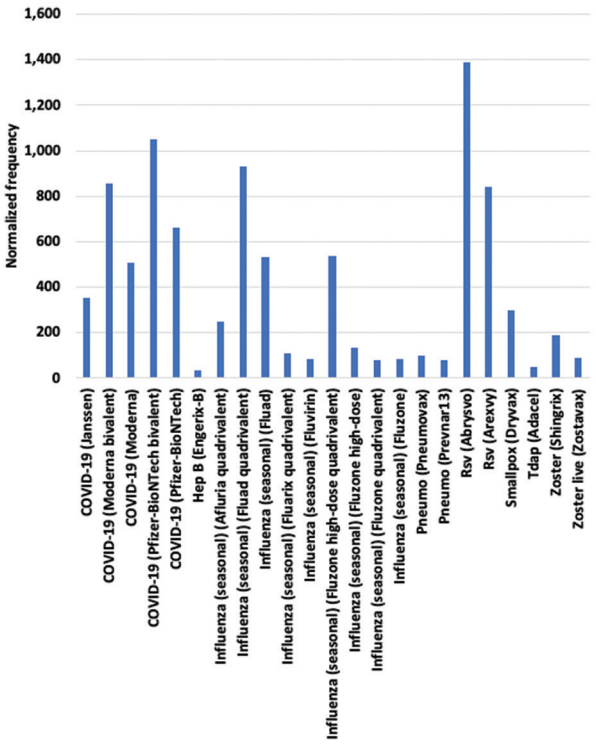

Figure 2. Atrial fibrillation adverse events normalized frequencies from the vaccine adverse events reporting system
Abbreviations: Hep: Hepatitis; HPV: Human papillomavirus; Pneumo: Pneumococcal; RSV: Respiratory syncytial virus; TDAP: Diphtheria, tetanus, and pertussis.

exceeding 200/100,000 VAERS reports, with nine >500/100,000 VAERS reports (Figure 2). COVID-19, influenza (seasonal), and RSV vaccines have four, three, and two vaccines with normalized frequencies ≥500/100,000 VAERS reports, respectively. Atrial fibrillation AEFI has been previously reported for COVID-19 vaccines.[9-11] Influenza (seasonal) Fluad quadrivalent, Fluzone high-dose quadrivalent, and Fluad were statistically different from Fluzone quadrivalent by Chi-square test with $p < 0.00001$. Ten vaccines with more than 5,000 VAERS reports have normalized frequencies of <20/100,000 VAERS reports (Hep A [Havrix], Hep A [Vaqta], Hib [ActHib], HPV [Gardasil 9], HPV [Gardasil], measles + mumps + rubella [MMR II], meningococcal conjugate [Menactra], pneumococcal [Prevnar], IPV [Ipol], and varicella [Varivax]). This suggests that the background population rate for atrial fibrillation ($B_{\text{atrial fibrillation}}$) may be >20/100,000 VAERS reports. For other cardiac AEs, atrial fibrillation exhibits Pearson correlation coefficients of 0.42 with arrhythmia, 0.24 with chest discomfort, 0.17 with chest pain, and 0.44 with palpitations.

3.3. Bradycardia AEs

Bradycardia is characterized by a heart rate that is too slow (<60 beats/min) while at rest. The highest normalized frequencies for bradycardia AEs were concentrated in childhood vaccines (Table S4). The normalized frequencies for bradycardia AEs are illustrated for infants aged 0 and 1 in VAERS in Figure 3. Notably, DTAP + IPV + Hep B + Hib (Hexavac) is no longer authorized. For infants under one, 27 vaccines have bradycardia normalized frequencies of more than 200/100,000 VAERS reports, and 12 have frequencies >500/100,000 VAERS reports (Figure 3). In comparison, for infants aged one, no vaccines have bradycardia normalized frequencies of more than 200/100,000 VAERS reports (Figure 3). For matched vaccine pairs for infants under 1, there are statistical differences for DTAP Infanrix versus Tripedia, DTAP + IPV Infanrix tetra versus Pentacel,

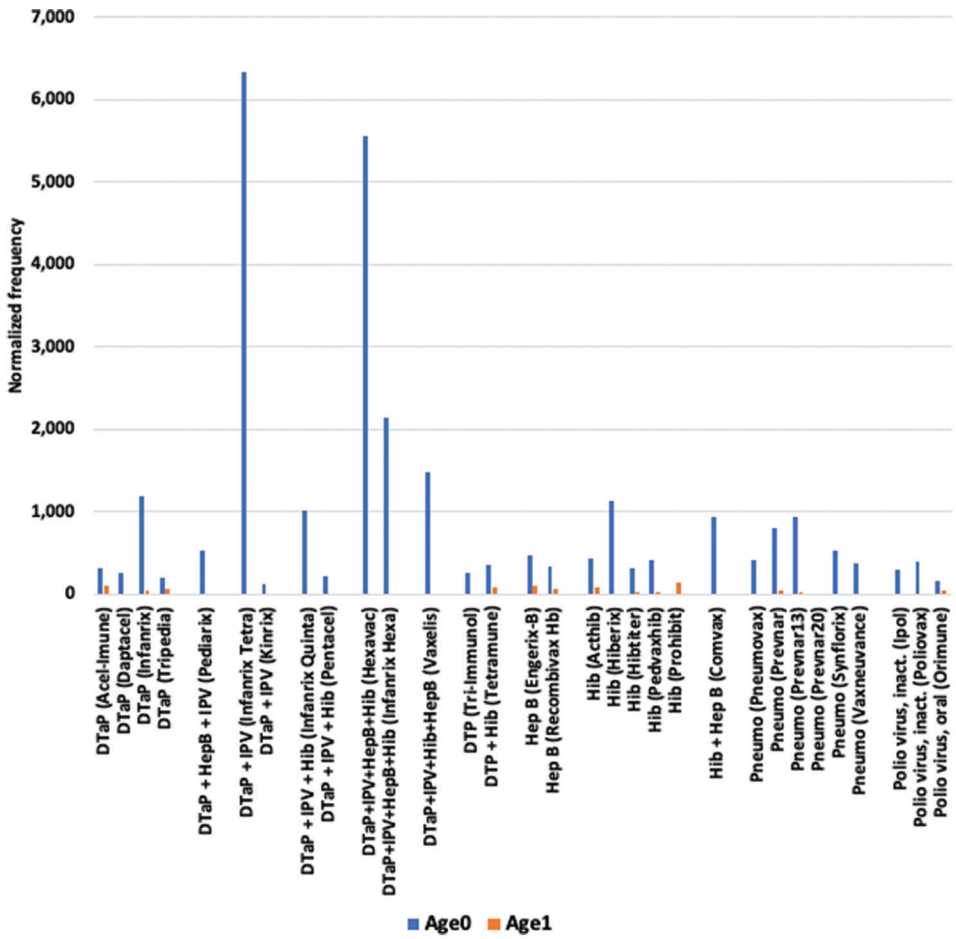

Figure 3. Bradycardia adverse events normalized frequencies for infants aged zero and one from the vaccine adverse events reporting system
Abbreviations: DTAP: Diphtheria, tetanus, and pertussis; Hep: Hepatitis; HIB: *Haemophilus influenzae* type B; HPV: Human papillomavirus; IPV: Inactivated poliovirus; Pneumo: Pneumococcal.

and Hib Hiberix versus HibTITER using Chi-square test ($p < 0.00001$). For infants aged 0 versus 1, three vaccines showed statistical differences: DTAP Infanrix ($p < 0.00001$), pneumococcal Prevnar ($p < 0.00001$), and pneumococcal Prevnar13 ($p < 0.00001$). Individual vaccines with normalized frequencies >500/100,000 VAERS reports include DTAP (Infanrix: 1,182), HIB (Hiberix: 1,124), DTP + IPV (Infanrix tetra: 6,329), DTAP + IPV + Hib (Infanrix quinta: 1,011), DTAP + IPV + Hep B + Hib (Infanrix hexa: 2,135), DTAP + IPV + Hib + Hep B (Vaxelis: 1,474), Hib + Hep B (Comvax: 931), and pneumococcal (Prevnar: 803, Prevnar13: 934, and Synflorix: 535) (Figure 3). Bradycardia has been previously reported in preterm infants and ELBW infants.[19-21] Five vaccines with more than 5,000 VAERS reports have bradycardia normalized frequencies of <20/100,000 VAERS reports (influenza [seasonal] [Afluria, FluMist, and Fluzone high-dose], and MMR II + varicella [Varivax and Proquad)], suggesting that $B_{bradycardia}$ may be <20/100,000 VAERS reports. For other cardiac AEs, bradycardia normalized frequencies have Pearson correlation coefficients of 0.22 with arrhythmia, 0.21 with cardiac arrest, 0.21 with palpitations, 0.28 with pericarditis, and 0.20 with tachycardia.

Specific concomitant vaccine combinations have higher bradycardia AEFI normalized frequencies (Figure 4). Twenty-two vaccines have bradycardia AEs >1,000/100,000 VAERS reports (Figure 4). Some vaccines occur multiple times in these concomitant combinations, including pneumococcal (Prevnar13) nine times and pneumococcal (Prevnar) four times, DTAP + IPV + Hep B + HIB (Infanrix hexa) six times, DTAP + Hep B + IPV (Pediarix) six times, rotavirus (RotaTeq) twice, rotavirus (Rotarix) twice, Hib (PedvaxHIB) twice, Hib (ActHib) twice, Hep A (Havrix) twice, DTAP (Infanrix) twice, and COVID19 (Pfizer-Biotech bivalent) twice (Figure 4). These concomitant vaccine combinations are consistent with both additive or synergy safety signals.

3.4. Cardiac arrest AEs

Cardiac arrest occurs when the heart stops beating. The normalized frequencies for cardiac arrest AEs are illustrated for infants aged 0 and 1 in VAERS in Figure 5. For infants aged zero, 25 vaccines have cardiac arrest normalized frequencies of more than 200/100,000 VAERS reports and 17 with more than 500/100,000 VAERS reports (Figure 5). In comparison, for infants aged one, four vaccines have cardiac arrest normalized frequencies of more than 200/100,000, and no vaccines have cardiac arrest normalized frequencies of more than 500/100,000 VAERS reports (Figure 5). Four pairs of matched vaccines for infants under one showed significant differences: DTAP Acel-Imune versus Daptacel ($p = 0.000058$), DTAP Tripedia versus Daptacel ($p = 0.00065$), poliovirus inactive Poliovax versus Ipol ($p = 0.000011$), and oral poliovirus oral Orimune versus inactive Ipol ($p < 0.00001$). Comparison of infants aged zero to one for the same vaccine showed significant differences for 13 vaccines: DTAP Acel-Imune ($p = 0.0033$), DTAP Infanrix ($p = 0.000186$), DTAP Tripedia ($p < 0.00001$), DTP+Hib Tetramune ($p = 0.0015$), Hep B Recombivax HB ($p = 0.0067$), Hib ActHib ($p = 0.0001$), Hib HibTITER ($p < 0.00001$), Hib PedvaxHIB ($p = 0.004671$), Hib+Hep B Comvax ($p = 0.00034$), pneumococcal Prevnar ($p < 0.00001$), pneumococcal Prevnar13 ($p < 0.00001$), poliovirus inactive Poliovax ($p = 0.00030$), and poliovirus oral Orimune ($p = 0.00019$). The normalized frequencies for infants under 1 year of age are higher than those for 1-year-old infants (Figure 5). Five vaccines with more than 5,000 VAERS reports have cardiac arrest normalized frequencies of <20/100,000 VAERS reports (HPV [Gardasil 9], influenza [seasonal] [Afluria, FluMist, and Fluzone high-dose], and DTAP [Adacel]), suggesting that the $B_{cardiac\ arrest}$ may be <20/100,000 VAERS reports. For other cardiac AEs, cardiac arrest normalized frequencies have Pearson correlation coefficients of 0.21 with bradycardia, −0.17 with palpitations, and 0.33 with tachycardia.

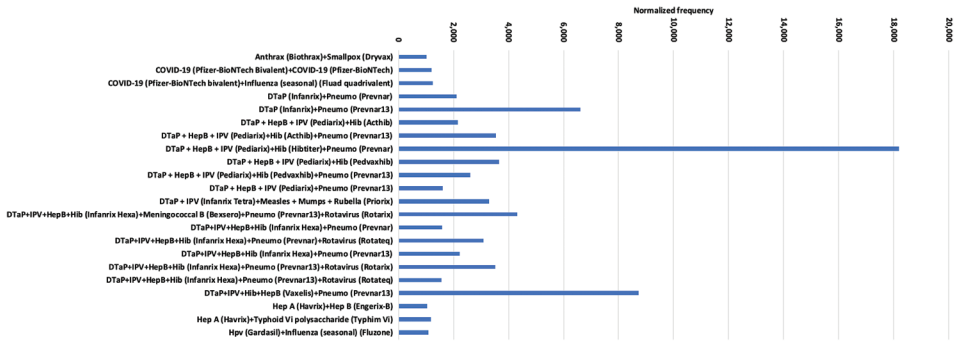

Figure 4. Bradycardia concomitant vaccine adverse events normalized frequencies from vaccine adverse events reporting system
Abbreviations: DTAP: Diphtheria, tetanus, and pertussis; Hep: Hepatitis; HIB: *Haemophilus influenzae* type B; HPV: Human papillomavirus; IPV: Inactivated poliovirus; Pneumo: Pneumococcal.

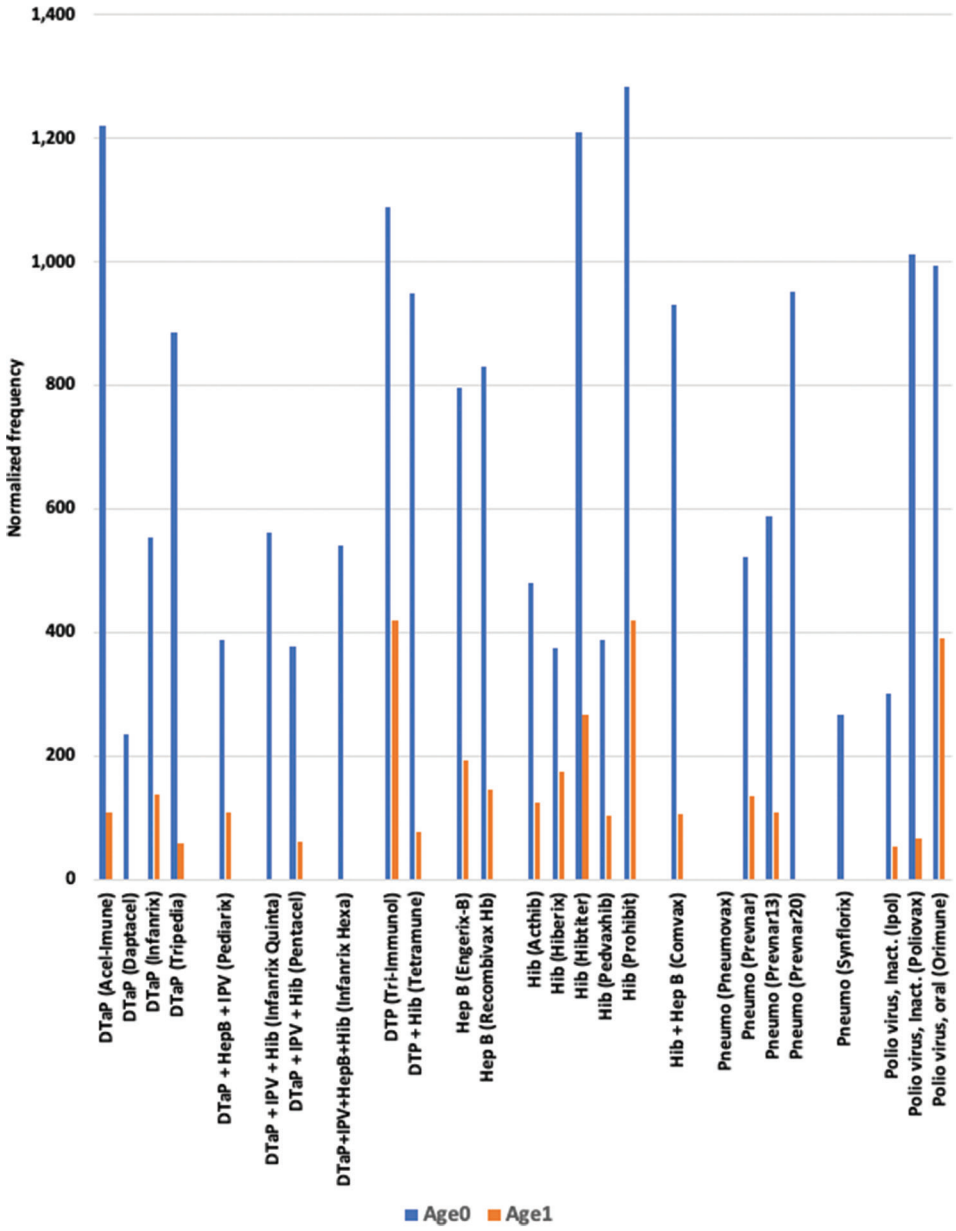

Figure 5. Cardiac arrest adverse events normalized frequencies for infants aged 0 and 1 from the vaccine adverse events reporting system
Abbreviations: DTAP: Diphtheria, tetanus, and pertussis; Hep: Hepatitis; HIB: *Haemophilus influenzae* type B; Pneumo: Pneumococcal.

Specific concomitant vaccine combinations have higher normalized frequencies exhibiting synergy safety patterns, such as Hib (ActHib) + pneumococcal (Prevnar13) + rotavirus (RotaTeq) at 7,547/100,000 VAERS reports and DTAP (Infanrix) + Hib (ActHib) + measles + mumps + rubella + varicella (Proquad) at 7,500/100,000 VAERS reports, in which both RotaTeq and Proquad contain live attenuated viruses. Other higher frequency concomitant vaccines include the live attenuated oral poliovirus (Orimune) or other combinations, including aluminum adjuvants (Table S5).

3.5. Chest discomfort and chest pain AEs

Fifty-eight vaccines have normalized frequencies for chest discomfort <500/100,000 (Figure 6). Fifty-five of these vaccines, except for pneumococcal (Prevnar20) and RSV (Abrysvo and Arexvy), overlap with chest pain AEs (Tables S6 and S7). Fifty-nine vaccines have chest discomfort normalized frequencies >200/100,000 VAERS reports, with 52 vaccines more than 500/100,000 VAERS reports (Figure 6). Sixty-five vaccines have chest pain normalized frequencies of more than 200/100,000 VAERS reports,

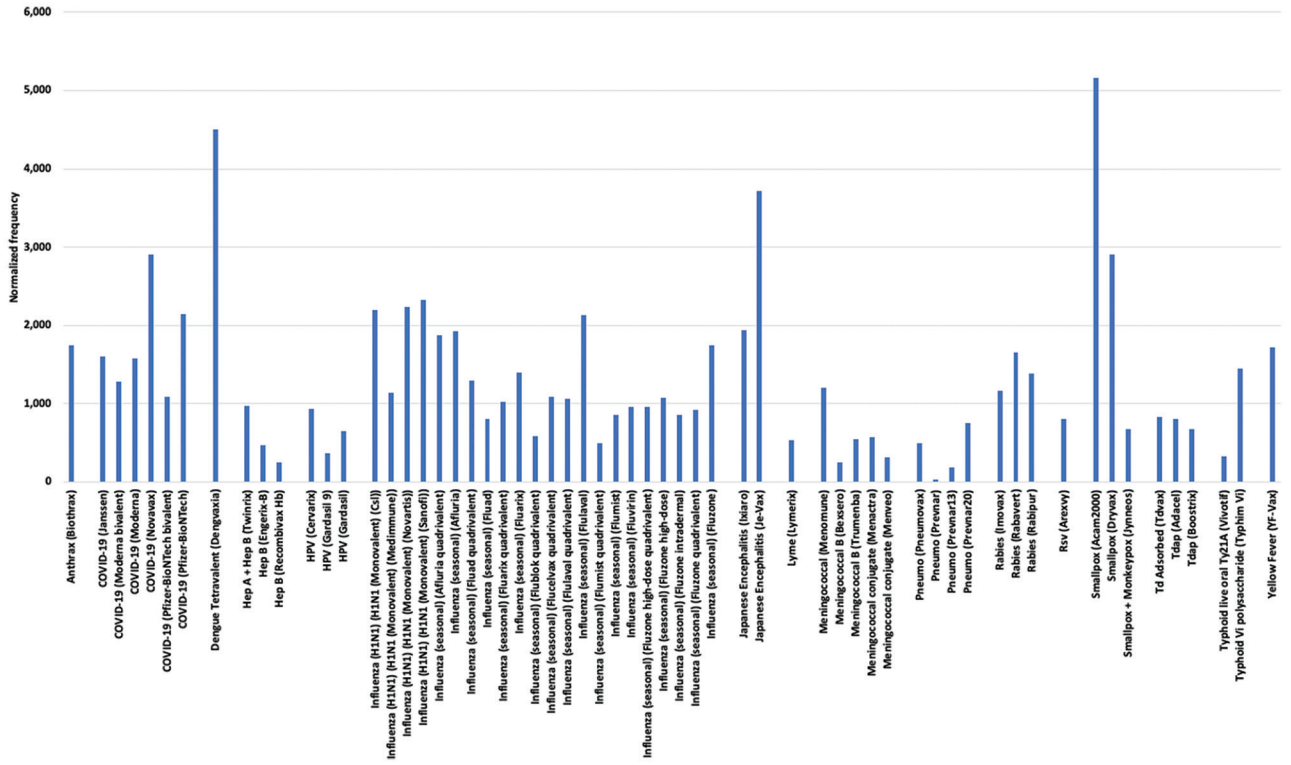

Figure 6. Chest discomfort adverse events normalized frequencies from the Vaccine Adverse Events Reporting System. Data shown for vaccines with 10 or more adverse events.

Abbreviations: Hep: Hepatitis; HIB: *Haemophilus influenzae* type B; HPV: Human papillomavirus; IPV: Inactivated poliovirus; Pneumo: Pneumococcal; RSV: Respiratory syncytial virus; TD: Tetanus-diphtheria; TDAP: Diphtheria, tetanus, and pertussis.

and 55 vaccines have more than 500/100,000 VAERS reports. Chest pain AEFI has been previously reported for COVID-19 vaccines.[7,12-15] Seven vaccines with more than 5,000 VAERS reports have chest discomfort normalized frequencies <20/100,000 VAERS reports (DTAP + Hep B + IPV [Pediarix], DTAP + IPV + HIB [PENTACEL], Hib [ActHib], Hib [PedvaxHIB], Hib + Hep B [Comvax], and rotavirus [Rotarix and RotaTeq]). These vaccines, primarily children's vaccines, represent a population of a different age than those in Figure 6. For other cardiac AEs, chest discomfort normalized frequencies have Pearson correlation coefficients of 0.24 with atrial fibrillation, 0.71 with chest pain, 0.53 with myocarditis, 0.60 with palpitations, and 0.66 with pericarditis. Likewise, for other cardiac AEs, chest pain normalized frequencies have Pearson correlation coefficients of 0.17 with arrhythmia, 0.71 with chest discomfort, 0.80 with myocarditis, 0.54 with palpitations, 0.76 with pericarditis, and 0.24 with tachycardia.

3.6. Myocarditis and pericarditis AEs

Myocarditis is an inflammation of the heart muscle (myocardium), while pericarditis is an inflammation of the sac surrounding the heart (pericardium). Seven vaccines have myocarditis normalized frequencies >200/100,000 VAERS reports, with six vaccines more than 500/100,000 VAERS reports (Figure 7). Eight vaccines have pericarditis normalized frequencies >200/100,000 VAERS reports, with five vaccines more than 500/100,000 VAERS reports (Figure 7). The normalized frequencies for myocarditis AEs are shown in Figure 8 for males and Figure 9 for females. Age-stratified results suggest linear relationships when plotted on log scales for both genders for multiple vaccines (Figures 8 and 9). Myocarditis/pericarditis has been previously reported for COVID-19[5,7,16-18] and smallpox[2] vaccines. Analysis of the World Health Organization's pharmacovigilance database detected associations between pericarditis and myocarditis with smallpox, anthrax, typhoid, encephalitis, influenza, and COVID-19 adenovirus type 5 (AD5)-vectored vaccines.[4] For COVID-19 mRNA vaccines, circulating spike proteins have been observed in vaccine recipients with myocarditis,[30] along with elevated cardiac troponin levels.[31] Myocarditis associated with COVID-19 mRNA vaccine predominantly affects males.[32] Gender differences in cardiac mast cell activation have also been observed.[33] Pericarditis AEs

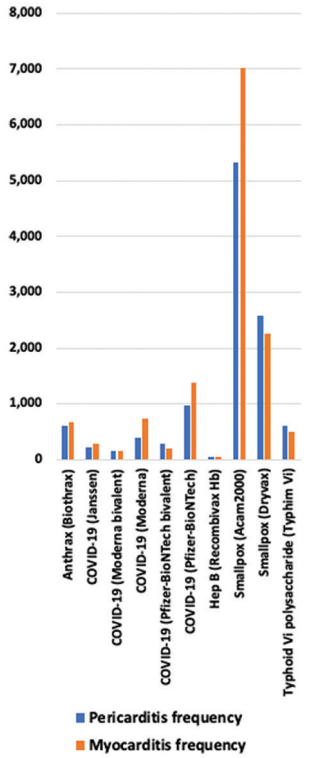

Figure 7. Myocarditis and Pericarditis adverse events normalized frequencies.

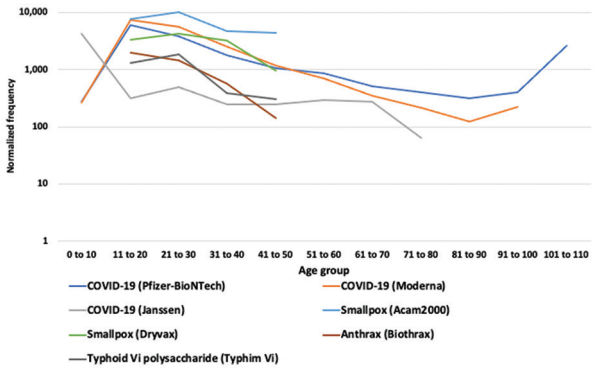

Figure 8. Myocarditis adverse events in males by age group normalized frequencies from the vaccine adverse events reporting system.

occur with a nearly identical pattern of normalized AEs as myocarditis AEs (Figure 7), consistent with a shared etiology for both cardiac AEs. Eleven vaccines with more than 5,000 VAERS reports have myocarditis normalized frequencies of <20/100,000 VAERS reports (DTAP [Daptacel], DTAP + Hep B + IPV [Pediarix], DTAP + IPV + Hib [Pentacel], DTP + Hib [Tetramune], Hep A [Vaqta], Hib [PedvaxHIB], influenza [seasonal] [Fluvirin and Fluzone high-dose], rotavirus [RotaTeq], varicella [Varivax], and zoster live [Zostavax]), indicating that the

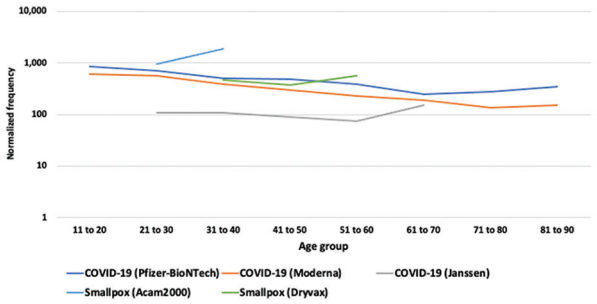

Figure 9. Myocarditis adverse events in females by age group normalized frequencies from the vaccine adverse events reporting system.

background population rate for myocarditis ($B_{myocarditis}$) may be <20/100,000 VAERS reports.

Fifteen vaccines with more than 5,000 VAERS reports have pericarditis normalized frequencies of <20/100,000 VAERS reports (DTAP [Daptacel], DTAP [Infanrix], DTAP [Tripedia], Hep A [Vaqta], Hib [ActHib], Hib [PedvaxHIB], influenza [H1N1 monovalent {Sanofi}], influenza [seasonal] [Fluvirin], measles + mumps + rubella [MMR II], pneumococcal [Prevnar and Prevnar13], poliovirus inactivated [Ipol], poliovirus oral [Orimune], DTAP [Adacel], and varicella [Varivax]), indicating that the background population rate for pericarditis ($B_{pericarditis}$) may be <20/100,000 VAERS reports. For other cardiac AEs, myocarditis normalized frequencies have Pearson correlation coefficients of 0.53 with chest discomfort, 0.80 with chest pain, 0.26 with palpitations, and 0.76 with pericarditis. Likewise, for other cardiac AEs, pericarditis normalized frequencies have Pearson correlation coefficients of 0.22 with arrhythmia, 0.28 with bradycardia, 0.66 with chest discomfort, 0.76 with chest pain, 0.76 with myocarditis, and 0.53 with palpitations.

3.7. Palpitations

Palpitations are characterized by feelings of the heart pounding, racing, or fluttering. The normalized frequencies for palpitation AEs exhibit gender differences across most vaccines (Figure 10). For females, 67 vaccines have palpitations, AEs normalized frequencies of more than 200 per 100,000 VAERS reports, and 57 vaccines have more than 500 per 100,000 VAERS reports (Figure 10). For males, 57 have palpitations, AEs normalized frequencies of more than 200/100,000 VAERS reports, and 35 vaccines have more than 500/100,000 VAERS reports (Figure 10). Palpitation AEFI has been previously reported for COVID-19[7,15] and smallpox[34] vaccines. Seven vaccines with more than 5,000 VAERS reports have normalized frequencies of <20/100,000 VAERS reports (DTAP [Tripedia], DTAP + IPV [Kinrix], Hib [HibTITER], Hib [PedvaxHIB], poliovirus oral [Orimune], and rotavirus [Rotarix and

RotaTeq]). These are primarily children's vaccines and represent a population of a different age than those in Figure 10. For other cardiac AEs, palpitation normalized frequencies have Pearson correlation coefficients of 0.23 with arrhythmia, 0.44 with atrial fibrillation, 0.21 with bradycardia, −0.017 with cardiac arrest, 0.60 with chest discomfort, 0.54 with chest pain, 0.26 myocarditis, 0.53 pericarditis, and 0.34 tachycardia.

3.8. Tachycardia

Tachycardia is characterized by a rapid heartbeat. Normalized frequencies for tachycardia AEs are shown in Figure 11, with 42 higher than 500 AEs per 100,000 vaccine administrations with reported AEs. Sixty vaccines have tachycardia AEs normalized frequencies of more than 200 per 100,000 VAERS reports, and 42 vaccines with more than 500/100,000 VAERS reports (Figure 11). No vaccines with more than 5,000 VAERS reports have normalized frequencies of <20/100,000 VAERS reports. Tachycardia AEFI has been previously reported for COVID-19[15] and smallpox[34] vaccines. For other cardiac AEs, tachycardia-normalized frequencies have Pearson correlation coefficients of 0.20 with bradycardia, 0.33 with cardiac arrest, 0.24 with chest pain, and 0.34 with palpitations.

4. Discussion

Multiple candidate safety signals were detected for the cardiac AEFIs examined, which can be clustered into four groups based on the associated vaccines. First, arrhythmia candidate safety signals were observed for COVID-19 vaccines and the HPV Cervarix vaccine. Second, atrial fibrillation candidate safety signals were observed for COVID-19 vaccines, three influenza vaccines (including two high-dose vaccines), and two RSV vaccines. Third, candidate safety signals were detected affecting infants aged 0 for both bradycardia and cardiac arrest AEFIs for specific vaccines; several vaccines have statistically significant lower normalized frequencies for the same vaccines from alternative sources, suggesting that differences in one or more causative components may be responsible. The dosage levels for these vaccines may need to be adjusted for younger infants based on age and body weight. Fourth, multiple candidate safety signals were observed for overlapping sets of vaccines for chest discomfort, chest pain, myocarditis, palpitations, pericarditis, and tachycardia AEFIs; the etiologies of these AEFIs are likely shared within each group across different vaccines.

Cardiac AEFIs may be triggered or caused by one or more components within vaccine shots, including vaccine components, adjuvants, excipients, or manufacturing contaminant(s). Endotoxins are a possible manufacturing contaminant that could contribute to these associations. Exposure to endotoxins has been shown to cause depression of left ventricular function in humans.[35,36] The toll-like receptor, TLR4, is activated by lipopolysaccharide of Gram-negative bacteria.[37] There, it is plausible that

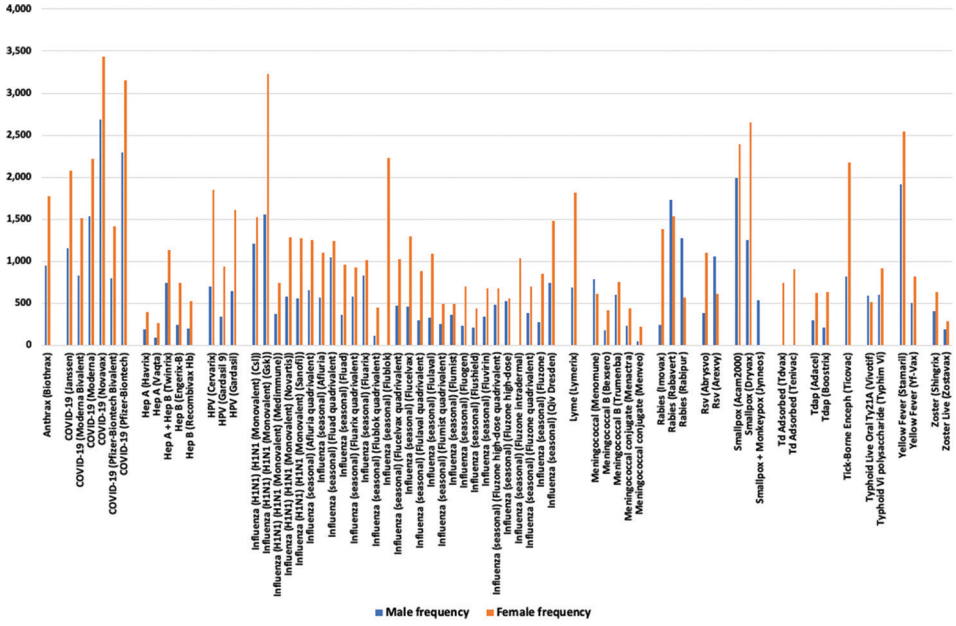

Figure 10. Palpitations adverse events normalized frequencies from the vaccine adverse events reporting system
Abbreviations: Hep: Hepatitis; HPV: Human papillomavirus; RSV: Respiratory syncytial virus; TD: Tetanus-diphtheria; TDAP: Diphtheria, tetanus, and pertussis.

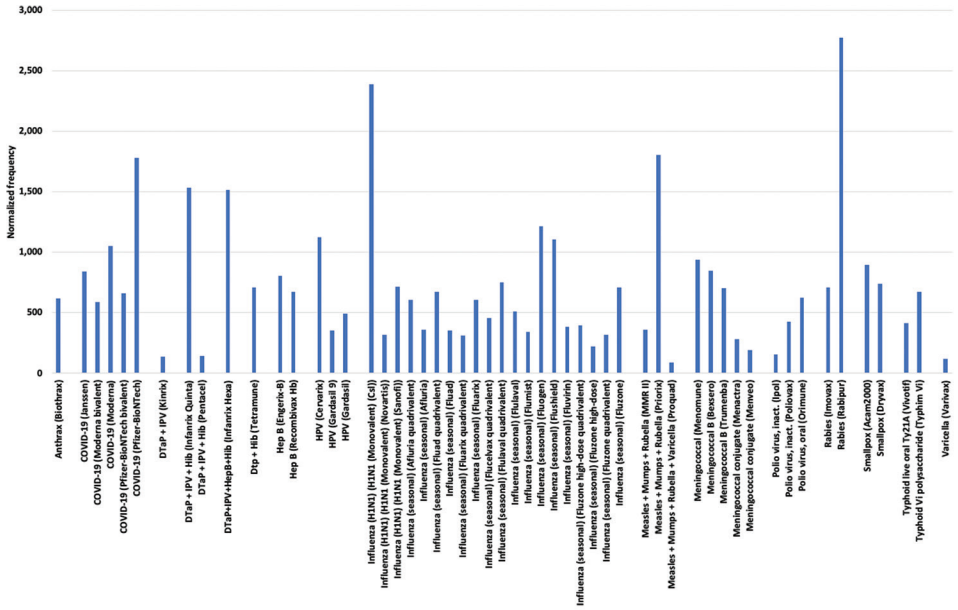

Figure 11. Tachycardia AEs normalized frequencies from the Vaccine Adverse Events Reporting System. Data shown for vaccines with 10 or more adverse events.

Abbreviations: DTAP: Diphtheria, tetanus, and pertussis; Hep: Hepatitis; HIB: *Haemophilus influenzae* type B; HPV: Human papillomavirus; IPV: Inactivated poliovirus.

manufacturing contaminants (e.g., endotoxins) may play a role in the etiology of some cardiac AEFI associations.

4.1. Immune system signaling molecules

Elevated levels of certain molecules are known to be associated with cardiac AEs. These molecules play a role in cardiac AEFIs, although their exact role is not fully elucidated. Cardiac AEs associated with the β-imanazolylethylamine derivative of histamine include altered blood pressure, coronary arterioles constriction, pulmonary arterioles constriction, altered heart rate, and heart failure, varying by dose and animal species.[38] It is well known that elevated histamine levels can induce a variety of cardiac AEs[38] Histamine and other inflammatory molecules are released as part of immune responses to immunization, which are intended to activate both innate and humoral immune responses to stimulate B cells and T cells that can recognize target pathogen proteins. Activated innate immune granulocytes, including mast cells, release histamine and other inflammatory molecules. Activated platelets are an additional source of histamine, serotonin, and other inflammatory molecules. Some individuals have different sensitivity thresholds to elevated histamine levels; histamine intolerance is associated with cardiac arrhythmias[39] and cardiac AEs.[40] Ingestion of alcohol, histamine-rich food, drugs that block diamine oxidase (DAO) (histamine metabolism) or release histamine, or pregnancy can affect an individual's histamine tolerance level.[40] Genetic variations in the DAO enzyme can impact histamine metabolism and tolerance threshold levels. Histamine-induced contraction of cardiac capillary cells has been proposed as an initial step in myocarditis etiology.[41] Elevated serotonin (5-hydroxytryptamine) is associated with some cardiac diseases and coronary artery disease;[42] serotonin affects the vascular wall, promotes smooth muscle cell proliferation, thrombogenesis, and mitogenesis,[42] and causes vasoconstriction.[42,43] The roles of elevated histamine, serotonin, and other inflammatory molecules in cardiac AEFIs can be explored in future studies.

Multiple cardiac AEFIs may result from immune response signaling molecules, including elevated levels of histamine, serotonin, and other inflammatory molecules. Cardiac AEs are associated with elevated histamine levels.[38-40] Elevated histamine and/or serotonin levels may be involved in cardiac capillary vasoconstrictions;[38,42,43] histamine-induced contraction of cardiac capillary cells may be involved in cardiac AEFIs, including myocarditis and pericarditis.[41] For COVID-19 vaccines, the spike protein disrupts cardiac pericytes through CD147 receptor-mediated signaling and another unknown mechanism.[44] The spike protein activates mast cells through TLR4 and angiotensin-converting enzyme 2 receptors.[45] Gender differences in mast cell activation are known,[33] consistent with different patterns of AEFI normalized frequencies for each gender observed in Figures 8 and 9. The first,

second, and fourth groups of clustered cardiac AEFIs may have elevated histamine, serotonin, and/or inflammatory molecule levels in the etiologies of arrhythmia (Figure 1), atrial fibrillation (Figure 2), chest discomfort (Figure 6), chest pain, palpitations (Figure 10), tachycardia (Figure 11), and additional cardiac AEFIs.

Hence, it is hypothesized that some cardiac AEFIs are associated with elevated levels of histamine, serotonin, and other inflammatory molecules released by immune responses to immunization. Therefore, some vaccine recipients may have lower threshold levels associated with these AEFIs, influenced by factors such as consumed foods, alcohol, drugs, and pregnancy.

4.2. Myocarditis and pericarditis AEFIS

Multiple candidate safety signals were observed for myocarditis and pericarditis for the same set of vaccines (Figure 7). The normalized frequencies are higher for males than females (Figures 8 and 9). Gender differences in mast cell activations are well-documented.[33]

It is hypothesized that the initial etiology of cardiac myocarditis and pericarditis AEFIs involves activation of cardiac mast cells followed by cardiac capillary vasoconstrictions from contracted pericyte cells and localized cardiac cell death from anoxia, leading to the release of troponin.

For myocarditis and pericarditis AEFIs, circulating spike proteins from COVID-19 vaccines contribute to the activation of mast cells, contraction of cardiac capillary pericyte cells, and release of inflammatory molecules from endothelial inflammation.[44-46] The proposed model is that the frequencies of myocarditis and pericarditis AEFIs are directly correlated with activation levels of cardiac mast cells/elevated histamine levels inducing contracted cardiac capillary pericyte cells causing vasoconstrictions and localized cardiac myocyte cell death from anoxia. This phenomenon is observed for anthrax, COVID-19, smallpox, tetanus-diphtheria adsorbed, tick-borne encephalitis, typhoid, and yellow fever vaccines (Figure 7).

4.3 Cardiac AEFIS comparisons across vaccines

Five vaccines were frequently observed across the cardiac AEFIs examined (Figures 1, 2, 6, 7, 10, and 11): Anthrax, COVID-19, influenza, smallpox, and typhoid. For the general population, the highest normalized frequencies were observed for specific cardiac AEFIs as follows: (i) arrhythmia was most prominent with the COVID-19 Pfizer-BioNTech vaccine (Figure 1), (ii) atrial fibrillation with the RSV Abrysvo vaccine (Figure 2), (iii) chest discomfort, myocarditis, and pericarditis with the smallpox ACAM2000 vaccine (Figures 6 and 7), (iv) palpitations with the COVID-19 Novavax vaccine (Figure 10), and (v) tachycardia with the rabies Rabipur vaccine (Figure 11). The etiology of these cardiac AEFIs remains unknown. However, the overall patterns are consistent with AEs associated with elevated histamine, possibly serotonin, and other inflammatory molecules. For the COVID-19 vaccines, myocarditis and pericarditis are linked to circulating spike protein, which likely serves as a trigger molecule.[30] Overall, COVID-19 vaccines are associated with all the examined cardiac AEFIs, although other vaccines sometimes exhibit higher normalized frequencies.

4.4. Bradycardia and cardiac arrest in infant vaccine recipients under the age of one

Some infants under 1 year of age appear to be sensitive to one or more components in specific vaccines, which are associated with both bradycardia and cardiac arrest AEFIs (Figures 3-5). By age one, the observed normalized frequencies are consistently much lower, often with statistical significance. For some vaccines, statistically significant differences in normalized frequencies are observed for the same vaccine from different sources for infants aged zero for both bradycardia and cardiac arrest AEFIs. This is likely due to differences in adjuvants or other components. For the specific vaccines with high normalized frequencies, shared vaccine components (such as live attenuated viruses), common adjuvants (e.g., aluminum), common excipients, or possible manufacturing contaminants (e.g., endotoxins) are likely causative. Elevated normalized frequencies were observed for some concomitant vaccine combinations (Figure 4). These combinations may indicate that certain combinations should be avoided, particularly those involving two or more aluminum-adjuvanted or live attenuated virus vaccines alongside other vaccines. The combination of multiple aluminum-adjuvanted vaccines could exceed tolerance threshold levels for some infants. Interestingly, the same pattern of AEs was observed for infants aged zero, where similar vaccines were associated with epilepsy AEs,[47] suggesting a shared neurocardiological etiology for all three of these AEs. Aluminum adjuvants have also been correlated with persistent asthma[48] and autism spectrum disorders.[49] Furthermore, cardiac AEs are associated with endotoxin exposures in humans.[35,36] Therefore, it is crucial to consider the potential for dosage levels being too high for younger infants.

Thus, it is hypothesized that the dose levels for infants with bradycardia and cardiac arrest AEFIs may be too high for their body weight and age, resulting in overstimulated immune responses. Potential causative components include live attenuated viruses, aluminum adjuvants, and several concomitant vaccine combinations.

The body weight of vaccine recipients is a crucial consideration in determining treatment dosages. Evidence of higher AEFI normalized frequencies in infants under the age of one than infants aged one suggests that the dosage of infant vaccines may need to be adjusted (i.e., reduced) for younger, smaller infants. Lyons-Weiler and Ricketson[50] and McFarland *et al*.,[51] advocate for reconsidering the safe dose levels of aluminum in immunotherapy for pediatric patients. The principle of Occam's razor should be applied to the vaccines, concomitant vaccine combinations, and potential causative components, including live attenuated vaccines and aluminum adjuvanted vaccines, particularly when examining vaccine excipients.[50] Adjuvants have been associated with autoimmune and inflammatory syndrome induced by adjuvants.[51] Concomitant administration of multiple aluminum adjuvanted vaccines may exceed the aluminum tolerance threshold for some infants, while other concomitant vaccine combinations may overstimulate immune responses in younger/or smaller infants.

4.5. Study limitations

Only a small subset of vaccine recipients' AEs is reported in the VAERS database. Reporting biases and exclusion of AEs would perturb calculated AEs normalized frequencies. To estimate population-based AEFI frequencies more accurately, increasing the population size to include asymptomatic vaccine recipients is essential.

4.6. Study recommendations

The results from this study suggest several avenues for future research. First, safety signals identified for vaccines with elevated AEFI normalized frequencies warrant further investigation in ongoing or future clinical studies. Second, infants aged zero have higher normalized bradycardia and cardiac arrest AEFIs than infants aged one for several vaccines and concomitant combinations (Figures 3-5). To mitigate these AEFIs, potential strategies include: (i) adjusting vaccine dosage to infant body weight and age, (ii) delaying immunization of some of these vaccines for infants aged under one until older, (iii) selecting alternative vaccines that have lower AEFIs frequencies, or (iv) avoiding concomitant vaccine combinations associated with increased risk levels (e.g., live attenuated viruses combined with aluminum adjuvant vaccines). Third, safer alternatives should be developed where live attenuated vaccines are unavailable. Fourth, the potential role of antihistamines as possible adjunctive therapies for myocarditis and pericarditis AEFIs should be evaluated. Lastly, developing COVID-19 alternative vaccines (e.g., T-cell vaccines targeting other SARS-CoV-2 proteins) that do not include the spike protein could reduce the risk of cardiac AEFIs.[52] Understanding the underlying etiology of these cardiac AEFIs is essential in developing strategies to minimize their occurrences.

5. Conclusion

Infant bradycardia and cardiac arrest AEFIs can be minimized by adjusting vaccine dosage levels based on body weight and age, delaying specific vaccines until infants are 1 year old, selecting alternative vaccine options with observed lower AEFI frequencies, avoiding concomitant vaccine combinations with higher combination risk levels, administrating live attenuated virus vaccines individually, or reducing or eliminating causative components (e.g., aluminum adjuvant). Myocarditis AEs in males and females can be modeled using mathematical log scale age relationships for COVID-19 vaccines. This may also apply to other vaccines, suggesting possible shared etiologies involving cardiac mast and pericyte cells. Several vaccines were found to have correlated cardiac AEFI association signals for chest discomfort, chest pain, palpitations, and tachycardia, with elevated histamine levels potentially contributing to the etiologies of these AEFIs. Alternatives to COVID-19 spike protein vaccines are recommended to mitigate the risks of myocarditis and pericarditis associated with current SARS-CoV-2 vaccines.

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Conflict of interest

The author declares no conflicts of interest.

Author contributions

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Data used in this work is available from the corresponding author upon reasonable request.

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ACCSCIENCE PUBLISHING

Brain & Heart

ORIGINAL RESEARCH ARTICLE

Factor analysis of electrocardiographic findings, anthropometric measures, and age in patients with chronic kidney disease

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Abstract

Chronic kidney disease (CKD) is a significant global health concern, frequently associated with cardiovascular complications resulting from autonomic nervous system dysfunction, which can be detected using electrocardiography (ECG). This study employed factor analysis to investigate the association between anthropometric measures, age, and ECG findings in patients with CKD. We conducted a cross-sectional study to evaluate the ECG findings of 25 male participants (aged 36 – 80 years) with stage 5 CKD who were randomly selected from the Nephrology Unit of a hospital in the Amazon region. All participants underwent anthropometric and blood pressure assessment before the ECG recording at a sampling rate of 1,000 Hz. Then, the participants were positioned supine and asked to breathe normally for 3 min. To analyze the ECG data, a bootstrap method was used to estimate statistical parameters from 1,000 resampled datasets. A two-step process involving principal component (PC) extraction and varimax rotation was used for factor analysis. The covariance matrix of the normalized data underwent eigenvalue decomposition. The first three PCs captured 68.7% of the total variability observed in the original dataset. The PR interval (iPR), RR interval (iRR), and corrected QT (QTc) interval contributed 0.843, 0.836, and –0.822, respectively, to PC1; body mass index (BMI) and abdominal circumference (AC) contributed 0.910 and 0.947, respectively, to PC2; and age had the largest contribution of 0.938 to PC3. In conclusion, BMI, AC, and age can be simple and reliable clinical tools for detecting underlying CKD in primary care. ECG changes in iPR, iRR, and QTc are common in patients with CKD, thus highlighting the potential role of machine learning in the early detection of cardiovascular disease.

Keywords: Chronic kidney disease; Electrocardiogram; Anthropometric measures; Factor analysis; Aging

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1. Introduction

Infectious diseases can cause a wide range of renal complications, manifesting as various clinical syndromes that may contribute to the development of hydroelectrolyte,

hormonal, and metabolic disorders.[1] These conditions can lead to a decline in kidney function characterized by a glomerular filtration rate (GFR) of <60 mL/min/1.73 m^2 of body surface area for more than 3 months.[2]

Individuals with chronic kidney disease (CKD) are at increased risk of developing cardiovascular complications. The increased sympathetic activity in these patients is thought to be due to underlying conditions such as hypertension, left ventricular hypertrophy, atherosclerosis, inflammation, and coronary artery disease.[3,4] While obesity is associated with increased mortality in the general population, this association appears to be reversed in individuals with CKD.[5]

Electrocardiography (ECG) is a widely accepted diagnostic tool used in renal therapy to record electrical activity in the heart. Its importance lies in its ability to detect cardiac pathologies and morphological abnormalities.[6,7] Patients with CKD often present with prolonged corrected QT (QTc) intervals and shortened RR intervals (iRR), both of which are prevalent in patients undergoing hemodialysis.[8] These ECG abnormalities are associated with left ventricular hypertrophy,[9] electrolyte imbalance-induced hypertension,[10] coronary artery disease, and heart failure.[11] The combination of these factors may ultimately increase the risk of sudden cardiac death in individuals with CKD.[12]

The sympathetic and parasympathetic divisions of the autonomic nervous system (ANS) are key regulators of heart rate, and their contrasting effects on cardiac function are reflected in heart rate variability analysis,[13] particularly in patients with CKD.[4] Thus, more and more focus is being directed toward the functionality of the neurocardiac axis and the crosstalk between brain and cardiac function.[14] During hemodialysis, acute shifts in serum electrolyte levels and significant fluid removal can lead to arrhythmias, characterized by reduced heart rate variability.[4]

Body mass index (BMI) exhibits a U-shaped relationship with clinical outcomes in patients with CKD. Overweight and mild obesity are associated with worse outcomes regardless of CKD severity.[5] Abdominal circumference (AC)[15] and age[16] have emerged as potentially valuable, simple, and reliable clinical indicators for detecting underlying CKD in primary care settings. These factors are particularly relevant given the increasing prevalence of chronic conditions such as hypertension, a well-established risk factor for CKD.[11]

Artificial intelligence in health is used to process the data through unsupervised learning algorithms that tend to improve through self-learning by machine learning,[17] suggesting increasingly accurate diagnostic hypotheses and the capability to find solutions to medical problems[18] and sports medicine.[19] A statistical technique known as factor analysis is used to reduce the dimensionality of a dataset by identifying a smaller number of underlying factors or components that are linearly related to the original variables. This method of data reduction will group the variables with the strongest correlations by rotating the factors.[20]

The study is relevant because it uses electrocardiogram data, a fundamental tool in biomedical engineering. The factor analysis aims to model the relationship between different physiological variables and CKD and to contribute to the development of tools and technologies for the early detection and treatment of kidney disease. The present study aims to describe the complex interactions of determinants that may predispose individuals with CKD to increased cardiovascular morbidity. By examining the relationships between anthropometric measures, age, and ECG findings using factor analysis, we hope to identify underlying factors that may influence cardiovascular risk in patients with CKD.

2. Materials and methods

2.1. Subjects

The study population consisted of 25 male subjects, aged between 36 and 80 years, with stage 5 CKD and an estimated GFR of <60 mL/min/1.73 m^2. These participants were randomly selected from the Nephrology Unit of the Macapá Hospital of Clinics. The participant selection process is detailed in Figure 1.

The study methodology was based on a previous study conducted by Nascimento *et al.*[21] The Human Research Ethics Committee of the Federal University approved the study protocol (CAAE: 16335119.8.0000.0003, no 3.560.083), and all participants gave written informed consent. This study followed the ethical guidelines of the Declaration of Helsinki (2008) and Resolution 510/2016 of the National Health Council.

Written informed consent was obtained from all participants. Exclusion criteria included a history of acute cardiovascular events within the previous 3 months, significant arrhythmias, implanted pacemakers or defibrillators, severe cognitive impairment that would prevent compliance with study instructions, and active infections. At the time of enrolment, medication lists were reviewed and patients taking medications known to significantly affect heart rate, such as calcium channel blockers and β-blockers, were included.

2.2. Anthropometric measurements

Potential participants were thoroughly oriented before commencing the study. They were provided with detailed

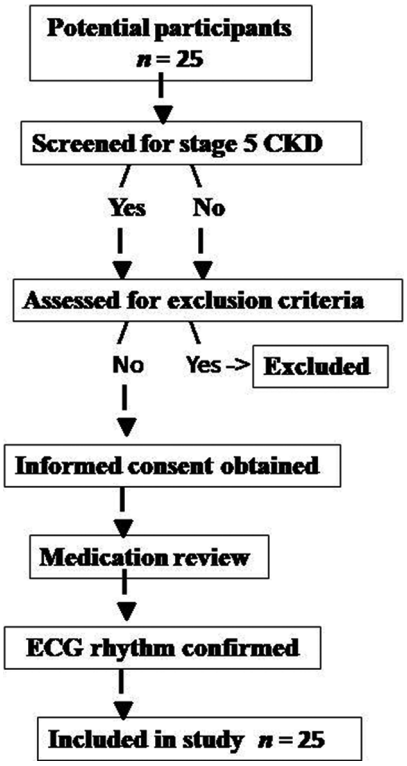

Figure 1. Patient eligibility
Abbreviations: CKD: Chronic kidney disease; ECG: Electrocardiogram.

explanations of the test procedures and the expected time commitment. To prepare themselves for the measurements, the participants were required to remove their shoes, wear light clothing, and ensure that they had no extraneous items. Height and weight were subsequently recorded in centimeters (cm) and kilograms (kg), respectively, using certified and calibrated mechanical scales (Filizola, Brazil). BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2). The AC was measured at the narrowest part of the torso between the ribcage and the iliac crest. A flexible tape measure (Cescorf, Brazil), with a measurement accuracy of 0.1 cm, was placed horizontally around the abdomen, ensuring a snug fit without compression, and the measurement was taken after a gentle exhalation. The consistency and reliability of the data were ensured by having all anthropometric measurements taken by the same experienced evaluator throughout the study.

2.3. Blood pressure assessment

The volunteer's blood pressure was measured on the left arm after 5 min of rest while sitting and in a quiet environment. A BP7100 digital device (Omron, Brazil) was used to record systolic and diastolic blood pressure. Hypertension was defined as a sustained blood pressure reading of 140 mm, of mercury (mmHg) or higher for systolic pressure and/or 90 mmHg or higher for diastolic pressure. If the two initial readings differed by more than 5 mmHg, a third measurement was taken to determine the final blood pressure value.[22]

2.4. Electrocardiogram acquisition

ECG was recorded during the 1st h of each participant's blood pressure assessment session. Participants were positioned supine for 3 min while breathing normally. The ECG data were acquired using a three-channel ECAFIX electrocardiograph (model 12S PC, Transforming state-of-the-art technology, Brazil) with 12 leads, 1,200 Hz sampling frequency, selectable filters in 60 Hz and 0.15 – 35 Hz, baseline variation and muscle tremor, 10 mm/mV gain, and 25 mm/s velocity.

2.5. Electrocardiogram analysis

ECG recordings were reviewed according to the guidelines of the Brazilian Society of Cardiology for the interpretation of resting electrocardiograms.[23] All participants were confirmed to be in sinus rhythm at the time of ECG recording by a qualified cardiologist, who also interpreted the ECG results for this study. No problems were found in the ECG measurement of the participants during the study.

The ECG findings were evaluated based on a set of parameters, including the PR interval (iPR), which was determined from the start of the P wave to the beginning of the QRS complex; the PR segment, which was measured from the end of the P wave to the beginning of the QRS complex; the QRS interval, which was measured from the start of the Q or R wave to the end of the S wave; the ST segment, which was measured from the end of the QRS complex to the beginning of the T wave; the iRR, which was measured as the time between two successive R waves; and the QTc, which was measured from the start of the Q wave to the end of the T wave. The QTc was calculated using the Bazett equation ($QTc = QT/\sqrt{RR}$).[24]

2.6. Data analysis

In this study, factor analysis was employed as a statistical technique to reduce the complexity of the data. This technique transforms a set of interrelated variables into a smaller number of independents, underlying factors, or components. These factors capture the shared variability present in the original variables. The process involves decomposing the covariance or correlation matrix, yielding eigenvalues and eigenvectors that represent the latent factors.[25] The eigenvalues indicate the amount of variance explained by each factor, while the eigenvectors, through their factor loadings, reveal the associations between the original variables and the derived factors. Factor loadings quantify the strength of these associations. To improve

interpretability, factor rotation is frequently used, aiming for a simplified structure in which each factor primarily influences a limited number of observed variables.[26] The eigenvectors associated with the chosen eigenvalues define the retained latent factors.

2.7. Statistical analysis

The data were summarized using descriptive statistics, with results presented as mean ± standard deviation or standard error. The Shapiro–Wilk test was employed to evaluate if the anthropometric data conformed to a normal distribution. To apply factor analysis, the data on anthropometric indicators, age, and ECG findings were normalized using log transformation. This ensured that all variables were on the same scale, equalizing their importance in the analysis. The bootstrap method was used to assess the statistical properties of the ECG results. This resampling technique generated 1,000 simulated datasets from the original data, allowing bias to be estimated and confidence intervals to be calculated.[27]

To evaluate the suitability of the data for factor analysis, Bartlett's test of sphericity was conducted. Factor analysis was then performed using the eigenvalue decomposition of the covariance matrix of the normalized data.[25] Principal component (PC) analysis was employed for component extraction,[28] followed by varimax rotation.[26] The PCs were ranked based on their eigenvalues, with the highest eigenvalue corresponding to the first component, the second highest to the second, and so forth. The selection of relevant PCs for further analysis was determined using the Broken-Stick test, in combination with scree plot visualization and eigenvalues exceeding 1.[29] All analyses were carried out using Matlab 2020b (Mathworks, USA) with a significance threshold of $\alpha = 0.05$.

3. Results

The anthropometric indicators, age, and blood pressure assessments of the participants are summarized in Table 1. The low variability, as indicated by standard deviations, suggests a homogeneous sample. The *p*-value for each variable shows that the data followed a normal distribution. In the CKD cohort, it was observed that 68% of the individuals have hypertension.

The statistical properties of the ECG results were assessed using the bootstrap method, in which 1,000 resampled data sets were generated. This approach produced estimates with minimal bias and confidence intervals encompassed by the sample mean of the group, as shown in Table 2.

Bartlett's test of sphericity demonstrated that the data are appropriate for factor analysis ($p<0.001$). The

Table 1. Anthropometric, demographic, and blood pressure characteristics of study participants

Variables	Mean±SD	CI	*p*
Age (years)	55.0±12.4	49.8 – 60.1	0.22
Height (cm)	166.1±7.1	163.1 – 169.1	0.20
Body mass (kg)	76.6±13.6	70.9 – 82.3	0.91
BMI (kg/m^2)	27.5±3.4	26.1 – 28.9	0.33
Waist circumference (cm)	100.5±12.0	95.1 – 107.3	0.12
Systolic blood pressure (mmHg)	151.5±27.6	140.1 – 162.9	0.15
Diastolic blood pressure (mmHg)	96.4±16.4	89.6 – 103.1	0.06

Note: Data are presented as mean±standard deviation with 95% confidence interval and Shapiro-Wilk.
Abbreviation: BMI: Body mass index.

Table 2. The electrocardiography parameters of the study participants analyzed using a bootstrap method

Variables	Mean±SE	Bootstrapping bias	CI
PR interval (ms)	163.2±6.0	0.200	150.4 – 176.1
PR segment (ms)	76.2±3.5	0.120	68.4 – 83.2
QRS interval (ms)	107.2±4.4	−0.004	99.2 – 115.2
ST segment (ms)	204.0±14.7	−0.006	176.0 – 232.0
RR interval (ms)	766.4±24.9	0.620	716.8 – 814.4
Corrected QT interval (ms)	469.0±7.0	−0.080	456.1 – 484.0

Note: Data are presented as mean±standard error with 95% confidence interval.

Broken-Stick test indicated that three PCs are the most representative of the eigenvalues, based on the inflection point illustrated in Figure 2A. Moreover, the eigenvalues exceeded 1, explaining 68.7% of the total variability present in the original dataset (Figure 2B).

The rotated factor loadings for the three PCs derived from the original variables are shown in Table 3. The results show that PC1 is predominantly influenced by iPR (0.843), iRR (0.836), and QTc (−0.822); PC2 by AC (0.947) and BMI (0.910); and PC3 by age (0.938).

4. Discussion

In this study, factor analysis was used to uncover the underlying relationships and patterns between anthropometric data, age, and ECG findings in a cohort of patients with CKD. The findings show that iPR, iRR, and QTc are associated with PC1, suggesting a common underlying influence of these ECG parameters in the CKD population. This finding is consistent with previous studies reporting prolonged QTc intervals and altered heart rate variability in CKD patients.[6,8] The association of AC and

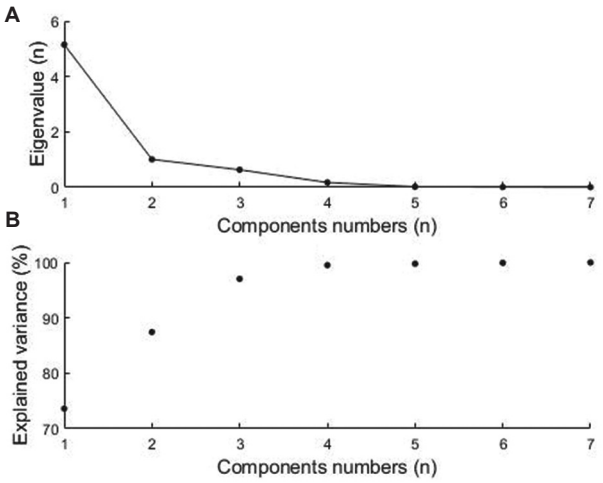

Figure 2. Scree plots of the principal components were evaluated based on (A) their corresponding eigenvalues and (B) the explained variance of the eigenvalues.

Table 3. The weighting coefficients of the original variables

Variables	PC1	PC2	PC3
Age	−0.036	−0.044	0.938
BMI	−0.002	0.910	−0.156
Waist circumference	−0.072	0.947	−0.052
PR interval	0.843	−0.034	−0.234
PR segment	0.496	−0.025	0.008
QRS interval	0.014	−0.536	−0.332
RR interval	0.836	−0.202	−0.035
Corrected QT interval	−0.822	−0.154	−0.066

Abbreviations: BMI: Body mass index; PC: Principal component.

BMI with PC2 suggests that abdominal obesity is likely related to a different aspect of CKD status than ECG factors. This is supported by previous studies suggesting that obesity, particularly abdominal obesity, is associated with adverse outcomes in CKD.[5,15] Age has the greatest effect on PC3, suggesting a unique influence of aging on certain aspects of the disease compared to the other variables. This is consistent with the increase in the prevalence of CKD with age.[16]

Hypertension, a major global health problem affecting more than 1.4 billion people, is a leading cause of morbidity and mortality.[30] The high prevalence of hypertension (68%) in our CKD cohort is consistent with previous studies[31] and highlights a strong association between these conditions. The observed mean systolic and diastolic blood pressure values of 151.5 ± 27.6 mmHg and 96.4 ± 16.4 mmHg, respectively, further underscore the severity of hypertension in this population. Our findings are consistent with the well-documented association between CKD and increased cardiovascular risk, with hypertension as the major contributing factor. Hypertension is known to cause specific electrocardiographic abnormalities, including increased P-wave dispersion, prolonged time from QRS onset to R-wave peak, and dispersion of the QTc interval. These changes are clinically important because they may precede the onset of left ventricular hypertrophy, a condition that can be detected by a standard 12-lead ECG.[32]

To estimate the statistical properties of the ECG parameters, we employed a bootstrap method, generating 1,000 resampled datasets from the CKD patient cohort. This approach generated robust estimates with low bias and confidence intervals that are statistically well-defined. The ECG is an important diagnostic and prognostic tool for patients with renal failure.[33] The ECG findings in patients with CKD may indicate subclinical myocardial disease,[34] sinus tachycardia,[35] left ventricular ejection fraction,[36] ischemic stroke,[37] electrolyte disturbances,[38] and profound cardiac fibrosis on histology.[39] The specific ECG changes observed in our study, such as the contribution of iPR, iRR, and QTc to PC1, suggest autonomic dysfunction and an increased risk of arrhythmias in CKD patients.

Prolonged QTc interval (36.6%), fragmented QRS complex (29.8%), Q waves (27.2%), poor R wave progression (24.6%), peaked T wave (22.0%), left ventricular hypertrophy (16.7%),[7] ST-segment elevation or depression (23.4%), prolonged QRS duration (19.2%), tachycardia (17.6%), and left and right atrial enlargement (17.6%)[8] are the most common abnormalities observed in the ECG findings of the CKD patients, suggesting an advanced stage of CKD requiring renal replacement therapy.[38] The findings of the present study are corroborated by prior investigations as iPR (0.843), iRR (0.836), and QTc (−0.822) are significantly associated with PC1, which is referred to as the ECG findings component.

A negative weighting coefficient of −0.822 suggests an inverse relationship between ANS activity and QTc interval, indicating that as ANS activity increases, the QTc interval tends to decrease, possibly reflecting an imbalance in the ANS that affects ventricular repolarization.[39] The prevalence of prolonged QTc intervals (exceeding 500 ms) in this study was 10.0%, as illustrated in Figure 3. A similar prevalence of 13.6% for left bundle branch block in hemodialysis patients was reported in a previous study.[40]

The observed electrocardiographic changes, particularly the prolonged QTc interval and altered heart rate variability,[4] are likely due to the complex interplay of renal dysfunction, electrolyte imbalance, and autonomic dysregulation and may contribute to an increased risk of sudden cardiac death.[6] CKD is associated with the

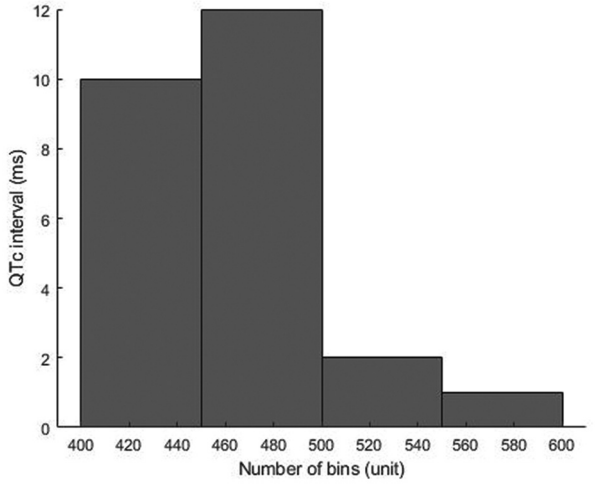

Figure 3. Histogram of QTc interval of ECG findings in study participants
Abbreviations: ECG: Electrocardiogram; QTc: Corrected QT.

accumulation of uremic toxins, which can impair cardiac function and contribute to the pathogenesis of left ventricular hypertrophy and fibrosis.[11] ECG abnormalities, whether minor or major, are associated with an increased risk of fatal cardiovascular disease, with the highest risks observed in patients with major abnormalities and lower GFR levels.[41] Specific ECG changes, such as pathological QTc interval and non-specific ST/T changes, are independently associated with all-cause mortality and major adverse cardiovascular events in hospitalized CKD patients.[42]

In a study conducted by Ajam *et al.*,[40] they discovered a higher prevalence of QTc prolongation in hospitalized CKD patients. This prevalence increases with worsening renal function and is associated with factors such as advanced age, impaired renal function, hemodialysis, serum potassium levels, and reduced left ventricular ejection fraction.

Effective obesity prevention and management are critical to reducing both the incidence and progression of CKD.[43] A previous study[5] has shown that overweight and mild obesity, as measured by BMI, are associated with worse outcomes in CKD patients, regardless of the severity of their kidney disease. In addition, measurements of abdominal adiposity, such as AC, have been consistently associated with increased morbidity and mortality in individuals undergoing maintenance hemodialysis.[15]

Our study supports the importance of assessing both BMI and AC for a comprehensive assessment of the nutritional and metabolic status of CKD patients and to identify those at increased risk of adverse outcomes.[5,15] Specifically, we found that BMI (0.910) and AC (0.947) have high weighting coefficients in PC2, which we identified as the anthropometric measures component.

The incidence and prevalence of CKD are known to increase with age,[21] a phenomenon likely driven by the natural aging of the kidneys and the higher prevalence of chronic health conditions such as hypertension, a well-established risk factor for kidney disease.[11] This is in agreement with the findings of this study, where age (0.938) was found to have the greatest contribution to PC3. The mean age of CKD patients in the study ranged from 39 to 61 years, highlighting the significant prevalence of cardiovascular risk factors in older populations.[44]

Machine learning is increasingly recognized as a valuable asset for diagnosis, treatment, and management within the biomedical field.[45-47] However, previous studies[7,8,33-38] did not employ factor analysis to characterize the anthropometric measures, age, and ECG findings associated with patients with CKD and hypertension, particularly with respect to high factor loadings in the first three PCs after varimax rotation.

To increase the applicability of these findings, future studies should seek to address the limitations of the current research by including a more heterogeneous group of participants that represent a range of ages and constitute both genders. Furthermore, studies should evaluate the effects of different renal replacement therapies on cardiovascular health and identify the prevalence of inflammatory phenotypes, with particular attention to the role of monocytes in promoting chronic inflammation in CKD patients, providing a clear relationship between inflammatory markers and specific electrocardiographic patterns.

5. Conclusion

This study suggests that factor analysis is a useful tool for understanding the complex interplay between ECG parameters, anthropometric measures, and age in patients with CKD. The identification of BMI, AC, and age as key factors in CKD, as evidenced by their contribution to PC2 and PC3, suggests that these readily available clinical measures can be used for risk stratification in primary care settings. Furthermore, the association between ECG changes and PC1 highlights the importance of routine ECG screening in CKD patients to identify those at higher risk of cardiovascular complications. These findings suggest that routine screening for ECG abnormalities in CKD patients may facilitate early identification of high-risk individuals, allowing for targeted cardiovascular risk management. However, while ECG findings are critical for assessing cardiovascular risk, other factors such as renal function and comorbidities also play a significant role in patient

outcomes, highlighting the need for a multifaceted approach to the management of CKD patients. The utilization of machine learning for the analysis of these ECG patterns has the potential to facilitate earlier detection and intervention, thereby potentially improving patient outcomes.

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Conflict of interest

The authors declare that they have no conflicts of interest.

Author contributions

Conceptualization: Wollner Materko
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Investigation: All authors
Methodology: All authors
Writing – original draft: Wollner Materko
Writing – review & editing: Derlane Gaia Barroso Nascimento, Alexandre Sousa da Silva

Ethics approval and consent to participate

The Human Research Ethics Committee of the Federal University approved the study protocol (CAAE: 16335119.8.0000.0003, nº 3.560.083), and the study followed the ethical guidelines of the Declaration of Helsinki (2008) and Resolution 510/2016 of the National Health Council. All subjects gave verbal informed consent for their ECG recordings and anthropometric measurements to be taken.

Consent for publication

All subjects had given verbal informed consent for the possible use of their anonymized data for scientific and publication purposes.

Availability of data

The original clinical data are not publicly available due to ongoing data protection standards.

Further disclosure

Part of the work was presented at the Amapá National Science and Technology Week on Artificial Intelligence, Brazil, 2020.

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ORIGINAL RESEARCH ARTICLE

Heart rate variability in the medium term following COVID-19: A case–control study

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Abstract

Acute coronavirus disease-19 (COVID-19) infection is known to be associated with adverse cardiovascular complications. However, data on its longer-term cardiovascular effects remain limited. This case–control study aims to investigate potential medium-term cardiovascular sequelae of COVID-19. A random selection of patients who tested positive for COVID-19 through nasopharyngeal swabbing constituted the case group, while the control group comprised individuals who tested negative for both swab and COVID-19 immunoglobulin G antibodies. A total of 233 subjects were recruited, including 161 cases and 72 controls. The median age was 45 years (interquartile range [IQR]: 35 – 57 years). The median follow-up duration was 173.5 (IQR: 129.0 – 193.3) days. There were no significant differences between cases and controls with respect to age, sex, cardiovascular risk factors, and comorbidities. The levels of N-terminal pro-B natriuretic peptide and troponin I at follow-up did not differ significantly between the two groups. However, the root mean square of successive differences (RMSSD) of R-R intervals was significantly lower in some cases. Neither of the groups had significant arrhythmias. There were no significant differences between the two groups in both awake and asleep blood pressure levels as well as in dipping blood pressure status. In conclusion, COVID-19 infection was associated with reduced heart rate variability (HRV) as manifested by low RMSSD. Given the established link between reduced HRV and increased risks of mortality and sudden cardiac death, these findings warrant further investigation into the long-term cardiovascular impact of COVID-19.

Keywords: Heart rate variability; Coronavirus disease-19; Long-term cardiovascular complications

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1. Introduction

The acute effects of coronavirus disease-19 (COVID-19) infection on the cardiovascular system are well-documented, but its medium-term implications are of growing concern.[1] Several mechanisms have been proposed to mediate cardiovascular dysfunctions, including persistent inflammation, endothelial dysfunction, metabolic derangements, thrombophilia, microclot formation, hematological abnormalities, alterations in the microbiome, and myocardial injury. An additional potential mechanism is reduced heart rate variability (HRV).

Emerging evidence suggests that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) can infect the vagus nerve,[2] in turn lead to reduce HRV. Low HRV is associated with increased cardiovascular risk and all-cause mortality in the general population[3,4] as well as in patients with heart failure.[5,6] A meta-analysis of eight studies with a total number of 21,988 participants found that low HRV was associated with a 1.35-fold increased risk of cardiovascular events among subjects without preexisting cardiovascular disease.[7]

Evidence also points to persistent autonomic dysfunction after COVID-19. For example, postural orthostatic hypotension has been reported at approximately 1 month,[8] and similar findings were observed at 3-month post-infection in Swedish patients.[9] A small study by Salem *et al.*[10] comprising 59 participants reported reduced heart rate response to head-up tilt tests and increased incidence of orthostatic hypotension in subjects 3 – 8-month post-COVID-19 infection, although no significant differences in HRV parameters were noted. In addition to postural orthostatic tachycardia syndrome, severely affected patients with long COVID symptoms also exhibit inappropriate sinus tachycardia.[11,12] Furthermore, subjects with post-acute sequelae of COVID-19 were shown to have initial orthostatic hypotension hemodynamic criterion characterized by a transient systolic blood pressure drop >40 mmHg within the first 15 s of standing, regardless of hospitalization status.[13] Global dysautonomia, as assessed using the composite autonomic symptom 31 total score, has also been reported to be elevated at 6 and 12 months following COVID-19 hospitalization.[14] Notably, autonomic dysfunction was observed in 66% of patients with long COVID symptoms and was found to be independent of hospitalization status, suggesting that the risk of autonomic dysfunction does not depend on the severity of the acute illness.[15]

Reduced HRV is an important manifestation of autonomic dysfunction.[16] Commonly used parameters of HRV include the standard deviation of N–N intervals (SDNN), and root means square of successive difference (RMSSD). The SDNN is an indicator of overall HRV, while the RMSSD is an indicator of short-term components of HRV.[17] The RMSSD is calculated as the square root of the mean of the squares of each N–N interval. It is considered a reliable marker of cardiac parasympathetic activity. Other relevant parameters include the standard deviation of all normal to normal R–R (NN) intervals (SDNN) and the standard deviation of the averages of R–R intervals over 5-min segments (SDANN), an indicator of long-term components of HRV.[17] A smaller study of 100 subjects previously reported reductions in these parameters after a medium-term follow-up of 20 weeks; however, no information was provided with regard to any medications taken by the study population that could affect the results.[18]

The aim of the present study was to compare HRV parameters, such as RMSSD, SDNN, SDANN, and the mean of the standard deviations of all NN intervals for all 5-min segments in 24 h (ASDNN), using 24-h Holter monitoring in post-COVID-19 patients versus controls at a medium-term follow-up of 24 weeks.

2. Methods

2.1. Patient recruitment

A case-control study was conducted. The study population consisted of subjects who had undergone nasopharyngeal swabbing for COVID-19 between September 2020 and March 2021. Participants were selected from a local laboratory database where all nasopharyngeal swabs were processed. This was done purposely so that the study population represents the normal population rather than individuals at high risk of post-COVID-19 complications, such as those who had been hospitalized during the acute infection or diagnosed with long COVID symptoms. Cases were defined as subjects with confirmed COVID-19 infection based on nasopharyngeal swab results. Controls were age- and gender-matched subjects tested negative for COVID-19 through nasopharyngeal swabbing from the same period. Furthermore, controls were required to test negative for COVID-19 immunoglobulin G antibodies at the time of recruitment to rule out prior SARS-CoV-2 infection. Exclusion criteria included individuals with dementia or mental illnesses resulting in the inability to provide informed consent, non-Caucasian subjects, and individuals younger than 18 or older than 75 years of age. A letter of information was sent to all eligible candidates. Subjects who were willing to participate received a telephone call within a few days to receive further explanation of the study protocol and were invited for assessment at the local hospital.

All cases and controls completed a standardized questionnaire covering medical history and comorbidities. The weight, height, and waist index were recorded for all participants.

2.2. Interventions

All participants underwent baseline blood investigations, including full blood count, renal and liver profiles, cholesterol levels, glycated hemoglobin (HbA1c) levels, troponin I levels, and N-terminal pro-B natriuretic peptide (NT-proBNP) levels. Twenty-four-hour ambulatory blood pressure monitoring (ABPM) was conducted using the Oscar 2 ABPM device (Suntech, USA) to determine

systolic and diastolic blood pressure during 24-h, asleep, and awake periods.

In addition, 24-h Holter monitoring (DigiTrak XT recorder, Philips Healthcare, USA) was performed to determine the minimum, maximum, and average heart rates, detect significant arrhythmias, and evaluate time-domain parameters of HRV, including SDNN, RMSSD, ASDNN, and SDANN. After computerized primary analysis, all recordings were manually reviewed and edited to eliminate ectopic beats and artifacts meticulously. Only recordings containing <5% artifacts and ectopics were included for analysis. HRV parameters were derived from the same time series free from artifacts. Only recordings with a duration exceeding 22 h were included in the analysis.

2.3. Statistical methods

The normality of distribution was assessed using the Kolmogorov–Smirnov test. Independent samples *t*-test was used to evaluate differences between cases and controls for normally distributed data while the Mann–Whitney U test was applied for non-normally distributed data. Variables that were statistically significant or approached significance in univariate analysis ($p<0.1$) were selected for multivariate analyses. The sample size was calculated to achieve 80% power to detect a moderate effect size ($d = 0.5$) at $\alpha = 0.05$. Statistical analysis was performed using SPSS version 23.0 (IBM, USA).

3. Results

A total of 233 subjects were recruited, comprising 161 cases and 72 controls. The median age of the study cohort was 45 years (interquartile range [IQR]: 35 – 57). Subjects were followed up for a median duration of 173.5 days (IQR: 129.0 – 193.3). Cases and controls did not differ significantly in age, sex, and anthropometric parameters, including body mass index and waist index (Table 1). There were also no differences in comorbidities and cardiovascular risk factors, such as diabetes, hypertension, hyperlipidemia, ischemic heart disease, heart failure, atrial fibrillation, cerebrovascular disease, chronic kidney disease, and obesity (Table 1). Given the relatively young age of the study population, the incidence of cardiovascular comorbidities was low. The participants represented a generally healthy population with minimal complications of the acute infection, as evidenced by the fact that only 13 participants (0.8%) required hospitalization. Importantly, there were no significant differences between cases and controls in terms of treatment taken, including β-blockers, which could affect the HRV parameters.

At the 24-week follow-up, blood investigations revealed no significant differences between cases and controls in troponin I and NT-proBNP levels (Table 2). Similarly, there were no significant differences in hematological parameters (hemoglobin level, red cell distribution width, white cell count, platelet count, and mean cell volume), HbA1c, estimated glomerular filtration rate, liver transaminases, and lipid levels. No significant differences were noted in all ABPM parameters assessed. Likewise, no significant arrhythmias were detected in either group during 24-h electrocardiogram monitoring (Table 3). There were also no significant differences in mean, minimum, and maximum heart rates. However, analysis of HRV revealed that subjects with prior COVID-19 infection exhibited lower RMSSD compared to controls ($p=0.03$) (Table 3).

Table 1. Baseline characteristics of the study population

Patient characteristics	Cases (n=161) (%)	Controls (n=72)	p-value
Age (years)[a]	45 (35.00 – 57.00)	44 (36.75 – 56.25)	0.93
Male gender[b]	63 (39.10)	33 (45.83)	0.39
Body mass index[a]	28.10 (25.00 – 32.30)	28.15 (24.53 – 32.15)	0.76
Waist index[a]	1.08 (0.97 – 1.24)	1.07 (0.96 – 1.22)	0.74
Current smoker[b]	40 (24.84)	23 (31.94)	0.32
Hypertension[b]	34 (21.18)	11 (15.28)	0.37
Hyperlipidemia[b]	26 (16.15)	8 (11.11)	0.42
Coronary artery diseases[b]	2 (1.24)	1 (1.39)	1.00
Heart failure[b]	0 (0)	1 (1.39)	0.31
Cerebrovascular diseases[b]	3 (1.86)	1 (1.39)	1.00
Diabetes mellitus[b]	16 (9.94)	5 (6.94)	0.62
Atrial fibrillation[b]	3 (1.86)	1 (1.39)	1.00
Chronic respiratory diseases[b]	23 (17.56)	8 (11.11)	0.68
Obesity[b]	61 (37.89)	27 (37.50)	1.00
β-blocker[b]	9 (5.59)	2 (2.78)	0.51
ACEi/ARB[b]	26 (16.15)	9 (12.50)	0.56
Aspirin[b]	8 (4.97)	4 (5.56)	1.00
Mineralocorticoid antagonists[b]	2 (1.24)	0 (0)	1.00

Notes: [a]Data are presented in median (interquartile range); [b]Data are presented in number (%); Obesity refers to a body mass index >30.
Abbreviations: ACEi: Angiotensin-converting enzyme; ARB: Angiotensin receptor blocker.

4. Discussion

The results revealed that patients previously infected with COVID-19 exhibited reduced RMSSD, a well-established

Table 2. Blood-test analysis of the study population

Parameters	Cases (*n*=161)	Controls (*n*=72)	*p*-value
White cell count ($\times 10^9$/L)[a]	6.72 (5.70 – 8.28)	7.41 (6.43 – 8.30)	0.12
Hemoglobin (g/dL)[a]	14.00 (12.90 – 14.80)	13.95 (12.90 – 15.05)	0.95
Platelet count ($\times 10^9$/L)[b]	276.80±63.20	272.27±63.77	0.62
Red cell distribution width[a]	12.70 (12.30 – 13.20)	12.65 (12.30 – 13.23)	0.94
Mean platelet volume (fL)[a]	10.90 (10.20 – 11.60)	10.80 (10.30 – 11.20)	0.4
eGFR (mL/min/ 1.73 m^2)[a]	101.00 (88.00 – 113.25)	98.50 (86.00 – 113.00)	0.49
Triglyceride (mmoL/L)[a]	0.97 (0.66 – 1.47)	0.84 (0.67 – 1.21)	0.41
Total cholesterol (mmol/L)[b]	5.10±1.00	4.93±0.93	0.25
HDL (mmoL/L)[a]	1.51 (1.25 – 1.80)	1.44 (1.25 – 1.69)	0.23
Non-HDL (mmoL/L)[b]	3.50±1.00	3.44±0.95	0.66
LDL (Mmol/L)[b]	3.00±0.90	2.96±0.87	0.9
ALP (U/L)[a]	65.00 (55.00 – 82.00)	67.00 (54.75 – 81.25)	0.94
AST (U/L)[a]	22.00 (18.00 – 26.00)	24.00 (19.00 –27.00)	0.31
ALT (U/L)[a]	17.00 (12.00 – 25.00)	19.00 (12.75 – 26.25)	0.37
Troponin (ng/L)[a]	4.00 (3.00 – 6.00)	3.50 (3.00 – 6.00)	0.29
NT-proBNP (pg/mL)[a]	30.00 (14.00 – 81.00)	31.50 (17.00 – 71.50)	0.54
HbA1c (%)[a]	5.40 (5.10 – 5.70)	5.40 (5.10 – 5.65)	0.57

Notes: [a]Data are presented in median (interquartile range). [b]Data are presented in mean±SD.
Abbreviations: ALP: Alkaline phosphatase; ALT: Alanine transaminase; AST: Aspartate transaminase; eGFR: Estimated glomerular filtration rate; HbA1c: Glycated hemoglobin; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; NT-proBNP: N-terminal pro-B natriuretic peptide.

Table 3. Parameters derived from 24-h electrocardiogram monitoring and 24-h ambulatory blood pressure monitoring in the study population

Parameters	Cases (*n*=161)	Controls (*n*=72)	*p*-value
Minimum HR (bpm)[a]	51.0 (46.0 – 55.0)	50.0 (45.0 – 53.0)	0.44
Maximum HR (bpm)[b]	127.5±17.4	127.1±15.8	0.89
Average HR (bpm)[a]	75.0 (70.0–80.0)	74.0 (69.0 – 80.0)	0.87
Ventricular ectopic beats[a]	0 (0 – 0)	0 (0 – 0)	0.27
Atrial fibrillation[a]	0 (0 – 0)	0 (0 – 0)	0.51
Longest R–R interval (s)[a]	1.40 (1.23 – 1.60)	1.50 (1.30 – 1.70)	0.26
ASDNN (ms)[a]	55.45 (44.98 – 67.30)	57.80 (48.00 – 67.10)	0.25
SDANN (ms)[a]	112.55 (90.80 – 137.30)	117.50 (100.00 – 137.90)	0.17
SDNN (ms)[a]	129.75 (108.88 – 152.95)	131.90 (118.50 – 163.30)	0.18
RMSSD (ms)[a]	34.30 (24.60 – 48.65)	38.60 (29.40 – 62.50)	0.03*
24-h systolic BP (mmHg)[a]	124.00 (112.25 – 137.75)	121.00 (111.50 – 1310)	0.26
24-h diastolic BP (mmHg)[a]	72.00 (66.25 – 80.00)	72.00 (67.00 – 79.00)	0.85
Awake systolic BP (mmHg)[a]	128.00 (117.00 – 141.00)	124.00 (115.00 – 135.00)	0.19
Awake diastolic BP (mmHg)[a]	76.00 (71.00 – 83.00)	76.00 (69.75 – 84.00)	0.75
Asleep systolic BP (mmHg)[a]	111.50 (102.00 – 126.00)	111.00 (98.50 – 119.00)	0.33
Asleep diastolic BP (mmHg)[a]	63.50 (57.00 – 71.00)	63.50 (56.25 – 68.00)	0.62

Notes: [a]Data are presented in median (interquartile range); [b]Data are presented in mea n±SD; *$p<0.05$.
Abbreviations: ASDNN: Average of the standard deviations of all N–N intervals for all 5-min segments in 24 h; BP: Blood pressure; HR: Heart rate; RMSSD: Root mean square of successive differences between normal heartbeats; SDANN: Standard deviation of the averages of R-R intervals in 5-min segments; SDNN: Standard deviations of N-N intervals in 5-min segments.

marker for HRV, at a medium-term follow-up of 24 weeks (approximately 5.7 months). One should note that this study involved a random selection of COVID-19 patients; patients with more severe COVID-19 symptoms, such as those requiring hospitalization, may demonstrate more pronounced changes in HRV. Of all the HRV parameters assessed, only RMSSD was significantly reduced – possibly due to its specific reflection of parasympathetic activity and the fact that SARS-CoV2 has been shown to infect the vagus nerve and impair its function.[2] In addition, it is possible that there was partial recovery following the infection, as identified by Santos-de-Araújo *et al.*[19] Their study found that both the recovery time since diagnosis

and patient age significantly influenced HRV recovery, particularly RMSSD, suggesting that COVID-19 exhibits a transient effect on the autonomic nervous system that improves gradually over time. Participants in the current study were randomly selected, unlike other studies where participants were specifically chosen, either because they were suffering from long COVID symptoms[20-22] or because they had been hospitalized[23] or admitted to ICU[24] during their initial infection. This could help explain why only RMSSD differed significantly between cases and controls. Nonetheless, the findings of the current study are clinically relevant, given the established link between reduced HRV and increased risk of cardiovascular disease. A meta-analysis encompassing 32 studies and 38,008 healthy participants reported that subjects in the lowest quartile of RMSSD had a combined hazard ratio of 1.56 for death compared to those in other quartiles.[25]

The mechanisms linking low HRV to cardiovascular disease are not completely understood. In a meta-analysis of 51 studies, Williams *et al.*[26] reported that various measures of HRV were negatively associated with several inflammatory markers. Importantly, markers of parasympathetic-mediated low HRV have been linked to increased inflammation.[27] Low vagally-mediated HRV is also associated with endothelial dysfunction.[28] Both subclinical inflammation and endothelial dysfunction are widely recognized to have an important role in the pathogenesis of atherosclerosis,[29] and both have been shown to persist in the aftermath of post-COVID-19 infection.[30,31] Endothelial dysfunction after COVID-19 infection has been demonstrated using various tests, including decreased flow-mediated dilatation,[32] increased L-selectin and P-selectin,[33] and reduced retinal venular flicker-induced dilation.[34] Furthermore, animal studies suggest a causal relationship between low parasympathetic activity and inflammation. For example, electrical stimulation of the vagus nerve in wild-type mice inhibits tumor necrosis factor (TNF) synthesis.[35] Furthermore, it has been reported to inhibit TNF synthesis in the liver, attenuate peak serum TNF levels, and prevent the onset of shock in rats during endotoxemia.[36]

HRV is partly mediated through baroreflexes. Arterial stiffness decreases baroreflex sensitivity,[37] and this may contribute to reduce HRV. Therefore, low HRV is also a marker for increased arterial stiffness, as confirmed in various patient groups, including those with type 2 diabetes,[37] hypertension,[38] renal disease,[39] and heart failure.[40] Arterial stiffness has been associated with increased all-cause and cardiovascular mortality, both in the general population[30,41] and specific patient groups, such as those suffering from diabetes[42,43] and those with peripheral arterial disease.[44] The mechanisms linking arterial stiffness with increased cardiovascular risk may be bidirectional, as atherosclerosis contributes to arteries stiffening, while increased arterial stiffness enhances mechanical stress on the vascular endothelium, thereby promoting atherogenesis.[45] Therefore, this dynamic may create a self-perpetuating cycle. In support of this, reduced HRV has been associated with subclinical atherosclerosis in subjects with type 2 diabetes.[46] The findings by Cai *et al.*[47] showed that sinoaortic denervation promoted atherosclerosis in Sprague-Dawley rats, supporting a causal role of reduced HRV and baroreflex sensitivity in the development of atherosclerosis.

The findings in our study are particularly significant given that the study cohort consisted of relatively young and healthy individuals. Therefore, the changes observed in HRV could not be attributed to underlying comorbidities. In addition, reduced HRV in cases was still present at the 24-week follow-up, thereby raising the suspicion that these findings may be long-lasting and could lead to an increased incidence of long-term cardiovascular implications. These alterations in HRV could be affected by factors such as the specific SARS-CoV-2 strain causing the primary infection and the subject's vaccination status at the time of infection. These considerations warrant further studies, including studies with extended follow-up periods.

Various large prospective studies have reported that reduced HRV predisposes an individual to atrial fibrillation. For example, in a study of 784 subjects with a mean age of 51 years, low HRV was associated with an increased risk of atrial fibrillation, with a hazard ratio of 2.81 (95% confidence interval [CI]: 1.64 – 4.81).[48] This association has been corroborated by additional studies.[49-51] Further evidence also comes from a Mendelian randomization study reporting that a genetically determined increase in SDNN was associated with an increased risk of atrial fibrillation (odds ratio: 1.60, 95% CI: 1.27 – 2.02, p=8.36 $\times$ 10^{-5}).[45] Wang *et al.*[52] also reported that reduced HRV predicts the incidence of type 2 diabetes in the general population. Therefore, our findings of reduced HRV approximately 5.6 months post-COVID-19 raise concerns regarding the potential of these long-term complications in affected individuals.

One of the strengths of this study was the rigorous confirmation of COVID-19 status in controls, achieved through both negative nasopharyngeal swab results and negative serological test results. Nonetheless, the possibility that some controls may have had previous COVID-19 infection cannot be ruled out. However, even if this occurred, this would, if anything, have diluted differences between groups. Despite this, the results

revealed a significant difference in RMSSD, highlighting the need for further investigation. Another strength is the inclusive approach used for selecting cases, which were identified based on a positive SARS-CoV-2 result from nasopharyngeal swabbing. This approach minimizes selection bias and enhances the generalizability of the findings to the broader population, as opposed to studies focusing solely on hospitalized patients. In addition, cases and controls were well-matched for baseline characteristics, including age, sex, and comorbidities, in this study.

The major limitation of the study is the limited sample size. While the study was powered to detect a moderate effect size, smaller effect sizes could have been missed. However, such a sample size was sufficient to allow for various investigations on the participants, such as 24-h Holter monitoring, to assess the consequences of COVID-19 on the cardiac autonomic nervous system. Given that the local population is predominantly Caucasian, the study was limited to this ethnic group. Therefore, the generalizability of the findings needs to be confirmed in other ethnic groups in future studies. Another limitation is that the Digitrak XT recorder used for HRV assessment did not provide separate daytime and nighttime HRV values, nor did it provide data on low-frequency HRV domains. Nevertheless, the sole HRV parameter that was found to be significantly different, RMSSD, is widely recognized as a reliable and sensitive marker of short-term autonomic neuropathy, as supported by numerous studies.[17] It is also the most frequently investigated HRV parameter in the study of COVID-19.[53] In addition, the data on participants' functional capacity, such as the 6-min walk test, was not collected. Future studies should address potential correlations between autonomic neuropathy and functional capacity in the post-COVID population.

5. Conclusion

The current study reports that, after a medium-term follow-up of approximately 24 weeks, COVID-19 was associated with lower HRV, as indicated by a reduced RSMMD, in a young population. This finding is highly relevant, as reduced HRV is associated with increased cardiovascular risk. It is therefore important to investigate whether HRV recovers over time or leads to a higher incidence of cardiovascular disease, highlighting the need for continued follow-up.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: Caroline Jane Magri
Data curation: Rachel Anne Xuereb
Formal analysis: Caroline Jane Magri
Investigation: Rachel Anne Xuereb
Methodology: Caroline Jane Magri, Stephen Fava
Writing – original draft: Stephen Fava
Writing – review & editing: All authors

Ethics approval and consent to participate

The study has been approved by the University of Malta Research Ethics Committee (Approval number: FRECMDS_2021_009). Written informed consent was obtained from each of the subjects following their participation in the study.

Consent for publication

Written informed consent was obtained from each of the subjects to publish their data (anonymized and collective).

Availability of data

The data can be obtained from the corresponding author, Dr. Caroline Jane Magri.

Further disclosure

The study has been presented at a local conference, the Maltese Cardiac Society Conference.

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ACCSCIENCE PUBLISHING

Brain & Heart

CASE REPORT

Unusual coexistence of congenitally corrected transposition of great arteries with type A interrupted aortic arch: A case report

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Abstract

Congenitally corrected transposition of the great arteries (CCTGA) accounts for <1% of all cases of congenital heart defect, a pathological condition characterized by the existence of both ventriculoarterial and atrioventricular (AV) discordance in the heart. CCTGA is more commonly associated with type B interrupted aortic arch (IAA) than type A variant. This is a more intricate and unusual presentation than dextro-transposition of the major arteries with an IAA. Herein, we present a case of an extraordinarily rare congenital cardiac complex defect. CCTGA and type A IAA were found in a 34-week preterm infant weighing 2.4 kg at delivery. Antenatally, the fetal echocardiogram suggested CCTGA in the form of an apically displaced left AV valve ventricular septal defect and transposed great arteries. The pulmonary trunk appeared larger than the aorta with three abnormal vessels. This study emphasizes the usefulness of sequential imaging modalities including fetal echocardiography to determine the majority of the anatomic details.

Keywords: Congenitally corrected transposition of great vessels; Interrupted aortic arch; Congenital heart disease; Fetal echocardiography

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1. Introduction

Congenitally corrected transposition of the great arteries (CCTGA) represents <1% of all cases of congenital heart defect, a pathological condition characterized by the existence of both ventriculoarterial and atrioventricular (AV) discordance in the heart.[1,2] In the healthy heart, the right ventricle (RV) supplies blood to the lungs, whereas the left ventricle (LV) provides blood to the entire body. The CCTGA features transposed major arteries and inverted ventricles, which can be associated with other cardiac and extracardiac lesions. CCTGA is often associated with significant hemodynamic and anatomical abnormalities, necessitating careful pre- and post-natal evaluation. Interrupted aortic arch (IAA) is a rare congenital abnormality of the aortic continuity between the ascending and descending aorta. According to Celoria and Pattorn,[3] IAA occurs in three forms: type A, which occurs below the left subclavian artery; type B,

which occurs between the left subclavian artery and the left common carotid artery; and type C, which occurs between the two carotid arteries. Type A IAA, although the least common, poses unique challenges in management due to its frequent association with other congenital heart defects.

The coexistence of CCTGA with IAA is an extremely rare association per the medical literature. Based on our knowledge, our case can be regarded as the fourth case to be described with such a presentation, since Cottrell *et al.*[4] disclosed the first instance of a comparable complex anomaly. This underscores the importance of detailed imaging and multidisciplinary coordination in managing such cases.

2. Case presentation

We describe a case of a 3-week-old female baby weighing 2.4 kg at delivery, who was delivered through a cesarean section in the 34th week of pregnancy in a mother who had no prior history of pertinent cardiac or other health issues. Pre-natal imaging was performed, but the exact diagnosis was challenging due to the complexity of the anomalies. Antenatally, the fetal echocardiogram suggested a ventricular septal defect and either transposition of the great arteries or a common arterial trunk. The baby had grade three respiratory distress when she was referred to our facility and admitted to the Neonatal Intensive Care Unit (NICU) (Figure 1).

The post-natal echocardiogram revealed situs solitus and levocardia; however, a type A IAA and CCTGA were demonstrated. The findings also demonstrated grade 1 tricuspid regurgitation, along with a typically normal coronary pattern and venous drainage. An interrupted portion of the left subclavian artery following the formation of the hypoplastic aortic arch was detected by computed tomography (CT) with contrast of the heart and great vessels. The descending aorta was supplied by a broad, curved patent ductus arteriosus that measured 18 mm in length and emerged from the left side of the main pulmonary artery. The CT showed a dilated dominant LV with a small-sized RV. Furthermore, the imaging supported the earlier echocardiographic results (Figure 2).

Based on the radiological findings, the baby was diagnosed with CCTGA together with type A IAA. Consequently, the baby was stabilized clinically on prostaglandin infusion 0.05 mic/kg/min in the NICU for 3 days and was referred for surgical repair, which involved aortic arch reconstruction and pulmonary artery banding. Post-surgical follow-up is critical in such cases to monitor for potential complications, including systemic ventricular failure or arrhythmias.

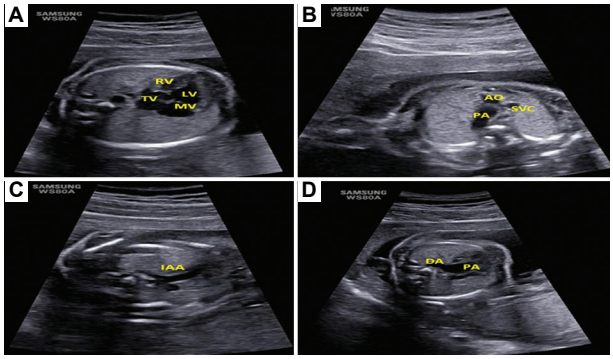

Figure 1. Fetal echocardiogram findings: (A) The four-chamber view demonstrates apical displacement of the posterior AV valve (tricuspid valve) and the presence of the moderator band, indicative of an abnormal AV connection. (B) The 3VT view reveals an abnormal spatial relationship between the great arteries. The pulmonary artery and ductal arch are positioned posteriorly and to the left of the aorta, consistent with CCTGA. The pulmonary artery appears larger than both the aorta and the SVC. (C) The aorta appears hypoplastic, with significant tapering distal to the origin of its first branch, suggesting coarctation or hypoplasia of the aortic arch. (D) The pulmonary artery is markedly enlarged and continues as the ductal arch, forming the descending aorta, indicating a ductal-dependent systemic circulation.
Abbreviations: 3VT view: Three vessel and tracheal view; AV: Atrioventricular; SVC: Superior vena cava; CCTGA: Congenitally corrected transposition of the great vessels.

3. Discussion

The cause of CCTGA is unknown, but it is thought to be caused by inappropriate heart looping during fetal development. Management for CCTGA is influenced by associated cardiac abnormalities such as ventricular septal defect, IAA, hypoplastic ventricles, or abnormal AV valves. Comprehensive imaging, including echocardiography and CT, plays a vital role in understanding anatomical complexity and planning surgical interventions.

Type A IAA is an uncommon fetal deformity caused by aberrant fourth aortic arch regression. It is often linked with other cardiac defects.[5] The coexistence of CCTGA with type A IAA is an exceptionally rare congenital condition. This combination poses unique challenges due to the hemodynamic implications and the complexity of surgical correction. This rare yet complex condition has been recorded 3 times before this instance, starting in the 1980s, as reported by Cottrell *et al.*[4] Subsequently, two more cases were reported by Sharfi *et al.* and Montaña-Jimenez *et al.* in 2020 and 2022, respectively.[5,6] This condition is more intricate and unusual than dextro-transposition of the major arteries compounded by an IAA. The first instance identified by Cottell *et al.*,[4] who employed two-dimensional echocardiography, angiography, and catheterization to support the diagnosis and arrange for surgery, was the

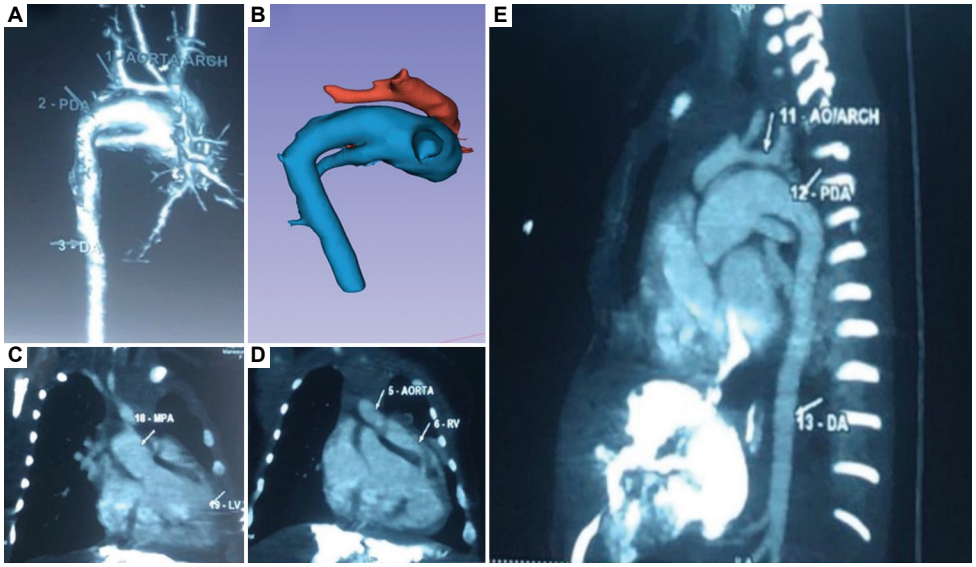

Figure 2. Multidetector cardiac CT of the heart and great vessels. (A) PDA continues as the DA. (B) PDA arises from the MPA, and the aortic arch is interrupted. (C) MPA arises from morphologic LV posteriorly and to the right. (D) Aorta arises from the morphologic RV anteriorly and to the left. (E) Hypoplastic distal arch with interruption and PDA continuing as DA.
Abbreviations: CT: Computed tomography; DA: Descending aorta; LV: Left ventricle; MPA: Main pulmonary artery; PDA: Patent ductus arteriosus; RV: Right ventricle.

only one of the documented cases to date that was not in preterm infants.

CCTGA has a broad and varied range of presentations. Imaging technology has made it feasible to diagnose such intricate defects. Advanced imaging modalities, including three-dimensional echocardiography and cardiac magnetic resonance imaging (MRI), are now integral in such diagnoses, enabling better visualization and pre-operative planning. Predicting CCTGA and related cardiac abnormalities can be aided by fetal echocardiography. Our analysis aligns with the findings of Vorisek *et al.*[7] such that early diagnosis and planning may lead to a significantly better short-term prognosis. This case emphasizes the importance of a multidisciplinary approach to ensure optimal outcomes in complex congenital cases.

4. Conclusion

CCTGA together with IAA represents an unusually complicated congenital heart condition. This report emphasizes the usefulness of pre-natal imaging and post-natal diagnostic modalities in such rare congenital heart defects. In addition, the usefulness of sequential imaging modalities including pre-natal echocardiography to feature the majority of the anatomic details, which may have a substantial impact on the definitive diagnosis for rare cardiac anomalies, is highlighted. Detailed imaging and early surgical intervention remain pivotal in improving outcomes for these patients.

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Conflict of interest

The authors declare they have no competing interests.

Author contributions

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Investigation: All authors
Writing – original draft: All authors
Writing – review & editing: All authors

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent from the parent was obtained for publication of the infant patient's data.

Availability of data

The database for this manuscript will be shared upon request to the corresponding author.

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ACCSCIENCE PUBLISHING

Brain & Heart

CASE REPORT

Brain pathology in human tetraploidy (92, XXYY): A case report

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Abstract

Tetraploidy is a rare chromosomal abnormality that is typically lethal *in utero*, with limited data on its effects on brain development. A comprehensive neuropathologic study of a tetraploid newborn (92, XXYY) at a corrected gestational age of 30 weeks is presented. Findings included hippocampal hypoplasia, partial corpus callosum agenesis, and neuronal heterotopies. In addition, the cerebral cortex showed sparse neurons across all laminae, along with molecular and meningeal glioneuronal heterotopies. The periventricular region demonstrated dispersed germline neurons, and the cerebellum exhibited matrix cell heterotopies in the dentate nuclei and numerous migrating Purkinje cells in the white matter, indicating immaturity. These brain abnormalities may explain the severe developmental delays and intellectual impairment seen in surviving patients. Unlike other severely unbalanced chromosomal aberrations that typically result in major brain malformations, tetraploidy appears to have a less severe effect on brain development. This report expands the knowledge of brain abnormalities in tetraploidy.

Keywords: Tetraploidy; Polyploidy; Brain; Neuropathology; Development

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1. Background

Human tetraploidy has rarely been described, with most contributions focusing on its genetic aspects. It is commonly associated with maternal partial moles, and both maternal and paternal genetic contributions may occur in a tetraploid pregnancy. Rare and dated descriptions of the phenotype of live-born infants have focused on pre- and/or postnatal growth retardation, delayed motor and mental development, and dysmorphisms – such as microphthalmia with corneal opacity, low-set ears, short philtrum, beaked nose, bifid uvula, single mono- or bilateral palmar crease – along with skeletal abnormalities and cardiac or renal defects with megaureters.[1-4] Reports of neurological and cerebral abnormalities are even rarer, with a few describing sacral myelomeningocele, hydrocephalus, microgyria, Arnold–Chiari malformation, aqueduct forking, ectopic gray matter,[2] and microcephaly with undefined encephalopathy.[3] The present comprehensive neuropathologic study of a tetraploid newborn focuses mainly

on cortical and cerebellar abnormalities that contribute to the intellectual deficit and developmental delay commonly observed in patients with this unusual chromosomal aneuploidy.

2. Case presentation

This neonate was born prematurely at a gestational age of 30 weeks, weighing 1,160 g, measuring 29 cm in length, with an occipitofrontal circumference of 29 cm. He died 14 h after birth due to severe respiratory distress syndrome caused by hyaline membrane disease associated with a large ventricular septal defect. Phenotypic features included dolichocephaly, large cranial fontanelles, low-set ears, bilateral microphthalmia with hypoplasia and corneal opacity (more pronounced in the left eye), a beak-like nose, small mouth with an arched upper lip, micrognathia, syndactyly of the second and third fingers of the right hand, bilateral single palmar crease, and cryptorchidism. The karyotype of cultured leukocytes and fibroblasts showed polyploidy (92, XXYY). Parental consent was obtained for a postmortem examination.

Following fixation in 10% formaldehyde solution for 2 months and external macroscopic examination, the brain was weighed (200 g) and sectioned coronally for both hemispheres, while the cerebellum was cut tangentially. Tissue blocks were sampled from the frontoparietal cortex, periventricular area, basal ganglia, hippocampal region, each level of the brainstem, and the cerebellum. Samples were embedded in paraffin, sectioned into serial 10-μm-thick slices, and stained using hematoxylin-eosin and Nissl cresyl violet methods.

Macroscopically, the cortical convolutions showed a developmental pattern commonly observed at approximately 28–30 weeks of gestation. The corpus callosum was represented only by a thin anterior membrane and a barely sketched genu, while the body and splenium were completely absent; the lateral ventricles were markedly dilated overall, and the frontal horns were verticalized (Figure 1A). The hippocampi were partially verticalized and hypoplastic, particularly in the presubicular parahippocampus, subiculum, and Ammon's horn, while the dentate gyrus was not identifiable (Figure 1B).

Mild hypoplasia was also observed in the basal ganglia and cerebellum. Microscopically, the periventricular germinal zone appeared reduced in volume and pale (Figure 2A). The cortex of both hemispheres was diffusely thin, with decreased neuronal density across all laminae (Figure 2B). Notably, the frontal cortex exhibited a predominantly tangential organization of the laminae, resembling a primitive "peigné" (comb-like) pattern (Figure 2C).

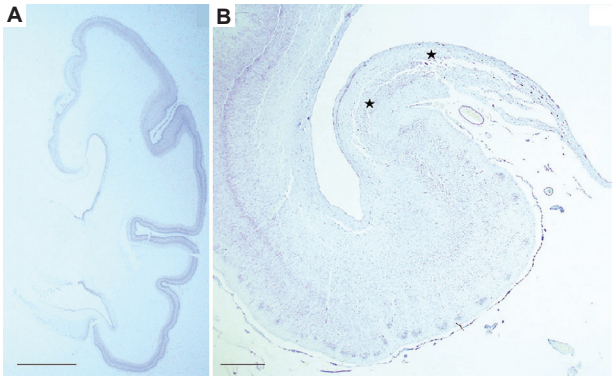

Figure 1. Nissl staining of the patient's brain regions. (A) The right hemisphere of the brain (scale bar: 2.1 cm, magnification: ×1) shows a simplified cortical convolutional pattern, with only primary fissures visible. The lateral ventricles are dilated, and the periventricular matrix is poorly developed. (B) The left hippocampus (scale bar: 1.5 cm, magnification: ×1.25) shows sectorial hypoplasia, with underdevelopment of the presubicular parahippocampus, subiculum, and Ammon's horn; the dentate gyrus is not visible (black stars).

Despite the cortical regions exhibiting tangential organization, the lamination pattern was generally preserved. In certain areas, small groups of neurons had detached from the superficial layers and migrated into the molecular lamina, forming discrete heterotopies (Figure 3A). Occasionally, larger cell clusters formed what appeared to be leptomeningeal glioneuronal heterotopies, probably due to a leakage in the pial-glial membrane (Figure 3B and C).

The cerebellum also showed notable abnormalities. The innermost layer of granular neurons contained a small number of migrated granule cells and a significant number of large polymorphic neurons, likely representing migrating Purkinje neurons (Figure 4A). Although matrix cells in the transient outer germinal layer were present in normal numbers, granule cells radially crossing the molecular layer following the outer-inner migration pattern were fewer than expected. A large number of migrating Purkinje cells were dispersed in the white matter. The dentate nucleus was compacted and underfolded, with a large number of irregular matrix cell nests intermingled within the hilum or along the outer margins of its convolutions (Figure 4B). These were particularly noticeable on the right hemisphere, where the corresponding cortical folia were smaller than those in the contralateral hemisphere, resembling a micropolygyric-like appearance (Figure 4C). In addition, while small clusters of germline neurons typically surround capillaries in the white matter, some formed distinct heterotopies partially detached from the dentate nucleus. The vermis was completely dysplastic, with small primitive vermis nests present (Figure 4D).

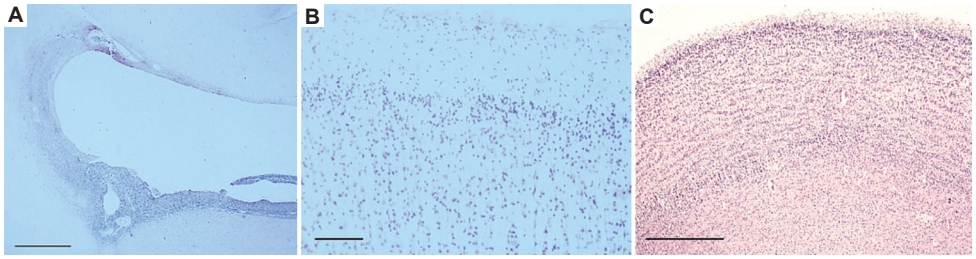

Figure 2. Subependymal region and cortical abnormalities. (A) Nissl staining of the periventricular germinal zone (scale bar: 1.5 cm, magnification: ×1.25). This area appears underdeveloped for the gestational age, with a paler appearance than commonly seen. Cell proliferation in the ganglionic eminence typically ceases by 26 – 27 weeks of gestation.[11] (B) Nissl staining of the upper cortex (scale bar: 1.3 cm, magnification: ×4). Neuronal density is reduced, with abnormally spaced nerve columns, particularly in the superficial laminae. (C) Hematoxylin and eosin staining of the immature cortex (scale bar: 2.1 cm, magnification: ×2.5). The tangential cortical assembly, referred to as a "*peigné*" pattern, is a normal feature during normal brain maturation, particularly in the frontal cortex, typically before 20 – 22 weeks of gestation. Its persistence in this case suggests a mild abnormal delay in cortical assembly and lamination.

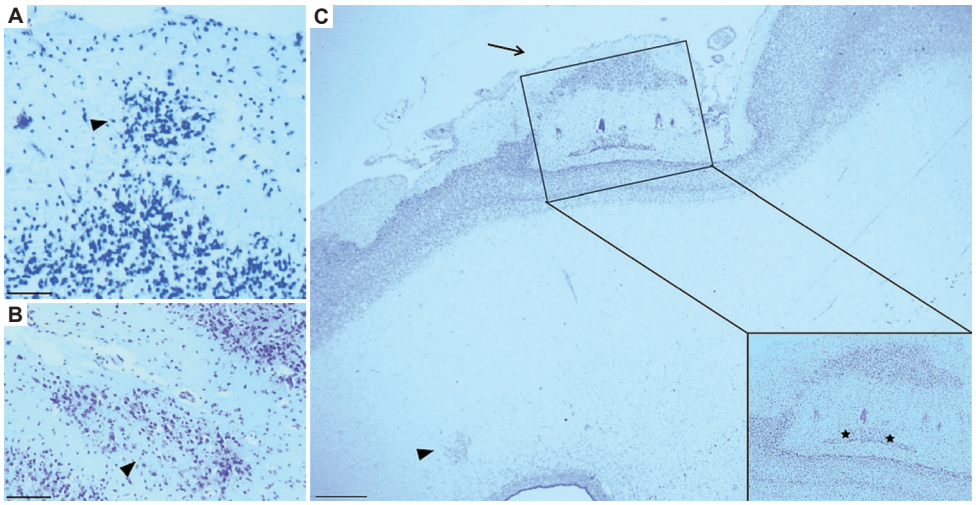

Figure 3. Types of heterotopy. (A and B) Nissl staining demonstrates nodular molecular heterotopies (scale bar: 1.3 cm, magnification: ×4). Tiny neuronal clusters are occasionally found in the molecular layer of normal newborns; however, when composed of a consistent number of cells forming a defined structure, they may reflect a defect in superficial cortical assembly (solid arrowheads). (C) Nissl staining reveals a large leptomeningeal glioneuronal heterotopy (scale bar: 1.5 cm, magnification: ×2.5). These voluminous glioneuronal heterotopies may extend into the meningeal space through breaches in the pial-glial membrane (thin arrow), with short residual segments of the membrane visible (inset, black stars; scale bar: 1.3 cm, magnification: ×4). Small nests of ectopic neurons in the white matter are also marked (filled arrowhead).

Overall, the brainstem had normal morphology, except for a reduced number of neurons in the main inferior olivary nucleus. At the pontobulbar level, the corticospinal tracts (CSTs) remained slightly compacted, and their transverse fibers showed limited interaction with the pontine nuclei and minimal tendency to cross the midline (Figure 5).

3. Discussion

The tetraploid newborn (92, XXYY) described here is consistent with the phenotype of previously reported cases.[1-4] Documented brain anomalies in human tetraploidy include sacral myelomeningocele, hydrocephalus, microgyria, Arnold–Chiari malformation, aqueductal bifurcation, ectopic gray matter,[3] and microcephaly with undefined encephalopathy.[2] The patient in this case report demonstrated abnormalities primarily in the cerebral hemispheres and cerebellum.

In the cerebral hemispheres, findings suggest a possible defect in germinal cells within the periventricular matrix, resulting in fewer cortical neurons, especially in superficial laminae. This could reflect a slowing or early arrest of late neuronal proliferation when daughter cells destined for superficial cortical layers are generated and begin migration. Moreover, this could also correlate with the partial agenesis of the corpus callosum, as axons from upper cortical neurons play a critical role in its formation through gene regulators, such as special AT-rich sequence-binding protein 2 (SATB2), SATB1, and Ctip2 in particular.[5] On the other hand, nerve cell heterotopies in the molecular lamina and meninges

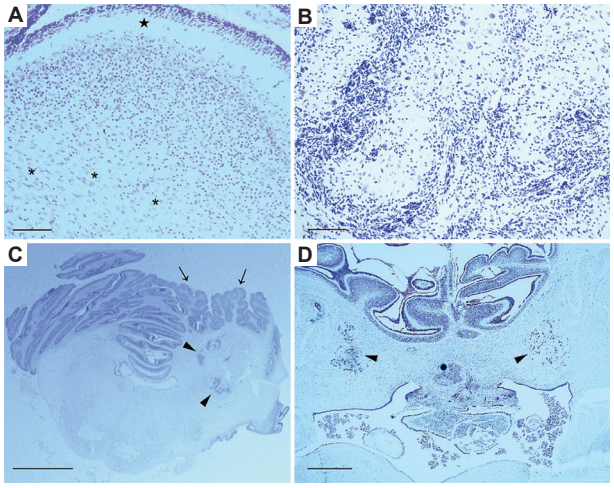

Figure 4. Cerebellar abnormalities. (A) Nissl staining of the cerebellar folium (scale bar: 1.3 cm, magnification: 4×). The outer matrix layer is well-formed, but the sparse migrating neurons crossing the molecular layer (black star) and a large number of macroneurons (asterisks), presumably Purkinje cells, within the core of the folium and beneath a primitive inner granular layer, indicate subtle developmental immaturity. (B) Nissl staining reveals matrix cell heterotopies in the dentate nucleus (scale bar: 1.3 cm, magnification: ×4). (C) Nissl staining of a cross-section through the entire cerebellum (scale bar: 2.1 cm, magnification: ×1). The right cerebellar folia show a micropolygyric-like pattern (thin arrows), which seems to correspond to the large number of matrix cells ectopically arrested in the dentate nucleus (solid arrowheads). (D) Nissl staining of the vermis at the pontobulbar junction (scale bar: 1.5 cm, magnification: ×1.25). The vermis is dysplastic, containing abnormal clusters of immature cells and a small primitive vermis nest (solid black circle). Matrix cell heterotopies in the dentate nuclei may partially develop independently within the white matter (solid arrowheads).

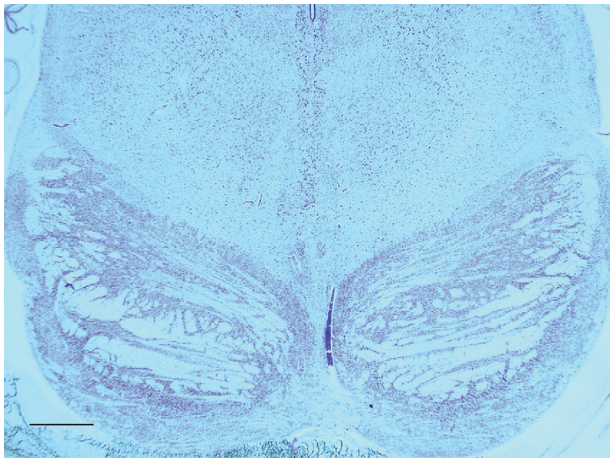

Figure 5. Nissl staining of the lower pons at brainstem level (scale bar: 1.5 cm, magnification: ×1.25). The absence of an initial midline crossing by the corticospinal tracts appears abnormal for a 30-week-old neonate.

suggest a defect in superficial intracortical assembly and possible breaches in the pial-glial membrane. Under normal conditions, cortical assembly is regulated by key cortical organizers, such as the reelin (RELN)–disabled homolog 1-very low-density lipoprotein receptor/apolipoprotein E receptor 2 signaling cascade, which oversees the correct positioning of incoming neurons in targeted laminae in close cooperation with Retzius-Cajal cells that stimulate RELN production. This complex mechanism can be disrupted in the presence of chromosomal aberrations, such as tetraploidy. In addition, RELN not only acts as a direct player in cortical lamination but also activates the neurogenic locus Notch homolog protein 1 signaling cascade to promote the transformation of progenitors into mature radial glial cells, which are known to be the critical guides for early neurons migrating to the cerebral cortex in an inside-out pattern.[6-9] Moreover, the "*peigné*" cortical organization observed – common before 20 – 22 weeks' gestation but unusual beyond this point – suggests developmental delay and an inability of migrated neurons to organize into regular vertical columns.[10-13]

The hippocampus showed mild signs of delayed maturation. While the apparent absence of the dentate gyrus may be partially artifactual, the poor development of the subiculum and Ammon's horn, along with the absence of the hippocampal fissure and early subiculum fissure, support this interpretation.[14] The cerebellum also showed signs of immaturity. Although the outer germ layer had a normal composition, few neurons crossed the molecular layer to reach the inner granular layer. Many Purkinje cells remained within the white matter. The cerebellar white matter retained an extraordinary number of matrix cells, clustered around small vessels, or intermingled with the dentate nucleus as matrix cell heterotopies. In addition, many folia of the right cerebellar hemisphere appeared particularly small and numerous, mimicking focal cerebellar micropolygyria (Figure 3C and D), possibly related to ectopic germline neurons abnormally arrested in the dentate nucleus. While retention of matrix cells in the cerebellar white matter is occasionally observed even in term neonates, their abundance here is atypical. Even considering the prematurity of this tetraploid neonate, the observed features should still be regarded as abnormal. For example, although the innermost cerebellar granule layer contained only a small number of granular cells, few neurons from the normal outer matrix migrated across the molecular layer, suggesting delayed or defective maturation. On the other hand, the dysplastic vermis was also evidence of disrupted cerebellar development. The absence of an initial midline crossing by the CSTs at the inferior pons may be considered abnormal, as uncrossed CSTs are often associated with genetic disorders.[15,16]

4. Conclusion

In summary, despite the absence of major brain abnormalities, this rare and peculiar aneuploidy is best

characterized by widespread delayed maturation – particularly affecting the cerebral cortex, hippocampus, and cerebellum – as well as subtle errors in neuronal migration in the cerebral cortex and cerebellum. Nonetheless, it appears to have a less severe impact on human brain development than more severely unbalanced aneuploidies.

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Conflict of interest

The authors declare that they have no competing interests.

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Supervision: Luca Reggiani Bonetti
Visualization: Tiziana Salviato
Writing-original draft: Elvio Della Giustina, Maria Carolina Gelli
Writing-review & editing: Elvio Della Giustina, Tiziana Salviato, Luca Reggiani Bonetti

Ethical approval and consent to participate

This study adheres to the ethical principles for medical research involving human subjects as outlined in the Helsinki Declaration of the World Medical Association. This manuscript does not need approval from the ethical committee of our university administration as it is not required for the publication of a single case of particular scientific interest (Regulations of the Ethical Committee of Area Vasta Emilia Nord, Italy, approved on September 22, 2020).

Consent for publication

Informed consent could not be obtained as the patient died many years ago; however, patient anonymity has been fully preserved.

Availability of data

Data are available from the authors upon reasonable request.

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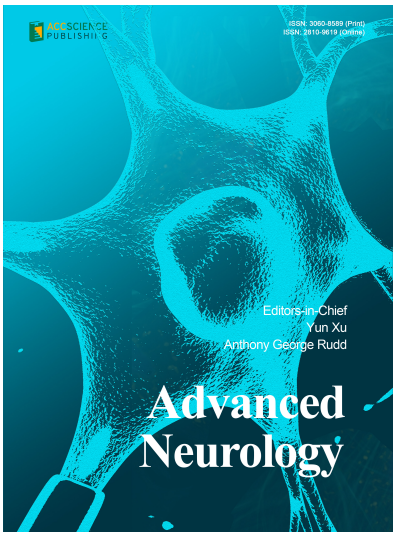

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