Can sarcopenia index serve as a predictor of myocarditis from mRNA based COVID-19 vaccine, insights from clustered cases and potential involvement of micro-RNAs in its pathogenesis.

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Abstract

Background:

With the current mass international roll out of several vaccines against SARS-Cov-2, several reports of unheeded complications have made headlines. One of which involves myocarditis with the now FDA fully approved vaccine, Pfizer, and others.

We hypothesize through this study that a dysregulated micro-RNA response resulting from such type of vaccines can be involved in triggering myocarditis.

Methodology:

Embase, Medline and the Cochrane Central Register were used to search for specific keywords such as “mRNA COVID-19 vaccines” AND “Myocarditis” for relevant publications up to 1st of September 2021. The systematic review was performed using PRISMA protocol

Results:

Literature review has identified 26 cases series and reports involving the development of myocarditis from mRNA vaccines, a total of 89 patients were included. Age range was clearly identified in 66 patients. Among those 66 patients, 94% were below 50 years of age, also out of 89 patients, 94% were males. Myocarditis developed, after a median time of 72 hours of the 2nd dose. 90 of cases of myocarditis developed myocarditis after the 2nd dose, the few patients developing myocarditis after the first dose were either predisposed by a history of myocarditis or a history of previous COVID-19 infection.

Conclusion:

In conclusion, interpretation of the results in view of the suggested hypothesis, reveals that the micro-RNAs implicated in myocarditis in general are as well implicated in the pathogenesis of severe COVID-19, this can explain why patients having a first dose with a history of COVID-19 can develop myocarditis from mRNA vaccines, also the relatively higher likelihood of this complication in males and younger aged individuals can be explained by the upregulation of key myocarditis related miRNAs in those two strata, due to higher muscle mass and suggests performing a sarcopenia index in recipients of the vaccine to correlate it with the likelihood of this complication. This could later set a cut-off of this easy bed-side index to stratify cases a higher risk of this rare complication.

Background

COVID-19 is the largest and deadliest pandemic to strike the globe to date. Since its beginning in China and Asia in 2019, it has led to the loss of many lives up to this day. The resultant global health crisis has compelled health authorities all over the world to provide emergency authorization to many vaccines, well before full FDA approval. This accelerated vaccine rollout in late 2020 has greatly reduced the incidence of severe COVID-19 complications, and hospitalizations.(1) However, a major setback of such emergency authorization was the rise of unexpected complications, such as HIT-like syndrome from adenovirus-based vaccines. (2)One of the most serious complications of the COVID-19 vaccines was post vaccination Myocarditis associated with the mRNA

vaccines. Myocarditis is a rare complication, which was more commonly occurring in young adults and adolescents. (3) As mentioned by Bozkurt et al, according to the US centers for disease control and prevention, Myocarditis/Pericarditis rates are =12.6 cases per million doses of second dose mRNA vaccine among individuals 12 to 39 years of age. (4) Interestingly, there is absence of reported cases of Myocarditis with non-mRNA vaccines such as Janssen.

Several mechanisms were suggested as to why the mRNA vaccines specifically lead to myocarditis. One hypothesis is that mRNA vaccines generate a very high antibody response, like multi-system inflammatory syndrome in children. Molecular mimicry between the protein of SARS-CoV-2 and self-antigens triggering an abnormal immune response has been proposed. (4) In this article we propose a totally different hypothesis related to micro-RNAs. MicroRNAs are short non-coding RNAs that play a crucial role in the regulation of gene expression during cellular processes. It is now established that some of the host-generated miRNAs are known to modulate the antiviral defense during viral infection. Recently, multiple DNA and RNA viruses have been shown to produce miRNAs known as viral miRNAs (v-miRNAs). We hypothesize that mRNA vaccines can either trigger the release of host miRNAs or contain themselves some miRNAs that can trigger this unwanted complication. This suggested hypothesis can have critical diagnostics and therapeutic implications.

Methodology

Embase, Medline and the Cochrane Central Register were used to search for specific keywords such as “mRNA COVID-19 vaccines” AND “Myocarditis” for relevant publications up to 1st of September 2021. The systematic review was performed using PRISMA protocol

Results

To date, 26 cases' series of myocarditis cases from mRNA vaccines have been reported, comprising a total of 70 cases. Table 1 summarizes the main characteristics of those cases (5) (6) (7) (8) (9) (10) (11) (12) (13) (14) (15) (16) (17) (18) (19) (20) (21) (22) (23) (24) (25) (26) (27) (28) (29) (30)

The collected cases series and reports comprised in total 89 cases. A quick analysis of the reported cases reveals that among cases or case series where recipients' ages were reported in details (66 cases out of 89), only 4 cases were above the age of 50 years while the remainder were below 50 years of age (Figure 1). Among the 89 cases, only 5 were females (Figure 2). Finally, yet importantly, 90% of patients (80) developed myocarditis after the second dose. 5 out of 9 patients developing myocarditis from the first dose had history of COVID-19 infection, while 2 had history of myocarditis from another viral illness and the remainder developed it after 7 and 16 days respectively from the first dose which is longer than the median time of development of myocarditis in other cases (72 hours). (Figure 3)

Discussion

A) Viruses inducing myocarditis alter host micro-RNAs expression

Many studies have identified several miRNAs that have a direct relationship with myocarditis. 94 types of miRNAs were studied using gene microarray analysis during viral myocarditis; 27 of which were downregulated

and 67 were upregulated during myocarditis in comparison with the controls. One of the miRNAs, called miRNA214 was found to be elevated in plasma during myocarditis. They promote cardiac inflammation by increasing the expression of TNF alpha and IL-6. Their presence in plasma could guide us towards using it as a noninvasive biomarker for diagnosing myocarditis.(28)

Many studies are suggesting the therapeutic role of microRNA in myocarditis. For example, the role of microRNA-155 in viral myocarditis caused by Coxsackievirus was explained, and macrophage infiltration was found to be a hallmark feature of viral myocarditis. As studies have shown that **microRNA-155** regulates the differentiation of macrophages, it was found that silencing the microRNA-155 found in cardiac muscles through affecting macrophage polarization and shifting the inflammatory mediators balance, resulted in increased levels of alternatively-activated macrophages (M2) and decreased levels of classically-activated macrophages (M1) in the heart, which will decrease risks associated with viral myocarditis as cardiomyopathy and heart failure and thus, may be a potential therapeutic target for viral myocarditis. This gives genetic evidence about the role of endogenous miR-155 in modulating macrophage polarization and protecting mice that were experimented on by CVB3-induced VM. (29,30)

Another study by Corsten et al revealed that anti-miR-155 therapy in VM (Viral Myocarditis) decreased monocyte-macrophages numbers and suppressed T-lymphocyte activation, along with inhibition of release of both pro- and anti-inflammatory cytokines, including TNF- α , IL-6, IL-10, and IFN- γ during the inflammatory phase. Furthermore, suppression of miR-155 reduced body weight loss caused by systemic illness, along with the numbers of circulating leukocytes induced by CVB3 infection. In addition to miRNA-155, **miR-146b** and **miRNA-21** were constantly upregulated during acute inflammation of both human and mouse VM that all contribute to the immune response and inflammatory process(29). miRNA 21 inhibits the pathway of inflammatory NF- κ B and antagonizes cardiac myocyte apoptosis in miRNA 21 gene carriers(31). **CVB3-upregulated miR-21** can cause heart muscle cell damage by disrupting cardiomyocyte interactions through depressing the levels of components in cell-cell interactions related to the cardiac function. Therefore, during the CVB3 infection, miR-21 expression may lead to the pathogenesis of VMC, and its suppression can reduce host injury(32) It is suggested to prepare miRNA21 mimics for achieving a cardioprotective mechanism. While to antagonize the suppressive effect of proinflammatory miRNAs, some prepared nucleotides were suggested as possible future inhibitors for proinflammatory miRNAs, namely anti-miRNAs oligonucleotides AMOs, antagomirs, locked nucleic acid LNA, antisense nucleotides, peptide nucleic acids and miRNA sponges.(30,33,34)

Furthermore, CVB3 reduces the expression of miR-21 which directly inhibits Programmed cell death 4 (PDCD4) resulting in non-stopping apoptosis and worsened myocarditis. CVB3 also cause miR-20b to repress ZFP-148; which is responsible of viral replication, while aberrant miR-20b increases anti-apoptotic proteins B cell lymphoma-2 (Bcl-2) and B-Cell lymphoma-extra large (Bcl-xl)(35). This shows that CVB3 tends to induce miRNAs that balance cardiac cell survival versus apoptosis to create an optimal environment for the virus to replicate. Interestingly, miR-590-5p released extracellularly by CVB3 inhibited pro-apoptotic factors, resulting in prolonged viral replication. Similarly, miR-98 (which can regulate cell apoptosis by interacting with FAS/FASL gene pair) was found to be downregulated in myocarditis patients. Adenosine deaminases acting on RNA bind with Dicer to increase miRNA-222 which inhibits expression of the gene responsible for PTEN (an apoptosis

associated protein) during CVB3 induced myocarditis. This shows that non-coding RNAs are important in determining cell fate in enteroviruses infection(36–38).

Another example concerning apoptosis is the **miR-29** family's downregulation which has been linked to the pathophysiology of tissue scarring, including heart disease. miR-29b was found to be down-regulated in people and animals with atrial fibrillation or congestive heart failure, and miR-29b protected against AngII-induced hypertensive cardiac remodeling via inhibiting the TGF/Smad3 signaling pathway. By modifying the extracellular matrix (ECM) and correcting erroneous promoter methylation, it also inhibited cell proliferation and migration. TUG1 taurine up-regulated gene was found to be adversely regulating miR-29b in this study. Overexpression of miR-29b altered TUG1's effect on cell apoptosis and inflammation, suggesting that miR-29b may have a pro-apoptotic and pro-inflammatory effect in LPS-damaged H9c2 cells(39).

Another example of miRNA being therapeutic is the fact that androgen receptors were found to be involved in increasing cardiac fibrosis through affecting micro RNA125b (**mir-125b**) by stimulating more collagen synthesis. Therefore, stopping the overexpression of ARs, the miR-125b will be inhibited and cardiac inflammation and fibrosis would be treated. This particularly encouraged treatment with degradation enhancer of AR that limits cardiac fibrosis in iDCM, thereby providing potentially a therapeutic approach for patients with iDCM.(36)

Moreover, after identifying a novel microRNA in mice and humans with myocarditis, they found that the human homologue (hsa-miR-Chr8:96) could be used to distinguish patients with myocarditis from those with myocardial infarction. This was identified after inducing autoimmune myocarditis in mice which produced interleukin 17(from TH17 cells) a characteristic feature of myocardial injury in the acute phase of myocarditis. The microRNA mmu-miR-721 was synthesized by Th17 cells and was present in the plasma of mice with acute autoimmune or viral myocarditis but not in those with acute myocardial infarction¹¹. Another example is the role of the miR-221/-222 family that shows that microRNA-221 (miR-221) and miR-222 levels are significantly elevated during acute VM caused by Coxsackievirus B3 (CVB3). That is upregulated in VM. The miR-221/-222 cluster was found to have antiviral and inflammatory immune responses to viral infection of the heart. Its inhibition increases viral load, inflammation, and overall cardiac injury upon VM(40).

Exosomes are membrane-bound extracellular vesicles involved in cell signalling⁹. A study by Fan et al, examined the expression of 10 candidate miRNAs in the serum exosome by qRT-PCR in 23 patients with Coxsackievirus B3 (CVB3) viral myocarditis (VM) and 12 controls. Among them, **miR-1, -27b, -148a and -133a are heart-associated; miR-146b, 30a, -155, -181d and -125a are immune-associated; miR-21** is fibrosis associated. The study described 5 miRNAs with disturbed expression in CVB3 VM patients which may be potentially used as biomarkers for VM diagnosis. Not only were they found in serum exosomes, but also, two of these miRNAs were found to have altered expression in cells after CVB3 infection. The miRNAs miR-30a and -181d were significantly up-regulated after CVB3 infection. The study further identified suppressor of cytokine signaling-3 (SOCS3) as a target for **miR-30a and -181d**, as predicted by bioinformatics tools and confirmed by dual luciferase assay and Western blot. In addition to this, up-regulated **miR-30a and -181d are responsible for the elevated IL-6** levels via modulating SOCS3 expression during CVB3 infection. Furthermore, miRNA inhibitors injection increased mice survival rate after CVB3 infection. Findings of this study suggest that miR-30a and -181d are responsible for the over-activated inflammatory response to CVB3 viral infection of the heart(41)

The development of newer modes of treatment of myocarditis was also suggested by a study where RT-qPCR showed **miR-141-3p** expression to be reduced in mice with experimental autoimmune myocarditis (EAM). In order to test its effect on the pathology of EAM, a group of mice were injected with miR-141-3p agomir. The results showed reduced LVEDd and LVEDs on echocardiography in the non-injected mice while LVEF and LVFS in miR-141-3p agomir injected mice were increased proving its protective effect. Existing literature has proven miRNAs to be involved in mediation of immune inflammation in cardiac diseases³¹. Overexpression of miR-141-3p was found to decrease myocardial inflammation through suppressing STAT4. In this study, the results showed a decrease in miR-141-3p levels with increased STAT4 levels, suggesting that STAT4 is a target gene for miR-141-3p.(42)

Lastly, through experimentation on mice it is found that **miRNA-98** showed suppression of IL-10 (a strong mediator from B-cells) causing protection and limitation of the severity of myocarditis which may be a new gate for targeted therapy for myocarditis. We can therefore conclude that microRNAs can be used as a diagnostic and therapeutic tool as medicine advances.(43)

B)Viral miRNAs interact with host genome, a new miRNA mediated interplay between host and viruses.

1-As mentioned earlier, discovery of viral miRNAs has become a point of focus in the last 10 years. Two different approaches have been used to identify v-miRNAs:(44)

a- The use of computational tools to predict the secondary structure of the precursor of v-miRNAs (pre-v-miRNAs). This approach usually results in a large number of false positives, however, it can lead to the identification of less abundant miRNA.

b-Sequencing of cloned small RNA molecules; however, less abundant miRNA may be left out.

2- Notably, more than 250 v-miRNAs have been identified, and the majority of them are accounted for in the DNA viruses of the herpesvirus family. Studies have indicated that viruses utilize the cellular machinery to encode miRNA. The detection of v-miRNAs in RNA viruses has been controversial, with a few reports suggesting non-canonical miRNA-like small RNAs produced during RNA virus infections; however, these small RNAs lack the canonical stem-loop structure found in miRNAs, so their biogenesis and function are not well-understood. (45)

The following reasons might explain the lack of v-miRNAs produced by RNA viruses during infection; a- the RNA viruses consists either +/- sense or double-stranded RNA (dsRNA) and replicate in the cytoplasm of the host cell, so the RNA molecules are not accessible to the miRNA biogenesis machinery in the nuclei; b-excision of pre-miRNA from the primary transcript might result in the destruction of RNA-based viral genomes; c-the generated v-miRNA may target the viral genome itself, resulting in cleavage of the viral genome.

3-Functions of viral miRNAs include the following;(46)

a-Improve cell survival:

A classic example is EBV miR-BART5, which controlled proliferation and established latent infection by targeting PUMA. PUMA is known to modulate apoptosis by p53, so by suppressing PUMA, EBV miRNAs alter the susceptibility to apoptotic agents and improve host cell survival.

b-Alter cytokine expression:

KSHV v-miRNAs reduce expression of C/EBP β p20 (LIP), a known negative regulator of IL6 and IL10 cytokines, to regulate the cytokine signaling in infected cells. This leads to overexpression of pro-inflammatory IL-6 leading to tissue damage.

c-Alter antiviral immune responses:

HCMV miRNAs have been shown to target host genes involved in the antiviral immune response. miR-UL112 blocks the natural killer (NK) cell-mediated recognition of virus-infected cells by inhibiting the expression of MICB, a stress-induced ligand essential for NK-cell activity.(46)

Table 2 summarizes the number of miRNAs released by different DNA and RNA viruses.

C)Why myocarditis from mRNA vaccines seems to decrease with age.

From table 1 we can conclude that most of the cases of myocarditis from mRNA vaccines occurs in individuals aged 50 years or below. Key miRNA involved in induction of myocarditis are expressed in skeletal muscles, an interesting example is miRNA 155, sarcopenia or loss of muscle mass is most pronounced after the age of 50 years, occurring steadily at a rate of 1 to 2% annually. This loss of muscle mass has been correlated to levels of micro RNAs, specifically microRNA 155, with aging, by Ong and colleagues. They found that miRNA 155 decreases with age. This perfectly matches our hypothesis and might also help in stratifying individuals at higher risk of myocarditis from mRNA vaccines by the sarcopenia index, the higher the index is, the lower the risk of myocarditis from mRNA vaccines. This also could also explain the predominance of male gender in the observed complication, having a higher muscle mass compared to females. (47)

D)Diagnostic and therapeutic implications:

1-Predicting mRNA-vaccines related myocarditis.

It is clear from the above that viral RNA can either alter the expression of host miRNA or use cellular machinery to form viral miRNAs. Farr, Rohani, Fani and others have used next generation sequencing to determine micro-RNAs implicated in severe COVID-19. Interestingly, we found that many of the miRNAs implicated in severe COVID-19, have been identified as potential targets for viral myocarditis as mentioned earlier (Table3). We summarized in Table 3 those miRNAs. The screening of the presence of such miRNAs can therefore be used to determine the likelihood of recipients of mRNA vaccines in developing myocarditis. This needs more studies regarding cost-effectiveness given the relative rarity of the complication. (48–50)

2-Therapeutic targets:

MicroRNAs (miRNA) have recently become attractive targets for therapeutic intervention. The rationale for developing miRNA therapeutics is based on the premise that aberrantly expressed miRNAs play key roles in the development of human disease, and that correcting these miRNA deficiencies by either antagonizing or restoring miRNA function may provide a therapeutic benefit. Myocarditis, and advanced or end-stage heart failure, poses significant challenge as all the available medications, including the newest sacubitril-valsartan or ivabradine, do not abolish the need for cardiac transplantation. Cardiac transplantation is a difficult procedure and is not always an available option due to long waiting times on transplant lists, and lack of standardized policy regarding brain0stem dead donors. Therefore, those conditions have become among the first where clinical trials of miRNAs therapeutics have been implemented.

a-Direct use of miRNAs

The microRNA-132-3p (miR-132) is a regulatory (noncoding) RNA that, in response to cardiomyocyte stress, is upregulated in cardiac tissue. It affects signaling pathways involved in cardiomyocyte growth, autophagy, calcium handling, and contractility. Thus, miR-132 appears as a potentially promising molecular pathophysiological target in HF treatment. CDR132L, a synthetic locked nucleic acid antisense oligonucleotide (ASO) inhibitor with a fully phosphorylated backbone, is a first-in-class miR-132 inhibitor.

A prospective, randomized, double-blind, placebo-controlled, dose-ranging study of intravenous CDR132L was performed by Täubel and colleagues on twenty-eight HF patients, with left ventricular ejection fraction between $\geq 30\%$ and $< 50\%$ or amino terminal fragment of pro-brain natriuretic peptide (NT-proBNP) > 125 ng/L at screening, were randomized to receive CDR132L (0.32, 1, 3, and 10 mg/kg body weight) or placebo (0.9% saline). CDR132L treatment resulted in a dose-dependent, sustained miR-132 reduction in plasma. Patients given CDR132L ≥ 1 mg/kg displayed a median 23.3% NT-proBNP reduction, vs. a 0.9% median increase in the control group. CDR132L treatment induced significant QRS narrowing and encouraging positive trends for relevant cardiac fibrosis biomarkers. CDR132L was safe and well tolerated, without apparent dose-limiting toxicity. A pharmacokinetic/pharmacodynamic dose modelling approach suggested an effective dose level at 1 mg/kg CDR132L.

It was found that not only the direct inhibition of a miRNA was proven useful, but that indirect inhibition can do wonders as well. (51)

b-Indirect modulation of miRNAs

***One method of indirect inhibition of a miRNA** included tackling a viral RNA helicase, responsible for miRNA expression. This has shown some encouraging results and has allowed us to ask a question; how can we correlate this discovery with the ongoing pandemic?

SARS COV2 is a single stranded RNA virus, and it has been recently established to cause myocarditis along with other cardiac morbidities, such as pericarditis and pericardial effusion. This is due to the highly ACE-2-expressive cardiomyocytes, with which the virus interacts, facilitating its entry.

Similarly, Coxsackievirus B3 is a single stranded RNA virus, which modern science has failed to find a vaccine against thanks to its everchanging surface capsid proteins allowing it to always escape the proper immune response.

To overcome this limitation, Soo-Hyeon Yun et al decided to investigate other CVB3 antiviral treatment options that tackle the virus throughout its life cycle such as a chemically modified enterovirus-2C inhibitor (E2CI). E2C is a viral RNA helicase that normally limits host protein synthesis. Accordingly, by inhibiting the E2C, a better chance is given to overcome virally induced cardiac morbidity. Soo-Hyeon Yun et al held a murine viral myocarditis model where CVB3 infected mice with & without E2CI were carefully studied. The 4-week survival rate of E2CI injected mice was significantly higher than their non-injected counterparts. Viral titers, myocardial inflammation, remodeling-induced cardiomyopathy all significantly dropped in treated mice.(52)

Comparably, Marie Pierre Lambert et al explored a similar correlation between certain RNA helicases and pro-neural microRNAs in mice, and how this intricate interplay can affect neurogenesis or lack of. According to the aforementioned paper, DDX17 & DDX5 are both ATP-dependent RNA helicases that virtually regulate most steps of gene expression, cell fate switches, biological transition and nuclear maturation of some miRNAs' precursors through interaction with their microprocessor components. REST factor suppresses a number of neuronal genes in non-neuronal cells & is especially regulated by said helicases. MiR-26a is the main DDX17/DDX5 dependent neuronal miRNA present in mammals expressed from 2 different genetic loci that generate 2 precursors: pri-mir26a1 and pri-mir26a2, where the miR-26a's main pool comes from the latter. It was found that, in the presence of DDX17, processing and cleavage of pri-mir26a2 were enhanced, resulting in lack of neurogenesis. On the other hand, silencing of DDX17 results in an accumulation of pri-mir26a2 due to its lack of proper processing and cleavage, which in return promotes neurogenesis. In addition to that, accumulated pri-mir26a2 exerted negative feedback on DDX17, which in exchange decreased REST factor's binding to its target promoters favoring further neurogenesis.

Taking the previous two models into consideration, we hypothesize that if we can conduct an inhibitory approach concerning SARS-COV2 viral helicases, we might be able to similarly upregulate certain beneficial myocardial miRNA which will promote reversed myocardial remodeling when it comes to virally induced myocarditis. (53)

REST=Repressor Element 1-silencing transcription

****Another promising method of indirect inhibition of a miRNA*** was displayed in the following drug's mechanism of action.

Pirfenidone, an oral, small molecule, anti-fibrotic agent that acts by inhibiting the activation of cardiac fibroblasts, and inhibiting the production of peptides, such as transforming growth factor- β . It also works by antisense oligonucleotides directed against cardiotropic long non coding RNA (miRNA, lncRNA), silencing miRNA -21 that promotes cardiac fibrosis, therefore it manages to diminish fibroblast proliferation and collagen type 1 production and crosslinking that causes heart fibrosis.

It is used in idiopathic pulmonary fibrosis.

In a randomized clinical trial conducted by Gavin A Lewis et al, to evaluate the efficacy of Pirfenidone in treatment of Heart Failure patients with preserved ejection fraction, Pirfenidone and Placebo were compared in the treatment of HFpEF in 47 participants of a mean age 78 years and mean myocardial Extracellular Volume 30%, shown by cardiac imaging 30%.

Results showed great reduction in ECV containing collagen and water from baseline in 52 weeks, where 100 capsules of pirfenidone that were taken (11 days ttt t target dose) resulted in mean ECV reduction at 52 weeks of 0.06%, with improvement in 8 out of 10 KCCQ score, including clinical improvements and log NT-proBNP reduction.

The reduction in log NT-proBNP with pirfenidone was suggested to be due to an improvement in left ventricular myocardial stiffness secondary to myocardial fibrosis regression.

The outcome of decrease in ECV in association with log NT-proBNP reduction, provides further support for its effect in decreasing heart fibrosis and thus the effectiveness of the drug in treatment of HFpEF, possibly through non-coding miRNA silencing. The drug is effective in the structural wise changes but not the hemodynamic changes occurring in Heart failure. So, RAAS inhibitors should be studied for cardiac hemodynamic effect, synergistically with pirfenidone.

Figure 4 summarizes the implications tackled in the article

Conclusion

We can conclude from the above that, miRNA upregulation or downregulation by mRNA vaccines might explain the myocarditis observed from such vaccines. This hypothesis explains why younger individuals are at higher risk of myocarditis, having a larger muscle mass with upregulation of key miRNA such as miRNA 155 being highly expressed in skeletal muscles. Recognition of this might lead to tailoring of multiple tools for risk stratification of this complication before receiving mRNA vaccines, such as sarcopenia index or testing for some key miRNAs (such as miRNA155). It can also have therapeutic tools by developing anti-sense miRNAs blocking the action of the implicated miRNAs and thus preventing the myocarditis process.

List Of Abbreviations

AMOs	Anti-miRNAs Oligonucleotides
Ang 2	Angiotensin 2
AR	Androgen Receptor
ASO	Anti-sense Oligonucleotide
Bcl-2	B-cell Lymphoma 2
Bcl-xl	B-cell Lymphoma extra large
CMV	Cytomegalovirus
COVID-19	Corona Virus Disease-2019
CVB3	Coxsackie Virus B3
DCM	Idiopathic Dilated Cardiomyopathy
E2CI	Enterovirus-2C inhibitor
EBV	Epstein Barr Virus
ECM	Extracellular Matrix
ECV	Extracellular Volume
FDA	Food and Drug Administration
HF	Heart Failure
HIT	Heparin-induced Thrombocytopenia
IFN	Interferon
IL	Interleukin
KSHV	Kaposi Sarcoma-like Herpes Virus
LNA	Locked Nucleic Acid
LVED	Left Ventricular End Diastolic
LVEF	Left Ventricular Ejection Fraction
LVFS	Left Ventricular Fractional Shortening
MICB	Micro-invasive Carcinoma of Breast
MiRNA	Micro RNA
MRNA	Messenger RNA
NK	Natural Killer
NT-proBNP	Amino Terminal Fragment of pro Brain Natriuretic Peptide
PCR	Polymerase Chain Reaction
PDCD4	Programmed Cell Death 4

RAAS	Renin Angiotensin Aldosterone System
REST	Repressor Element 1 Silencing Transcription
SARS	Severe Acute Respiratory Syndrome
SOCS-3	Suppressor of Cytokine Signaling3
TNF	Tumor Necrotic Factor
TUG	Taurine Up-regulated Gene
VMC	Viral Myocarditis

Tables

Table 1: Reported myocarditis cases from mRNA vaccines							
Reference number in the text and authors	Number of cases	Age Range	Sex	Type of involved vaccine	Vaccine dose after which myocarditis developed	Median time of onset of myocarditis after vaccination (in hours)	Remarks
5 Singh et al	1	24	M	Pfizer-BioN	2nd	72	
6 Hudson et al	2	22 & 24	M	Pfizer-BioN	2nd	72	
7 William et al	1	34	M	Moderna	2nd	72	
8 Tailor	1	44	M	Moderna	2nd	120	
9 Acharya et al	1	18	M	Pfizer-BioN Tech	2nd	72	
10 Dickey	6	17-37 (100% <50 y age)	M	Pfizer-BioN Tech & Moderna	2nd	72	
11 Vidula et al	2	18-19	2M & 3F	Pfizer-BioN Tech & Moderna	2nd	"50"	The series included 5 cases, among which only two were having myocarditis
12 Patrignani et al	1	56	M	Pfizer-BioN Tech	1st	4	History of COVID-19 infection
13 Tano et al	1	29	M	Moderna	1st	6	History of myocarditis 8 years before
14 Cereda et al	1	21	M	Pfizer-BioN	2nd	2	
15 Kim IC et al	1	24	M	Pfizer-BioN Tech	2nd	24	
16 Ryan , Montgomery et al	23	20-51 (Exact age distribution not reported among cases)	M	7 received Pfizer-BioN Tech & 16 received Moderna	2 nd in all but 3 cases	50	The three cases developing myocarditis from first dose had previous COVID-19 infection
17 Kim HW et al	4	23-70 (75% <50 y age, 25% >50 y age)	3M 1 F	2 received Pfizer-BioN 2 Received Moderna	2nd	"50"	
18 Muthukumar et al	1	52	M	Moderna	2nd	72	
19 Abu Mouch et al	6	16-45 (100% <50	M	Pfizer-BioN	2 nd in 5	"48"	The only patient

		<i>y age)</i>		Tech	and 1 st in 1		developing myocarditis in this series after first dose, developed it after 16 days of this dose
20 Larson et al	8	21-56 (87.5% <50 y age, 12.5% >50 y age)	M	5 received Pfizer and 3 received Moderna	2 nd in all but one	"72"	The only patient developing myocarditis in this series after first dose, had previous COVID-19 infection
21 Marshall et al	7	14-19 (100% <50 y age)	M	Pfizer-BioN	2nd	"72"	
22 Albert et al	1	24	M	Moderna	2nd	96	
23 Bautista et al	1	39	M	Pfizer-BioN	2nd	144	
24 Rosner et al	7	19-39	M	Pfizer-BioN	2nd except in 1 case	72	The only patient developing myocarditis in this series after first dose, developed it after 7 days of this dose
25 Ammirati et al	1	56	M	Pfizer-BioN	2nd	72	
26 McLean et al	1	16	M	Pfizer-BioN	2nd	60	
27 D'Angelo et al	1	30	M	Pfizer-BioN	2nd	72	
28 Snapiriet al	7	16-18	M	Pfizer-BioN	2nd except in 1 case	48	The case developing myocarditis after 1st dose had positive COVID19 serology
29 Mansour et al	2	25	M	Moderna	2nd	27	
30 Minocha et al	1	21	F	Pfizer-BioN	2nd	48	Previous history of myocarditis 8 month ago

Table 2: DNA and RNA viruses producing miRNAs, the numbers of miRNAs discovered for each

Virus Family	Type	Number of encoded pre-miRNAs and miRNAs
γ -Herpesvirus	DNA	40 pre-miRNAs and 4 mature miRNAs
β -Herpesvirus	DNA	26 miRNAs related mainly to HCMV
α -Herpesvirus	DNA	24 functional miRNAs
Papillomavirus	DNA	Four (two by HPV16, one by HPV38, and one by HPV68)
Hepadnavirus	DNA	only one
Adenovirus	DNA	encodes two miRNAs
Polyomavirus	DNA	one pre-miRNA at the 3' end that encodes two mature miRNAs
Influenza Virus	RNA	encodes small viral leader miRNAs
Ebola Virus	RNA	seven mature miRNAs from four pre-miRNAs
HIV-1	RNA	five putative pre-miRNAs

Abbreviations: DNA: Deoxy-Ribonucleic acid, HCMV: Human Cytomegalovirus, HIV: Human immunodeficiency virus, HPV: Human Papilloma Virus, miRNA: Micro Ribonucleic acid.

Table 3: Host miRNA profiles shared in viral myocarditis as well as severe COVID-19 (References in text:41, 49,50)

	Functions
-5p, 3p and -3p ated	They are expressed on immune cells and play a role in both innate immunity and myocardial infarction. They regulate the synthesis and release of pro-inflammatory cytokines in the heart through Toll-like (TRL) receptors and their downstream signaling cascade, which includes the transcription nuclear factor-kappa B (NF-κB). The three were among the most deregulated miRNAs upon SARS-CoV infection.
-5p ated	Significantly up-regulated in severe COVID-19 infection. One of the miRNAs that are persistently modulated in both human and mouse viral myocarditis. It attributes to myocardial damage by modulating monocyte-macrophage cardiac infiltration and T lymphocyte activation. It is expressed in immune cells and involved in both innate immune response and myocardial infarction or HF. Toll-like (TRL) receptors and their downstream signaling cascade, involving the transcription nuclear factor-kappa B (NF-κB), control the synthesis and secretion of pro-inflammatory cytokines in the heart.
3p ated	It inhibits the release of anti-inflammatory cytokines and triggers the release of pro-inflammatory cytokines by targeting PDCD4 (Programmed Cell Death 4), one of the components of the NF-κB pathway. Initially, high levels were linked to serious disease. However, upon further classification into low and high miR concentrations divided by the median concentration, Lower miR-21 levels were associated with more ventilation and vasopressor days, as well as a greater rate of extracorporeal membrane oxygenation (ECMO) and renal replacement therapy. Despite possible association, further research is necessary due to inconsistent results. It's expressed on immune cells and plays a role in both innate immunity and myocardial infarction. It regulates the synthesis and release of pro-inflammatory cytokines in the heart through Toll-like (TRL) receptors and their downstream signaling cascade, which includes the transcription nuclear factor-kappa B (NF-κB).
-3p gulated	Through increasing glucose metabolism and inhibiting granulocyte activation, it appears to have cardio-protective and anti-inflammatory properties. As a result, diabetes and CVDs have been linked to a reduction in miR-223-3p levels in tissue and plasma.
-5p, with a-5p ated	They are responsible for fine-tuning of macrophage inflammatory response via regulation of NF-κB activity through a unique regulatory network. The activation of NF-κB by a stressor, promotes miR-155-5p production, which amplifies NF-κB activity and allows for a powerful macrophage activation. MiR-146a-5p transcription is enhanced as the inflammatory response progresses, blocking its targets IRAK1 and TRAF6, and decreasing NF-κB activation.
-3p iR-499- ated	They were found to be increased in the plasma of individuals with viral cardiomyopathy, and their levels were found to correlate with myocardial damage as measured by Troponin T levels. They were significantly up-regulated in COVID-19 patients, inducing myocardial damage. Increased levels were linked to elevated procalcitonin and lactate levels. In COVID-19 survivors, upregulation of miR-21, miR155, miR-208a, and miR-499 could be a predictor of chronic myocardial injury and inflammation. Despite, the fact that troponin levels were higher in the

	Influenza-ARDS group, COVID-19 had higher levels of cardiac specific miR-208a and miR-499.
b, miR-d miR-	It has been discovered to target ACE2, and in vitro investigations have shown that miR-200c regulation regulates ACE2 expression.
ated	It is involved in CVDs and is upregulated by oxidative stress. This indicates that miR200c-mediated regulation of ACE2 may be essential for SARS-COV-2 entry.
a	It is associated with macrophage infiltration, cardiac injury, enhanced LV function, and clinical prognosis.
gulated	

Abbreviations:

ACE: Angiotensin Converting Enzyme, COVID-19: Coronavirus disease 2019, CVD: Cardiovascular disease, IL-1R-associated kinase 1: IRAK, LV: Left Ventricle, miR: Micro-Ribonucleic acid, NF: Nuclear Factor, PD: Programmed death, SARS-CoV: severe acute respiratory syndrome coronavirus, TLR: Toll like receptor.

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Figures

Figure 1

Age Distribution among patients developing myocarditis after mRNA-based COVID-19 vaccines Abbreviations: COVID-19: Coronavirus disease 2019, mRNA: messenger Ribonucleic acid

Figure 2

Sex Distribution among patients developing myocarditis after mRNA-based COVID-19 vaccines Abbreviations: COVID-19: Coronavirus disease 2019, mRNA: messenger Ribonucleic acid

Figure 3

Patients developing myocarditis after 1st dose vs. 2nd dose of mRNA-based COVID-19 vaccines Abbreviations:
COVID-19: Coronavirus disease 2019, mRNA: messenger Ribonucleic acid

THE POTENTIAL ROLE OF MICRO RNAs IN mRNA VACCINES' MYOCARDITIS

mRNA

mRNA vaccines might interact with human cellular machinery to upregulate certain micro RNAs, notably miRNA 155 which causes myocarditis

Diagnostic implications

Screening for certain miRNA such as 155 before receiving mRNA vaccines might help to determine who is at high likelihood of this complication

Therapeutic Implications

Recipients who develop this complication might benefit from inhibitory therapy to implicated micro RNA Such as anti sense miRNA 155 or pirfenidone or helicase inhibitors

Why are most cases below the age of 50?

Due to loss of muscle mass after age of 50 with subsequent reduction of key micro RNAs such as 155 being highly expressed in muscles

Sarcopenia Index can be used to stratify recipients of mRNA vaccine -The lower the index the lower the muscle mass, the lower the likelihood of myocarditis from mRNA vaccines.

Figure 4

The potential role of micro-RNAs in mRNA-based vaccines Abbreviations: COVID-19: Coronavirus disease 2019, mRNA: messenger Ribonucleic acid, miRNA: Micro Ribonucleic acid