Elenco dei rischi associati alla vaccinazione anti SARS-COV-2 secondo il documento EMA di settembre 2022

Important identified risks	Myocarditis and pericarditis
Important potential risks	Vaccine-associated enhanced disease (VAED) including vaccine associated enhanced respiratory disease (VAERD)
Missing information	Use in pregnancy and while breast feeding
	Use in immunocompromised patients
	Use in frail patients with co-morbidities (eg, chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)
	Use in patients with autoimmune or inflammatory disorders
	Interaction with other vaccines Long term safety data

Incidenza di mio-pericardite ed eventi cardiovascolari acuti in Israele tra vaccinati vs non vaccinati

Increased emergency cardiovascular events among under-40 population in Israel during vaccine rollout and third COVID-19 wave (Scientific Communication 2022)

Cardiovascular adverse conditions are caused by coronavirus disease 2019 (COVID-19) infections and reported as side-effects of the COVID-19 vaccines. Enriching current vaccine safety surveillance systems with additional data sources may improve the understanding of COVID-19 vaccine safety. Using a unique dataset from Israel National Emergency Medical Services (EMS) from 2019 to 2021, the study aims to evaluate the association between the volume of cardiac arrest and acute coronary syndrome EMS calls in the 16–39-year-old population with potential factors including COVID-19 infection and vaccination rates. **An increase of over 25% was detected in both call types during January–May 2021, compared with the years 2019–2020.** Using Negative Binomial regression models, the weekly emergency call counts were significantly associated with the rates of 1st and 2nd vaccine doses administered to this age group but were not with COVID-19 infection rates. While not establishing causal relationships, the findings raise concerns regarding vaccine-induced undetected severe cardiovascular side-effects and underscore the already established causal relationship between vaccines and myocarditis, a frequent cause of unexpected cardiac arrest in young individuals. Surveillance of potential vaccine side-effects and COVID-19 outcomes should incorporate EMS and other health data to identify public health trends (e.g., increased in EMS calls), and promptly investigate potential underlying causes.

The Incidence of Myocarditis and Pericarditis in Post COVID-19 Unvaccinated Patients—A Large Population-Based Study (J.Clin.Med 2022)

Myocarditis and pericarditis are potential post-acute cardiac sequelae of COVID-19 infection, arising from adaptive immune responses. We aimed to study the incidence of post-acute COVID-19 myocarditis and pericarditis. Retrospective cohort study of 196,992 adults after COVID-19 infection in Clalit Health Services members in Israel between March 2020 and January 2021. Inpatient myocarditis and pericarditis diagnoses were retrieved from day 10 after positive PCR. Follow-up was censored on 28 February 2021, with minimum observation of 18 days. The control cohort of 590,976 adults with at least one negative PCR and no positive PCR were age- and sex-matched. Since the Israeli vaccination program was initiated on 20 December 2020, the time-period matching of the control cohort was calculated backward from 15 December 2020. Nine post-COVID-19 patients developed myocarditis (0.0046%), and eleven patients were diagnosed with pericarditis (0.0056%). In the control cohort, 27 patients had myocarditis (0.0046%) and 52 had pericarditis (0.0088%). Age (adjusted hazard ratio [aHR] 0.96, 95% confidence interval [CI]; 0.93 to 1.00) and male sex (aHR 4.42; 95% CI, 1.64 to 11.96) were associated with myocarditis. Male sex (aHR 1.93; 95% CI 1.09 to 3.41) and peripheral vascular disease (aHR 4.20; 95% CI 1.50 to 11.72) were associated with pericarditis. Post COVID-19 infection was not associated with either myocarditis (aHR 1.08; 95% CI 0.45 to 2.56) or pericarditis (aHR 0.53; 95% CI 0.25 to 1.13). **We did not observe an increased incidence of neither pericarditis nor myocarditis in adult patients recovering from COVID-19 infection.**

OpenSAFELY: Effectiveness of COVID-19 vaccination in children and adolescents

Colm D Andrews[1], Edward P K Parker[2], Elsie Horne[4], Venexia Walker[4], Tom Palmer[4], Andrea L Schaffer[1], Amelia CA Green[1], Helen J Curtis[1], Alex J Walker[1], Lucy Bridges[1], Christopher Wood[1], Victoria Speed[1], Christopher Bates[3], Jonathan Cockburn[3], John Parry[3], Amir Mehrkar[1], Brian MacKenna[1], Sebastian CJ Bacon[1], Ben Goldacre[1], Miguel A Hernan[5], Jonathan AC Sterne[4], The OpenSAFELY Collaborative, and William J Hulme[1].

Abstract

Background Children and adolescents in England were offered BNT162b2 as part of the national COVID-19 vaccine roll out from September 2021. We assessed the safety and effectiveness of first and second dose BNT162b2 COVID-19 vaccination in children and adolescents in England.

Methods With the approval of NHS England, we conducted an observational study in the OpenSAFELY-TPP database, including a) adolescents aged 12-15 years, and b) children aged 5-11 years and comparing individuals receiving i) first vaccination with unvaccinated controls and ii) second vaccination to single-vaccinated controls. We matched vaccinated individuals with controls on age, sex, region, and other important characteristics. Outcomes were positive SARS-CoV-2 test (adolescents only); COVID-19 A&E attendance; COVID-19 hospitalisation; COVID-19 critical care admission; COVID-19 death, with non-COVID-19 death and fractures as negative control outcomes and A&E attendance, unplanned hospitalisation, pericarditis, and myocarditis as safety outcomes.

Results Amongst 820,926 previously unvaccinated adolescents, the incidence rate ratio (IRR) for positive SARS-CoV-2 test comparing vaccination with no vaccination was 0.74 (95% CI 0.72-0.75), although the 20-week risks were similar. The IRRs were 0.60 (0.37-0.97) for COVID-19 A&E attendance, 0.58 (0.38-0.89) for COVID-19 hospitalisation, 0.99 (0.93-1.06) for fractures, 0.89 (0.87-0.91) for A&E attendances and 0.88 (0.81-0.95) for unplanned hospitalisation. Amongst 441,858 adolescents who had received first vaccination IRRs comparing second dose with first dose only were 0.67 (0.65-0.69) for positive SARS-CoV-2 test, 1.00 (0.20-4.96) for COVID-19 A&E attendance, 0.60 (0.26-1.37) for COVID-19 hospitalisation, 0.94 (0.84-1.05) for fractures, 0.93 (0.89-0.98) for A&E attendance and 0.99 (0.86-1.13) for unplanned hospitalisation. Amongst 283,422 previously unvaccinated children and 132,462 children who had received a first vaccine dose, COVID-19-related outcomes were too rare to allow IRRs to be estimated precisely. A&E attendance and unplanned hospitalisation were slightly higher after first vaccination (IRRs versus no vaccination 1.05 (1.01-1.10) and 1.10 (0.95-1.26) respectively) but slightly lower after second vaccination (IRRs versus first dose 0.95 (0.86-1.05) and 0.78 (0.56-1.08) respectively). There were no COVID-19-related deaths in any group. Fewer than seven (exact number redacted) COVID-19-related critical care admissions occurred in the adolescent first dose vs unvaccinated cohort. Among both adolescents and children, myocarditis and pericarditis were documented only in the vaccinated groups, with rates of 27 and 10 cases/million after first and second doses respectively.

Conclusion BNT162b2 vaccination in adolescents reduced COVID-19 A&E attendance and hospitalisation, although these outcomes were rare. Protection against positive SARS-CoV-2 tests was transient.

Journal of Infection and Chemotherapy 31 (2025) 102485

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journal homepage: www.elsevier.com/locate/jic

Original Article

SARS-CoV-2 mRNA vaccine-related myocarditis and pericarditis: An analysis of the Japanese Adverse Drug Event Report database

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ARTICLE INFO

Keywords:
Japanese Adverse Drug Event Report database
BNT162b2
mRNA-1273
Myocarditis
Pericarditis

ABSTRACT

Background: The association between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA vaccines and myocarditis/pericarditis in the Japanese population has not been systematically investigated. This study was aimed at clarifying the association between SARS-CoV-2 mRNA vaccines (BNT162b2 and mRNA-1273) and myocarditis/pericarditis as well as influencing factors by using the Japanese Adverse Drug Event Report database.

Methods: Reporting odds ratios (RORs) and 95 % confidence intervals (95 % CIs) for the association between the vaccines and myocarditis/pericarditis were calculated using data from the database (April 2004–December 2023). Age, sex, onset time, and outcomes in symptomatic patients were evaluated.

Results: The total number of reports was 880,999 (myocarditis: 1846; pericarditis: 761). The adverse events associated with the vaccines included myocarditis (919 cases) and pericarditis (321 cases), with the ROR [95 % CIs] being significant for both (myocarditis: 30.51 [27.82–33.45], pericarditis: 21.99 [19.03–25.40]). Furthermore, the ROR [95 % CIs] of BNT162b2 and mRNA-1273 were 15.64 [14.15–17.28] and 54.23 [48.13–61.10], respectively, for myocarditis, and 15.78 [13.52–18.42] and 27.03 [21.58–33.87], respectively, for pericarditis. Furthermore, most cases were ≤30 years or male. The period from vaccination to onset was ≤8 days, corresponding to early failure type based on analysis using the Weibull distribution. Outcomes were recovery or remission for most cases; however, they were severe or caused death in some cases.

Conclusion: In the Japanese population, SARS-CoV-2 mRNA vaccination was significantly associated with the onset of myocarditis/pericarditis. The influencing factors included age of ≤30 years and male. Furthermore, although most adverse events occurred early after vaccination, overall outcomes were good.

JAMA Cardiology | Original Investigation

SARS-CoV-2 Vaccination and Myocarditis in a Nordic Cohort Study of 23 Million Residents

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IMPORTANCE Reports of myocarditis after SARS-CoV-2 messenger RNA (mRNA) vaccination have emerged.

OBJECTIVE To evaluate the risks of myocarditis and pericarditis following SARS-CoV-2 vaccination by vaccine product, vaccination dose number, sex, and age.

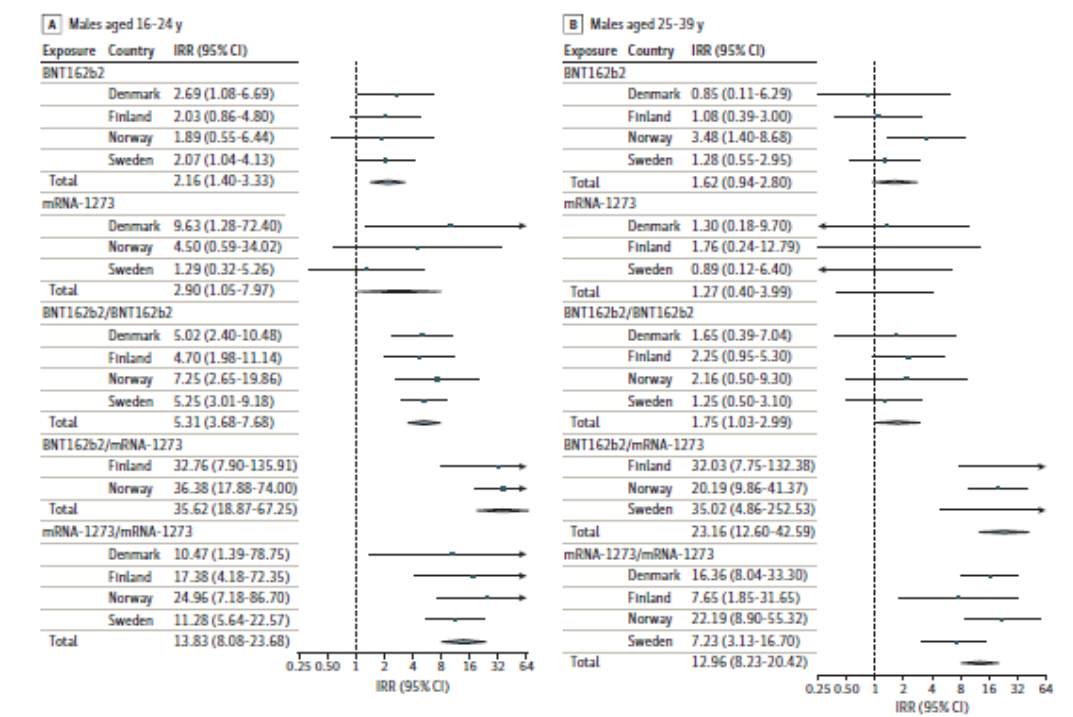
DESIGN, SETTING, AND PARTICIPANTS Four cohort studies were conducted according to a common protocol, and the results were combined using meta-analysis. Participants were 23 122 522 residents aged 12 years or older. They were followed up from December 27, 2020, until incident myocarditis or pericarditis, censoring, or study end (October 5, 2021). Data on SARS-CoV-2 vaccinations, hospital diagnoses of myocarditis or pericarditis, and covariates for the participants were obtained from linked nationwide health registers in Denmark, Finland, Norway, and Sweden.

EXPOSURES The 28-day risk periods after administration date of the first and second doses of a SARS-CoV-2 vaccine, including BNT162b2, mRNA-1273, and AZD1222 or combinations thereof. A homologous schedule was defined as receiving the same vaccine type for doses 1 and 2.

MAIN OUTCOMES AND MEASURES Incident outcome events were defined as the date of first inpatient hospital admission based on primary or secondary discharge diagnosis for myocarditis or pericarditis from December 27, 2020, onward. Secondary outcome was myocarditis or pericarditis combined from either inpatient or outpatient hospital care. Poisson regression yielded adjusted incidence rate ratios (IRRs) and excess rates with 95% CIs, comparing rates of myocarditis or pericarditis in the 28-day period following vaccination with rates among unvaccinated individuals.

RESULTS Among 23 122 522 Nordic residents (81% vaccinated by study end; 50.2% female), 1077 incident myocarditis events and 1149 incident pericarditis events were identified. Within the 28-day period, for males and females 12 years or older combined who received a homologous schedule, the second dose was associated with higher risk of myocarditis, with adjusted IRRs of 1.75 (95% CI, 1.43-2.14) for BNT162b2 and 6.57 (95% CI, 4.64-9.28) for mRNA-1273. Among males 16 to 24 years of age, adjusted IRRs were 5.31 (95% CI, 3.68-7.68) for a second dose of BNT162b2 and 13.83 (95% CI, 8.08-23.68) for a second dose of mRNA-1273, and numbers of excess events were 5.55 (95% CI, 3.70-7.39) events per 100 000 vaccinees after the second dose of BNT162b2 and 18.39 (9.05-27.72) events per 100 000 vaccinees after the second dose of mRNA-1273. Estimates for pericarditis were similar.

CONCLUSIONS AND RELEVANCE Results of this large cohort study indicated that both first and second doses of mRNA vaccines were associated with increased risk of myocarditis and pericarditis. For individuals receiving 2 doses of the same vaccine, risk of myocarditis was highest among young males (aged 16-24 years) after the second dose. These findings are compatible with between 4 and 7 excess events in 28 days per 100 000 vaccinees after BNT162b2, and between 9 and 28 excess events per 100 000 vaccinees after mRNA-1273. This risk should be balanced against the benefits of protecting against severe COVID-19 disease.



Clinical Infectious Diseases

MAJOR ARTICLE

Analysis of Myocarditis Among 252 Million mRNA-1273 Recipients Worldwide

Walter Straus,[1] Veronica Urdaneta,[1] Daina B. Esposito,[1] James A. Mansi,[2] Cesar Sanz Rodriguez,[2] Paul Burton,[2] and José M. Vega[1]

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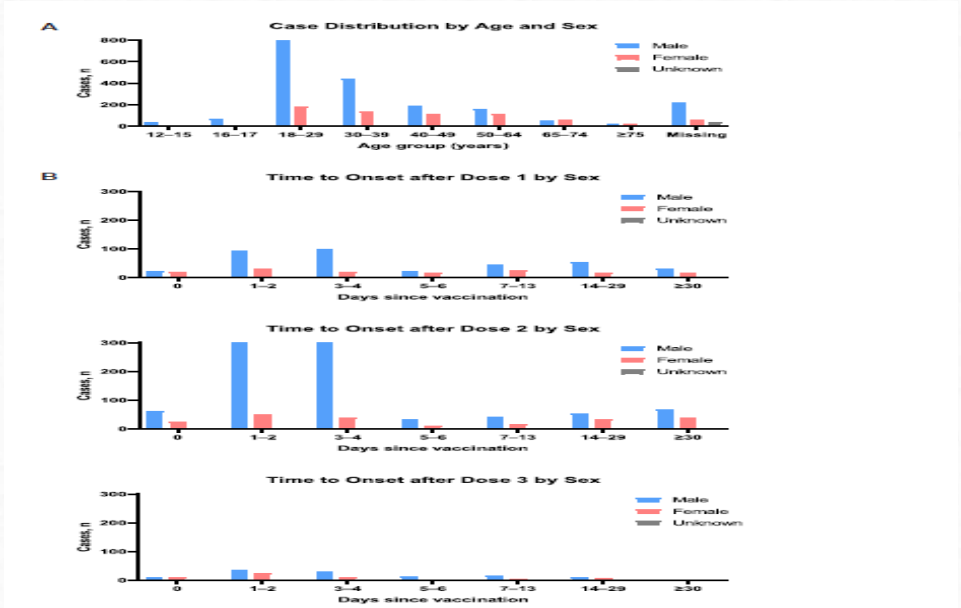
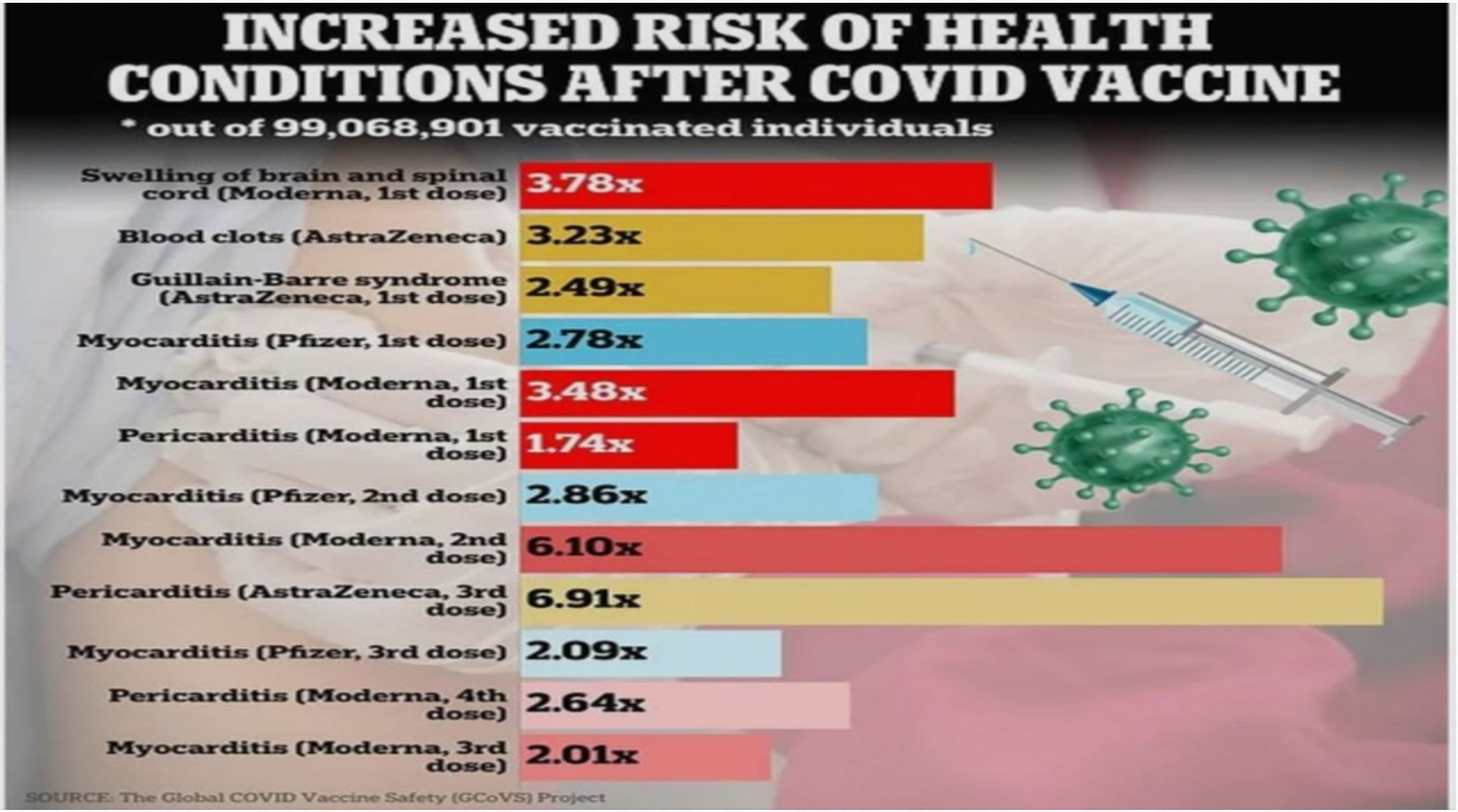
Background. Growing evidence indicates a causal relationship between SARS-CoV-2 infection and myocarditis. Post-authorization safety data have also identified myocarditis as a rare safety event following mRNA COVID-19 vaccination, particularly among adolescent and young-adult males after dose 2. We further evaluated the potential risk by querying the Moderna global safety database for myocarditis/myopericarditis reports among mRNA-1273 recipients worldwide.

Methods. Myocarditis/myopericarditis reports from 18 December 2020 to 15 February 2022 were reviewed and classified. The reported rate after any known mRNA-1273 dose was calculated according to age and sex, then compared with a population-based incidence rate to calculate observed-to-expected rate ratios (RRs).

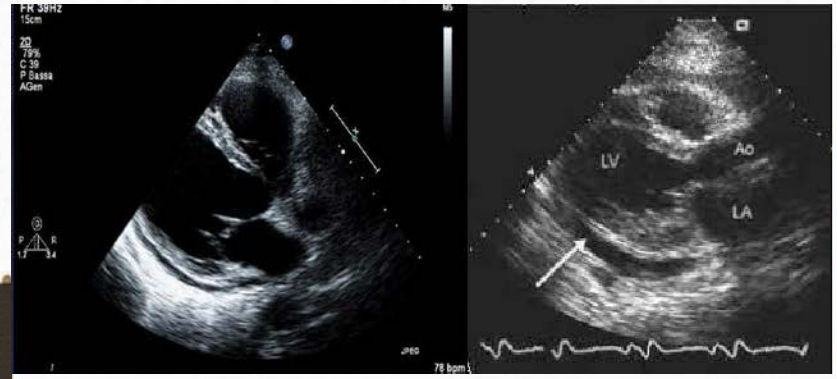
Results. During the study period, 3017 myocarditis/myopericarditis cases among 252 million mRNA-1273 recipients who received at least 1 dose were reported to the Moderna global safety database. The overall reporting rate was 9.23 per 100 000 person-years, which was similar to the expected reference rate (9.0 cases per 100 000 person-years; RR [95% confidence interval (CI)], 1.03 [.97–1.08]). When stratified by sex and age, observed rates were highest for males aged <40 years, particularly those 18–24 years (53.76 per 100 000 person-years), which was higher than expected (RR [95% CI], 3.10 [2.68–3.58]). When considering only cases occurring within 7 days of a known dose, the observed rate was highest for males aged 18–24 years after dose 2 (4.23 per 100 000 doses administered).

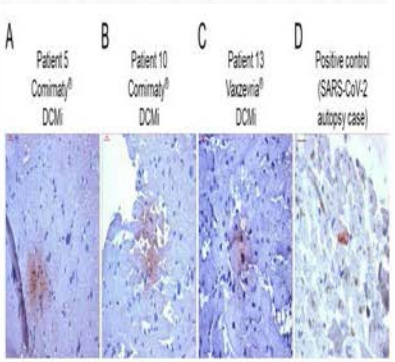
Conclusions. Myocarditis/myopericarditis rates were not higher than expected for the overall population of mRNA-1273 recipients but were higher than expected in males aged 18–24 years, with most cases occurring 7 days after dose 2.




INCREASED RISK OF HEALTH CONDITIONS AFTER COVID VACCINE
* out of 99,068,901 vaccinated individuals
Swelling of brain and spinal cord (Moderna, 1st dose)
3.78x
Blood clots (AstraZeneca)
3.23x
Guillain-Barre syndrome (AstraZeneca, 1st dose)
2.49x
Myocarditis (Pfizer, 1st dose)
2.78x
Myocarditis (Moderna, 1st dose)
3.48x
Pericarditis (Moderna, 1st dose)
1.74x
Myocarditis (Pfizer, 2nd dose)
2.86x
Myocarditis (Moderna, 2nd dose)
6.10x
Pericarditis (AstraZeneca, 3rd dose)
6.91x
Myocarditis (Pfizer, 3rd dose)
2.09x
Pericarditis (Moderna, 4th dose)
2.64x
Myocarditis (Moderna, 3rd dose)
2.01x
SOURCE: The Global COVID Vaccine Safety (GCoVS) Project

Miopericarditi e vaccinazione anti SARS-COV-2





1.Azione diretta della proteina spike sul tessuto miocardico (Int.J.Mol.Sci. 2022;23:6940) dimostrata mediante biopsia endomiocardica.

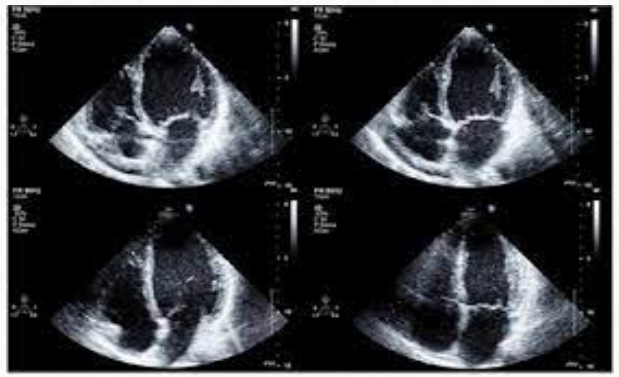
2.Azione combinata del vaccino e della variante naturale vaccino-resistente per effetto ADE

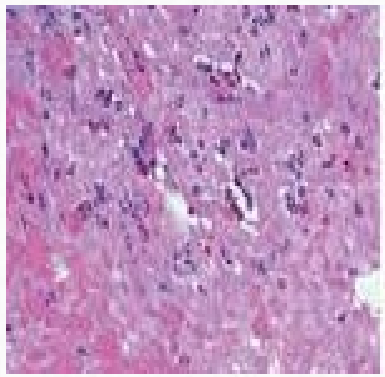
3.Azione autoimmune per reazione crociata con la titina o connectina miocardica.

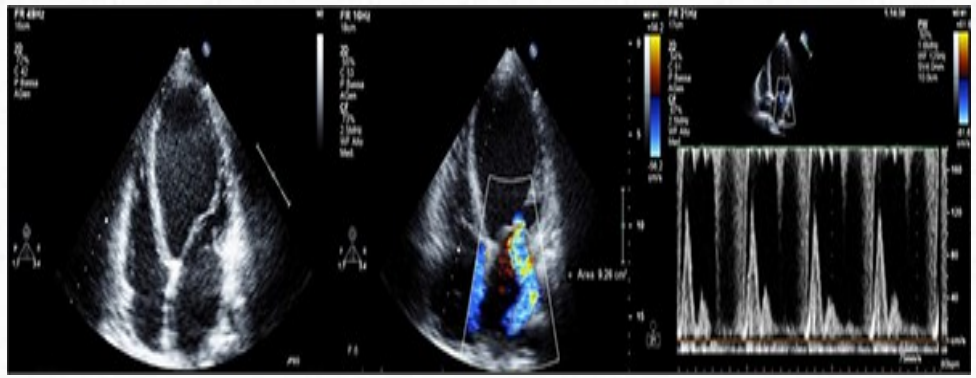
4.Riattivazione di virus cardiotropi (es, EBV,CVM, HIV-1) in relazione allo stato di immunodeficienza indotto dal vaccino (VAIDS).

5.Miocardite ipereosinofila (sindrome ipereosinofila, spesso associata a reazione allergica ad eccipienti del vaccino come PEG, polisorbato 80 e trometamina)

6.Miocardite catecolaminergica (necrosi a banda di contrazione) per incremento dei livelli di catecolamine







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Difficult-to-treat recurrent pericarditis after SARS-CoV-2 vaccination

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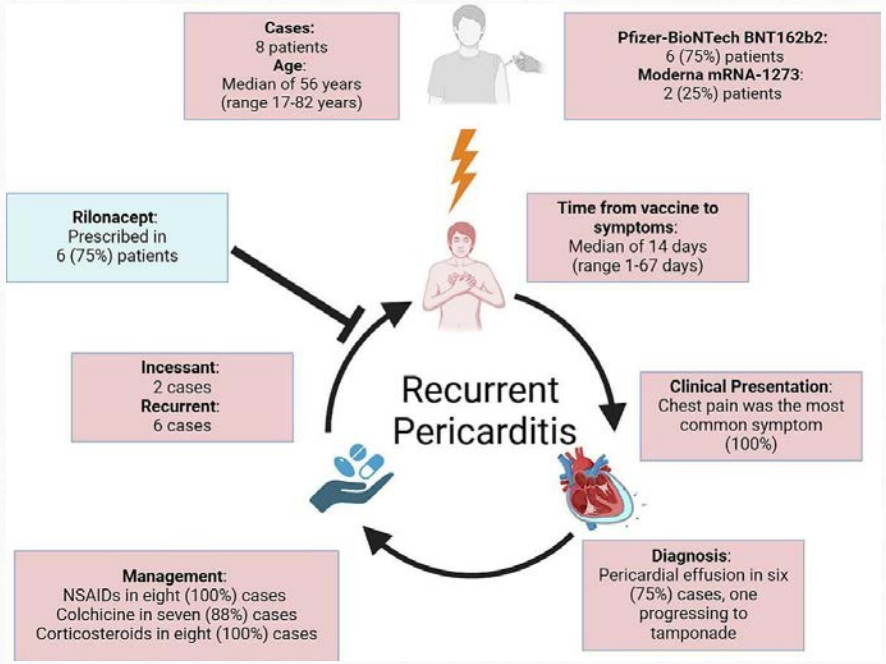
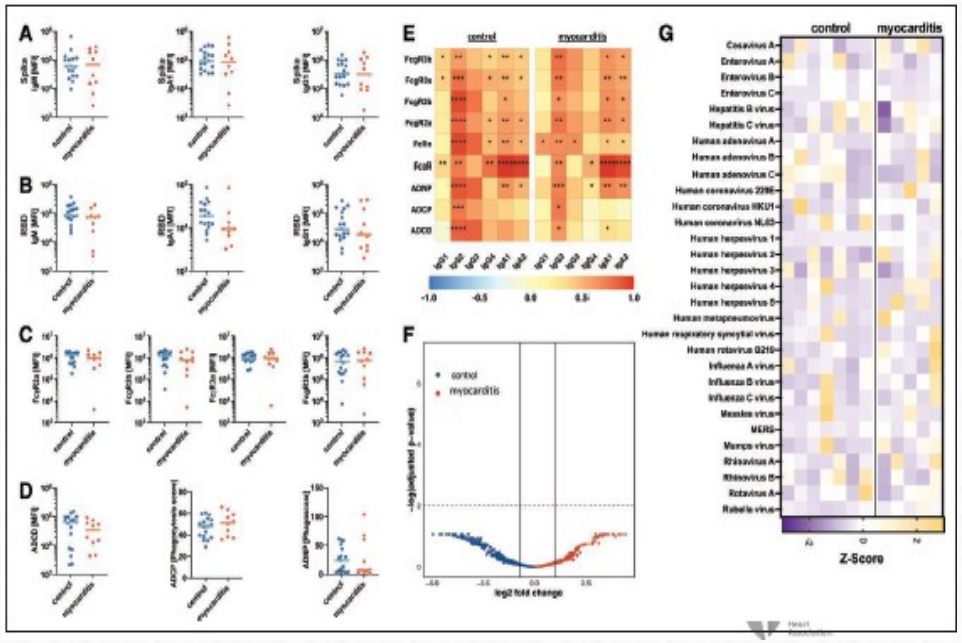
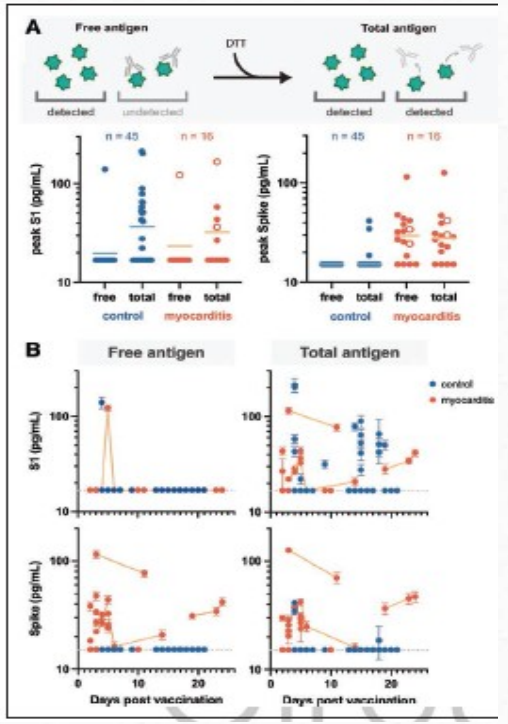
Introduction:
Pericarditis is a recognized but rare complication of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) vaccination. While most cases are self-limited, some develop recurrent, difficult-to-treat pericarditis, requiring prolonged management. The exact pathophysiology remains unclear, but vaccine-related immune activation and inflammasome-mediated responses have been implicated.
Methods:
We reported eight cases of difficult-to-treat pericarditis temporally associated with SARS-CoV-2 vaccination, seen at a single center between October 2021 and January 2025. Diagnosis followed ESC 2015 guidelines, and all patients tested negative for acute SARS-CoV-2 infection.
Results:
The median age was 56 years, with six receiving Pfizer-BioNTech BNT162b2 and two Moderna mRNA- 1273. For six individuals, this was their first episode of pericarditis, whereas two had a prior history of pericarditis. The median time to symptom onset was 14 days. Chest pain was reported by all patients, requiring emergency visits in six cases. Pericardial effusion was present in six patients, with one progressing to tamponade. Cardiac magnetic resonance revealed pericardial late gadolinium enhancement in three of seven patients. All patients received nonsteroidal anti-inflammatory drugs and seven were treated with colchicine. Due to inadequate response to first-line therapies, corticosteroids were administered in all eight cases. Due to persistent symptoms, six patients initiated rilonacept therapy, which led to complete symptom resolution.
Conclusions:
Pericarditis following SARS-CoV-2 vaccination can evolve into a recurrent, difficult-to-manage inflammatory condition. Effective treatment may require IL-1 blockade to disrupt the autoinflammatory cycle. Prompt recognition and early escalation of therapy are essential to reduce morbidity and prevent complications.

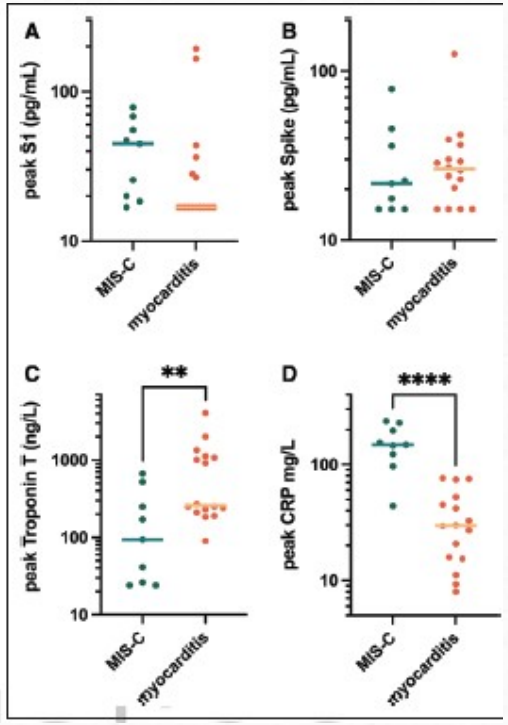


Circulating Spike Protein Detected in Post–COVID-19 mRNA Vaccine Myocarditis

Lael M. Yonker, MD*; Zoe Swank, PhD*; Yannic C. Bartsch, PhD*; Madeleine D. Burns, MS; Abigail Kane, MD; Brittany P. Boribong, PhD; Jameson P. Davis, BS; Maggie Loiselle, BS; Tanya Novak, PhD; Yasmeen Senussi, MBBS; Chi-An Cheng, PhD; Eleanor Burgess, MS; Andrea G. Edlow, MD; Janet Chou, MD; Audrey Dionne, MD; Duraisamy Balaguru, MD; Manuella Lahoud-Rahme, MD; Moshe Arditi, PhD; Boris Julg, MD, PhD; Adrienne G. Randolph, MD; Galit Alter, PhD; Alessio Fasano, MD†; David R. Walt, PhD†







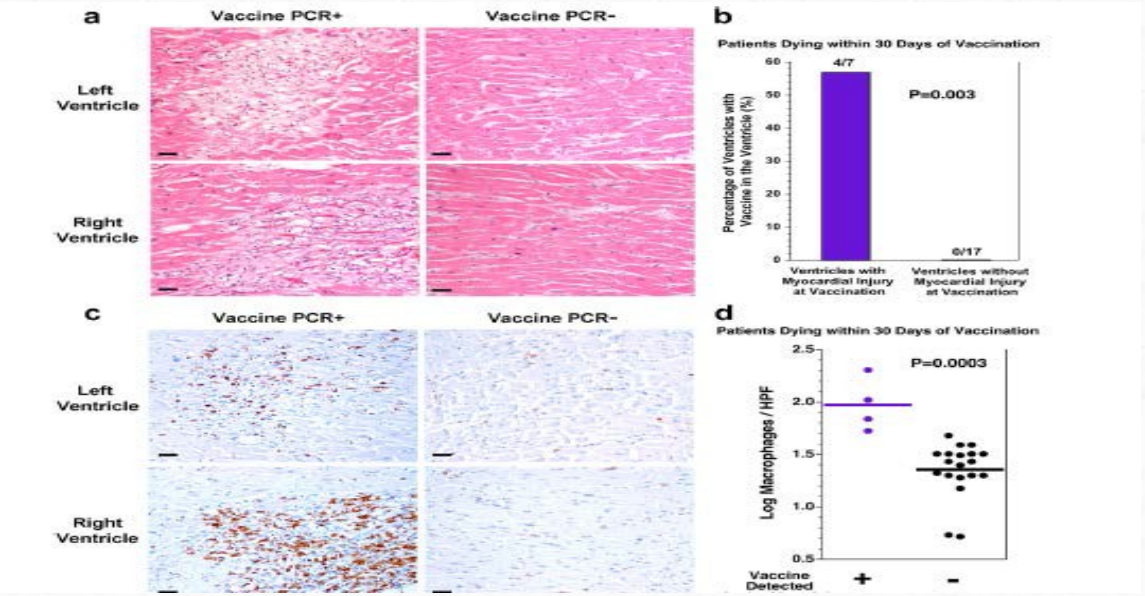
Circulation,2023

Duration of SARS-CoV-2 mRNA vaccine persistence and factors associated with cardiac involvement in recently vaccinated patients

Aram J. Krauson[1], Faye Victoria C. Casimero[1,2], Zakir Siddiquee[1] and James R. Stone[1,2]

At the start of the COVID-19 pandemic, the BNT162b2 (BioNTech-Pfizer) and mRNA-1273 (Moderna) mRNA vaccines were expediently designed and mass produced. Both vaccines produce the full-length SARS-CoV-2 spike protein for gain of immunity and have greatly reduced mortality and morbidity from SARS-CoV-2 infection. The distribution and duration of SARS-CoV-2 mRNA vaccine persistence in human tissues is unclear. Here, we developed specific RT-qPCR-based assays to detect each mRNA vaccine and screened lymph nodes, liver, spleen, and myocardium from recently vaccinated deceased patients. Vaccine was detected in the axillary lymph nodes in the majority of patients dying within 30 days of vaccination, but not in patients dying more than 30 days from vaccination. Vaccine was not detected in the mediastinal lymph nodes, spleen, or liver. Vaccine was detected in the myocardium in a subset of patients vaccinated within 30 days of death. Cardiac ventricles in which vaccine was detected had healing myocardial injury at the time of vaccination and had more myocardial macrophages than the cardiac ventricles in which vaccine was not detected. These results suggest that SARS-CoV-2 mRNA vaccines routinely persist up to 30 days from vaccination and can be detected in the heart.

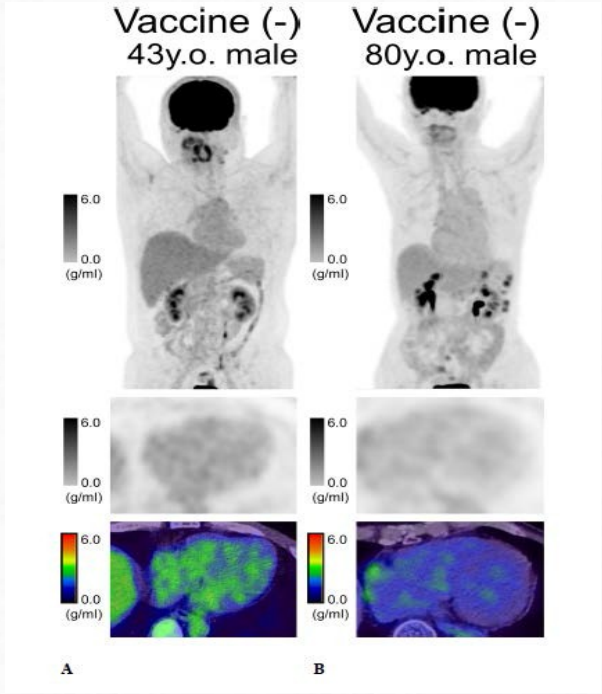
npj Vaccines (2023)8:141 ; https://doi.org/10.1038/s41541-023-00742-7

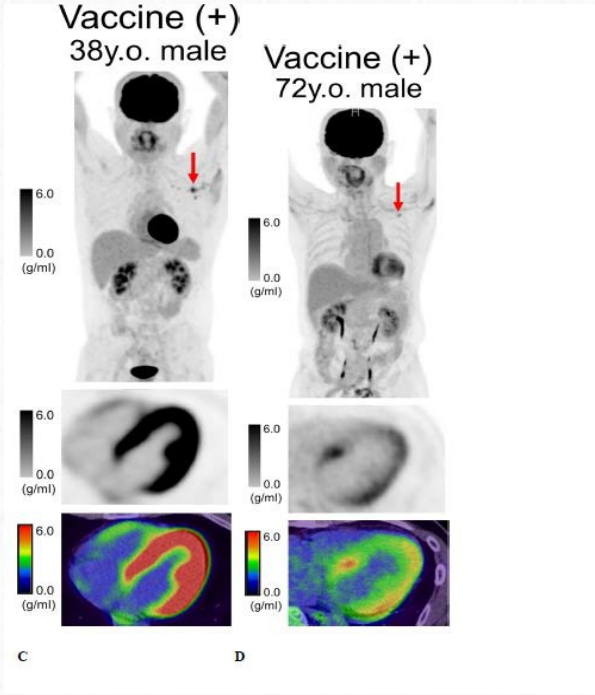


Assessment of Myocardial ^{18}F-FDG Uptake at PET/CT in Asymptomatic SARS-CoV-2-vaccinated and Nonvaccinated Patients

Manuscript type: Original Research

Takehiro Nakahara MD, PhD [a], Yu Iwabuchi MD, PhD [a], Raita Miyazawa MD[a], Kai Tonda MD[a], Tohru Shiga MD, PhD [a,b], H. William Strauss MD[c], Charalambos Antoniades MD, PhD [d], Jagat Narula MD, PhD [e], and Masahiro Jinzaki MD, PhD [a]





Radiology,2023

Cardiac side effects of RNA-based SARS-CoV-2 vaccines: Hidden cardiotoxic effects of mRNA-1273 and BNT162b2 on ventricular myocyte function and structure

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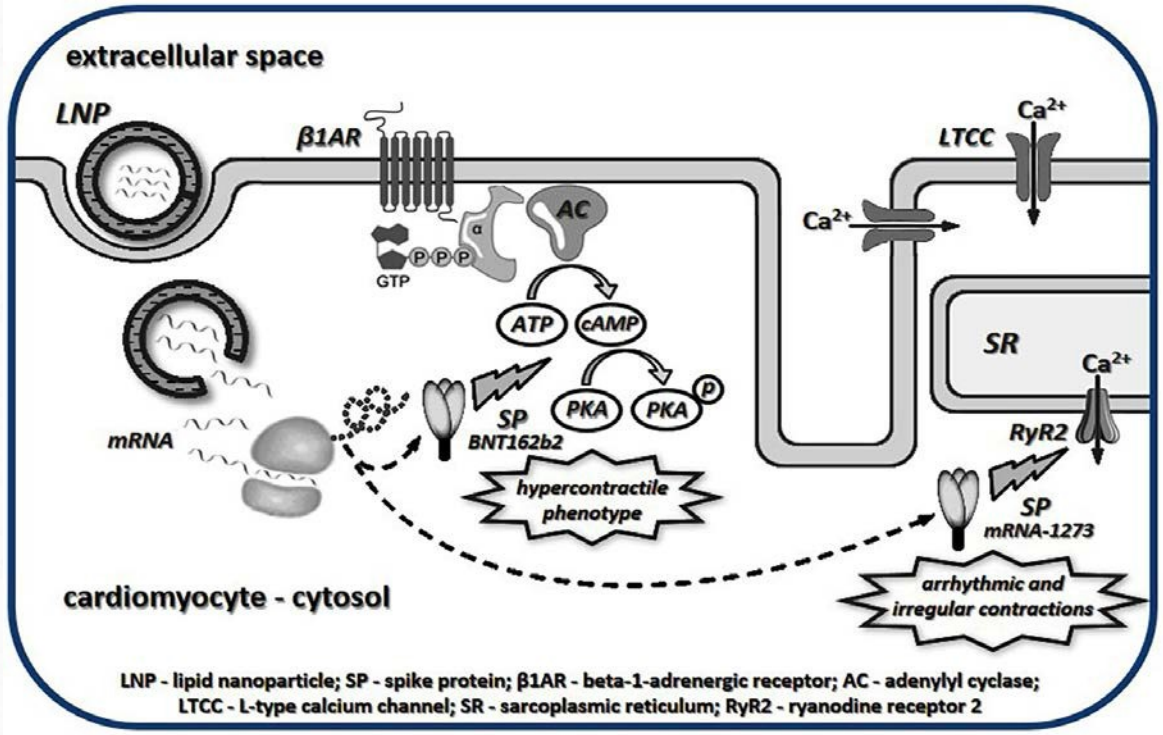
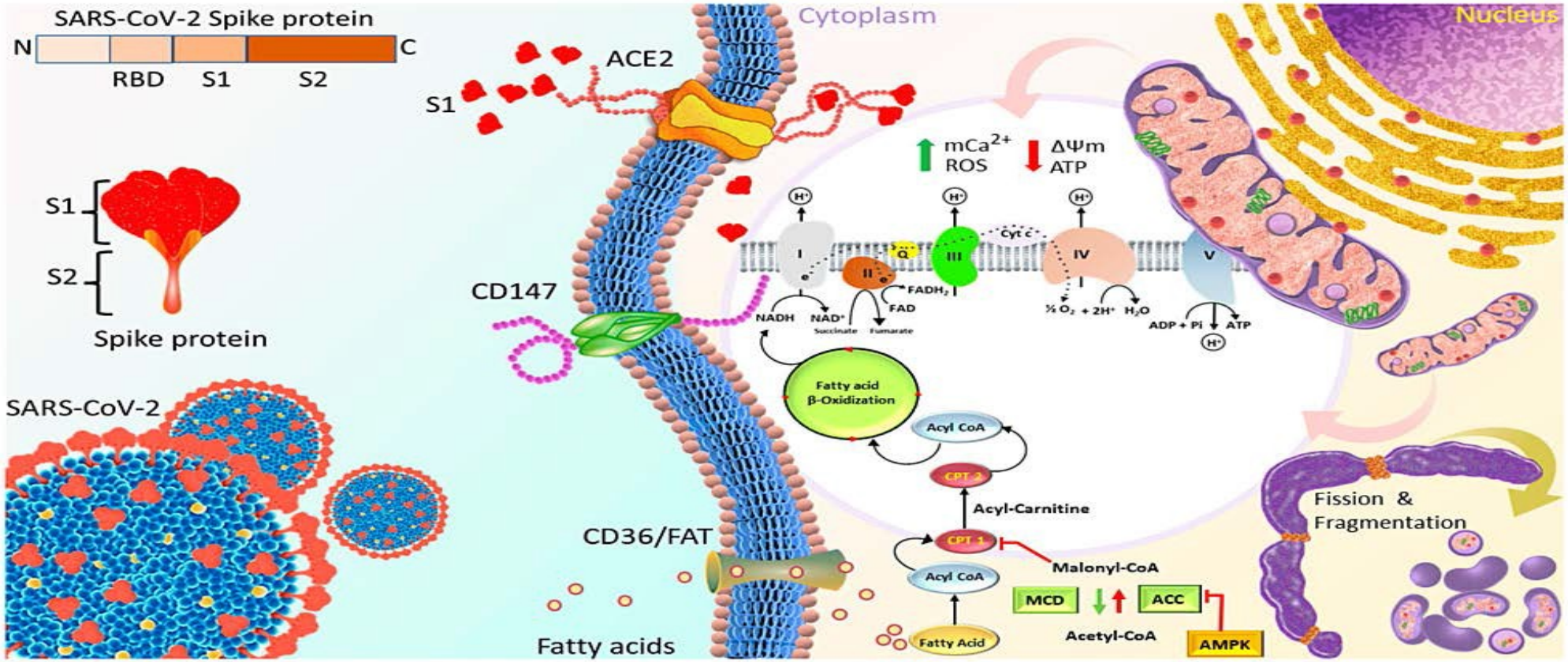
[3]Pharmahungary Group, 6722 Szeged, Hungary

British J.Pharmacol. 2023



Proposed Mechanisms Through Which S1 of Spike Protein Induced Cardiac Mitochondrial Dysfunction, Which Leads to Cardiac Injury in COVID-19 Patients.



Cureus 2023

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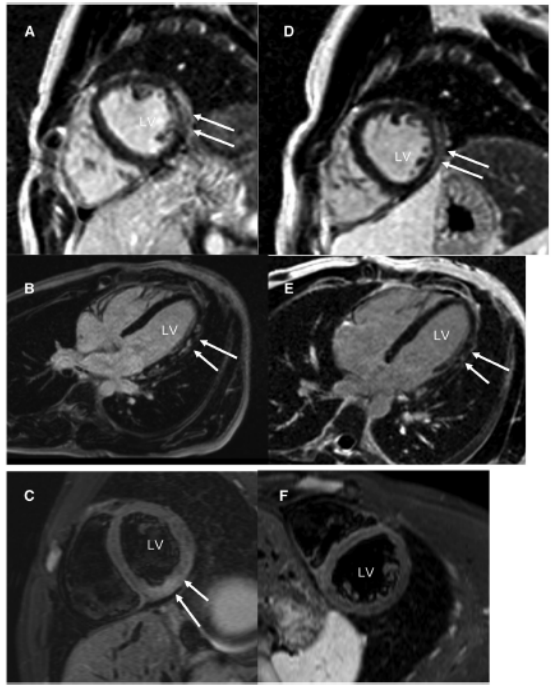
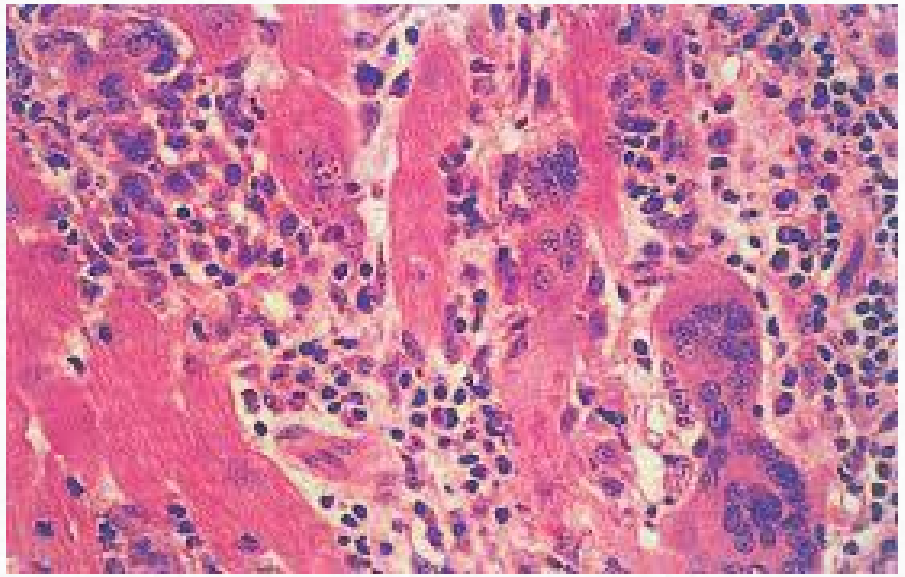
GRAND ROUNDS

Persistent Cardiac Magnetic Resonance Imaging Findings in a Cohort of Adolescents with Post-Coronavirus Disease 2019 mRNA Vaccine Myopericarditis

Jenna Schauer, MD[1], Sujatha Buddhe, MD, MS[1], Avanti Gulhane, MD, DNB, FSCMR[2], Eyal Sagiv, MD, PhD[1], Matthew Studer, MD[1], Jessica Colyer, MD, MBA[1], Sathish Mallenahalli Chikkabyrappa, MD[1], Yuk Law, MD[1], and Michael A. Portman, MD[1]





Cardiac manifestations and outcomes of COVID-19 vaccine-associated myocarditis in the young in the USA: longitudinal results from the Myocarditis After COVID Vaccination (MACiV) multicenter study

Supriya S. Jain,[a,*] Steven A. Anderson,[b] Jeremy M. Steele,[c] Hunter C. Wilson,[d] Juan Carlos Muniz,[e] Jonathan H. Soslow,[f] Rebecca S. Beroukhim,[g] Victoria Maksymiuk,[a] Xander Jacquemyn,[h] Olivia H. Frasch,[i] Brian Fonseca,[j] Ashraf S. Harahsheh,[k] Sujatha Buddhe,[l] Ravi C. Ashwath,[m] Deepika Thacker,[n] Shiraz A. Maskatia,[o] Nilanjana Misra,[p] Jennifer A. Su,[q] Saira Siddiqui,[r] Danish Vaiyani,[s] Aswathy K. Vaikom-House,[t] M. Jay Campbell,[u] Jared Klein,[v] Sihong Huang,[w] Christopher Mathis,[x] Matthew D. Cornicelli,[y] Madhu Sharma,[z] Lakshmi Nagaraju,[aa] Jocelyn Y. Ang,[ab] Santosh C. Uppu,[ac] Preeti Ramachandran,[ad] Jyoti K. Patel,[ae] Frank Han,[af] Jason G. Mandel,[ag] Jyothsna Akam-Venkata,[ah] Michael P. DiLorenzo,[ai] Michael Brumund,[aj] Puneet Bhatla,[ak] Parham Eshtehardi,[al] Karina Mehta,[am] Katherine Glover,[c] Matthew L. Dove,[d] Khalifah A. Aldawsari,[e] Anupam Kumar,[f] Spencer B. Barfuss,[g] Adam L. Dorfman,[i] Prashant K. Minocha,[j] Alexandra B. Yonts,[k] Jenna Schauer,[l] Andrew L. Cheng,[q] Joshua D. Robinson,[y] Zachary Powell,[t] Shubhika Srivastava,[n] Anjali Chelliah,[r] Yamuna Sanil,[ab] Lazaro E. Hernandez,[v] Lasya Gaur,[h] Michael Antonchak,[ak] Marla Johnston,[q] Jonathan D. Reich,[h] Narayan Nair,[h] Elizabeth D. Drugge,[a] and Lars Grosse-Wortmann[am]

Summary

Background We aimed to study the clinical characteristics, myocardial injury, and longitudinal outcomes of COVID-19 vaccine-associated myocarditis (C-VAM).

Methods In this longitudinal retrospective observational cohort multicenter study across 38 hospitals in the United States, 333 patients with C-VAM were compared with 100 patients with multisystem inflammatory syndrome in children (MIS-C). We included patients ≤30 years of age with a clinical diagnosis of acute myocarditis after COVID-19 vaccination based on clinical presentation, abnormal biomarkers and/or cardiovascular imaging findings. Demographics, past medical history, hospital course, biochemistry results, cardiovascular imaging, and follow-up information from April 2021 to November 2022 were collected. The primary outcome was presence of myocardial injury as evidenced by late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) imaging.

Findings Patients with C-VAM were predominantly white (67%) adolescent males (91%, 15.7 ± 2.8 years). Their initial clinical course was more likely to be mild (80% vs. 23%, $p < 0.001$) and cardiac dysfunction was less common (17% vs. 68%, $p < 0.0001$), compared to MIS-C. In contrast, LGE on CMR was more prevalent in C-VAM (82% vs. 16%, $p < 0.001$). The probability of LGE was higher in males (OR 3.28 [95% CI: 0.99, 10.6, $p = 0.052$]), in older patients (>15 years, OR 2.74 [95% CI: 1.28, 5.83, $p = 0.009$]) and when C-VAM occurred after the first or second dose as compared to the third dose of mRNA vaccine. Mid-term clinical outcomes of C-VAM at a median follow-up of 178 days (IQR 114–285 days) were reassuring. No cardiac deaths or heart transplantations were reported until the time of submission of this report. LGE persisted in 60% of the patients at follow up.

Interpretation Myocardial injury at initial presentation and its persistence at follow up, despite a mild initial course and favorable mid-term clinical outcome, warrants continued clinical surveillance and long-term studies in affected patients with C-VAM.

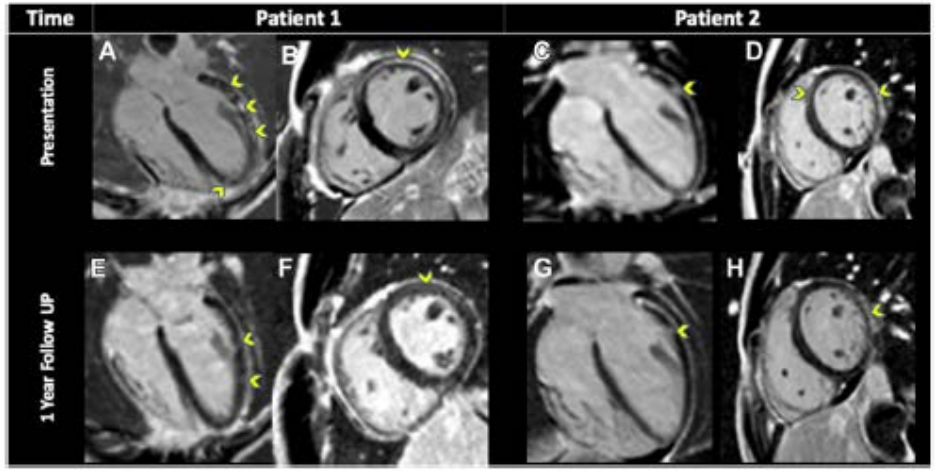
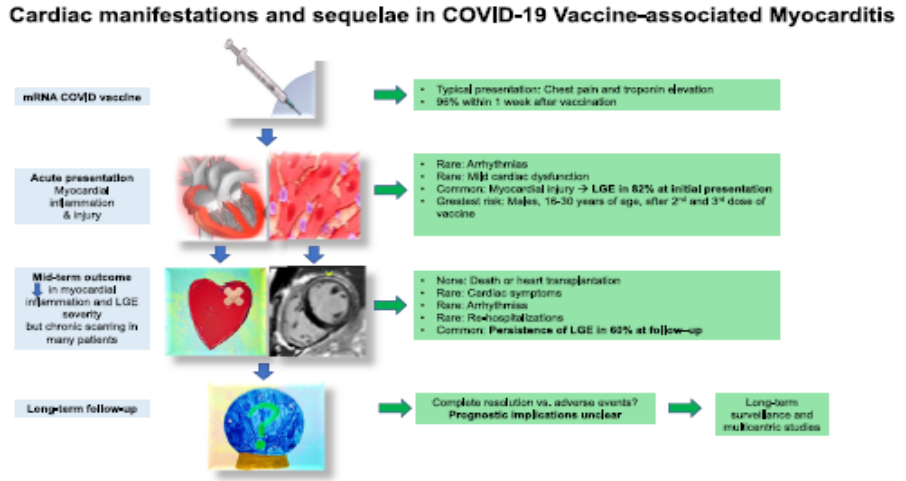
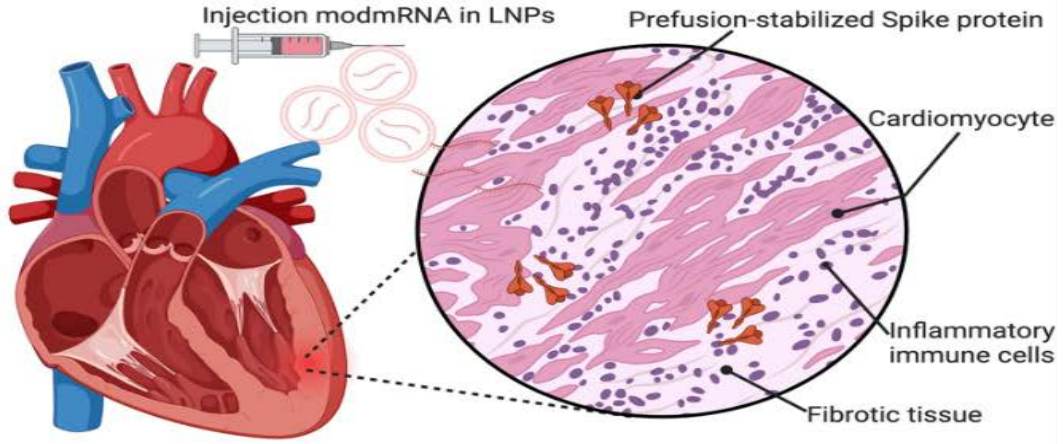


Fig. 3: Late gadolinium enhancement (LGE) by cardiac magnetic resonance (CMR) imaging of the left ventricle in two patients with COVID-19 vaccine-associated myocarditis (CVAM) at presentation and at one year follow-up. Patient 1 demonstrates marked multifocal LGE (A and B, yellow arrow heads) at presentation with notable improvement after one year (E and F, yellow arrows). Patient 2 shows LGE at presentation (C and D, yellow arrows) with persistence at one year (G and H, yellow arrows).



E-Clinical Medicine, 2024



Abbreviations: modmRNA - modified mRNA, LNPs - lipid nanoparticles

Young Males (HIGHEST RISK)

Age & Sex: Young males (12–24 years) face the highest risk—up to 7x higher myocarditis incidence post-modmRNA vaccination compared to their female counterparts.

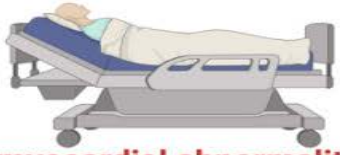
Hormonal Influence: Testosterone may amplify the immune response, increasing myocardial inflammation.

Dose & Timing: Risk spikes after the second dose, with higher rates linked to shorter dosing intervals.

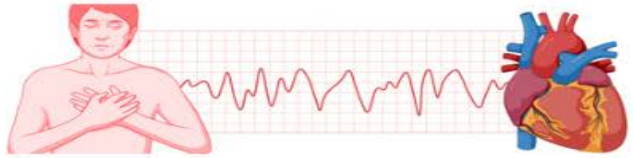
Moderna vs. Pfizer: mRNA-1273 (Moderna) has up to 3–5x higher myocarditis risk compared to BNT162b2 (Pfizer), likely due to its higher modmRNA concentration.

Genetic & Immune Factors: Certain genetic markers and immune dysregulation may contribute to increased susceptibility.

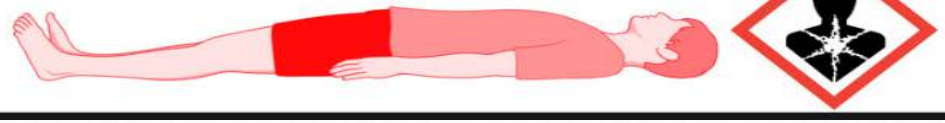
~84-96% of modmRNA myocarditis cases require **hospitalization**

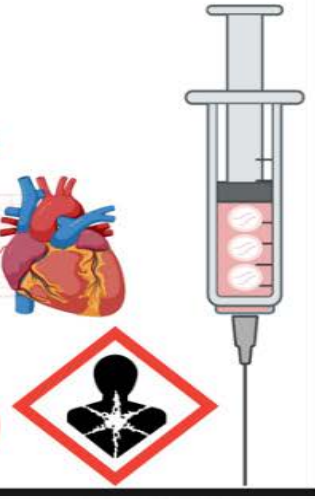


>50% show long-term **myocardial abnormalities**



~10%-20% fatality rate





🚫 ***Misconception 1:*** Infection causes more myocarditis.

✔ ***Fact:*** ModmRNA shots pose higher risk.

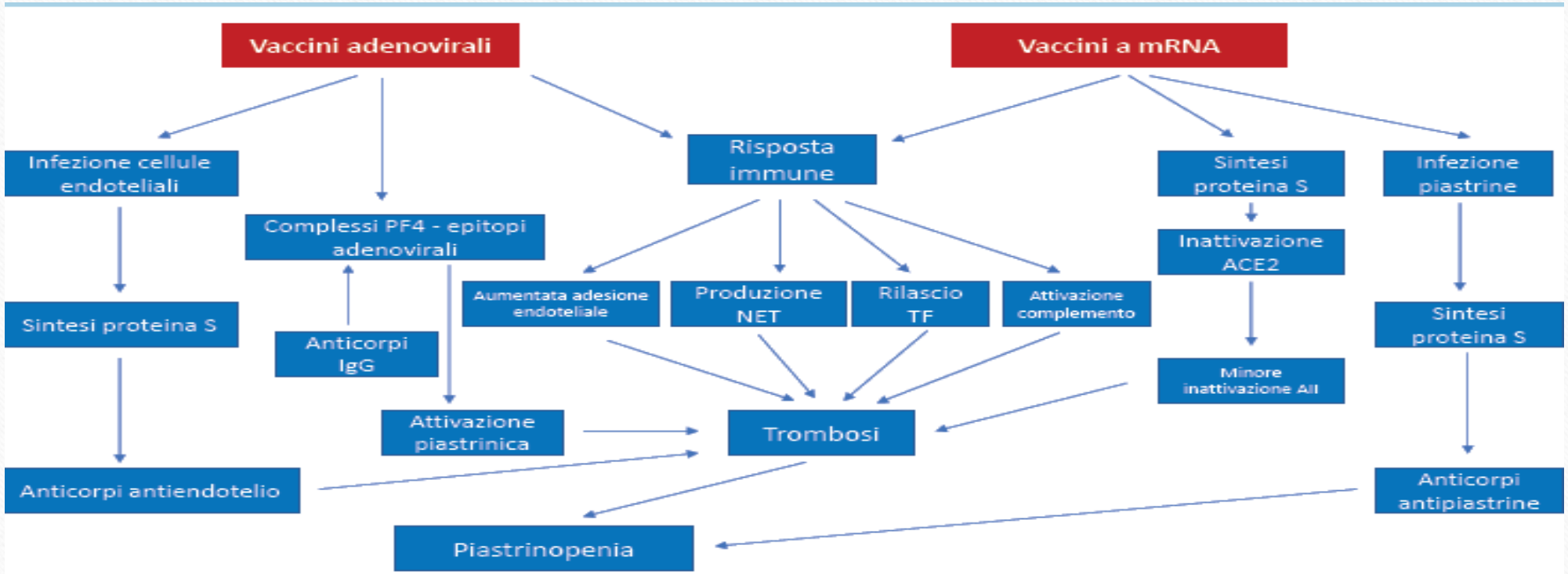
🚫 ***Misconception 2:*** ModmRNA-related myocarditis is mild.

✔ ***Fact:*** Long-term damage and death documented.

🚫 ***Misconception 3:*** Risk-benefit ratio favors modmRNA shots.

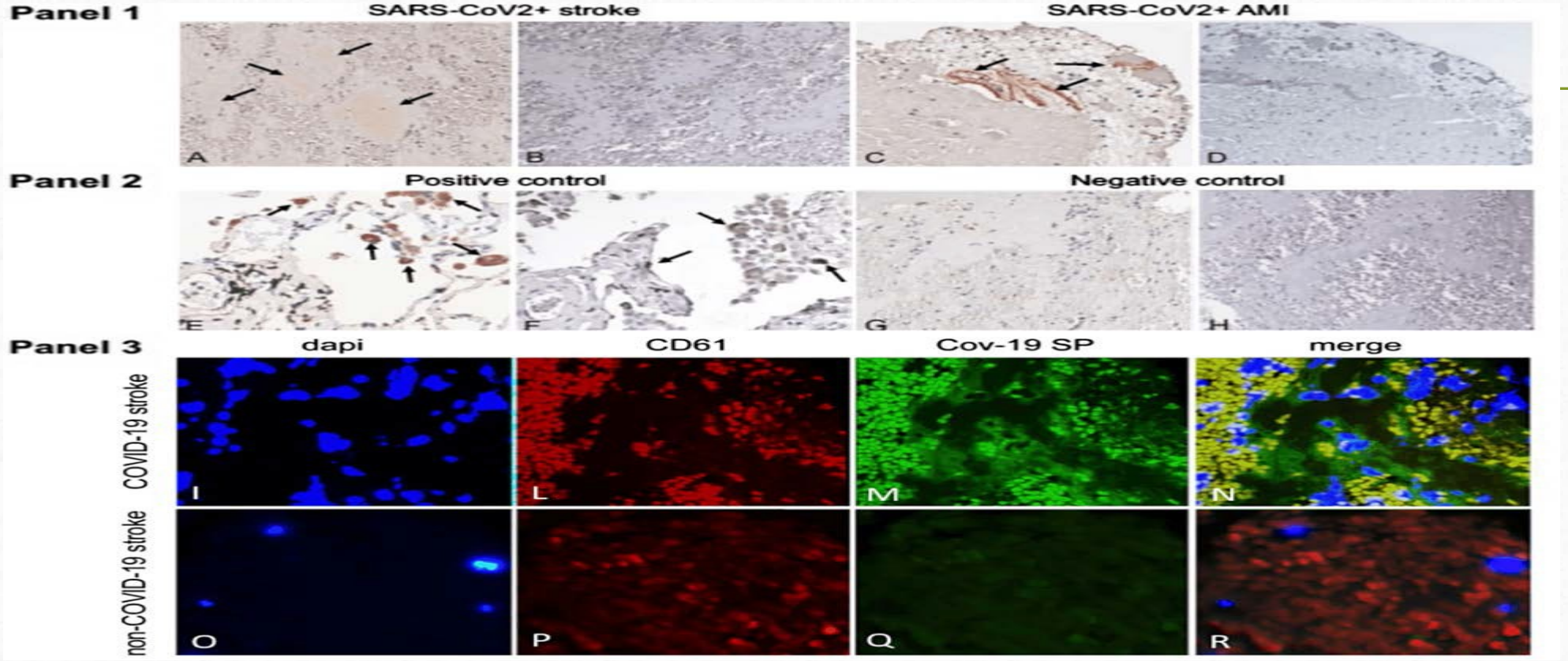
✔ ***Fact:*** Strong evidence contradicts this claim.

Meccanismi ipotizzati per l'insorgenza di trombosi dopo vaccinazione anti SARS-COV-2



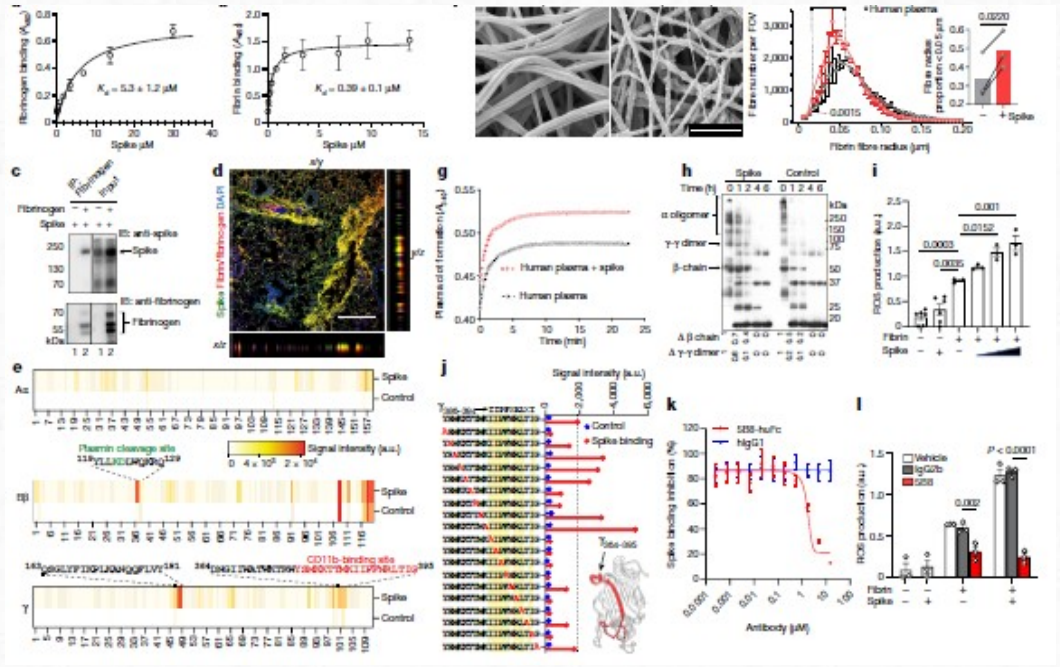
GIC 2021: 41:969-80

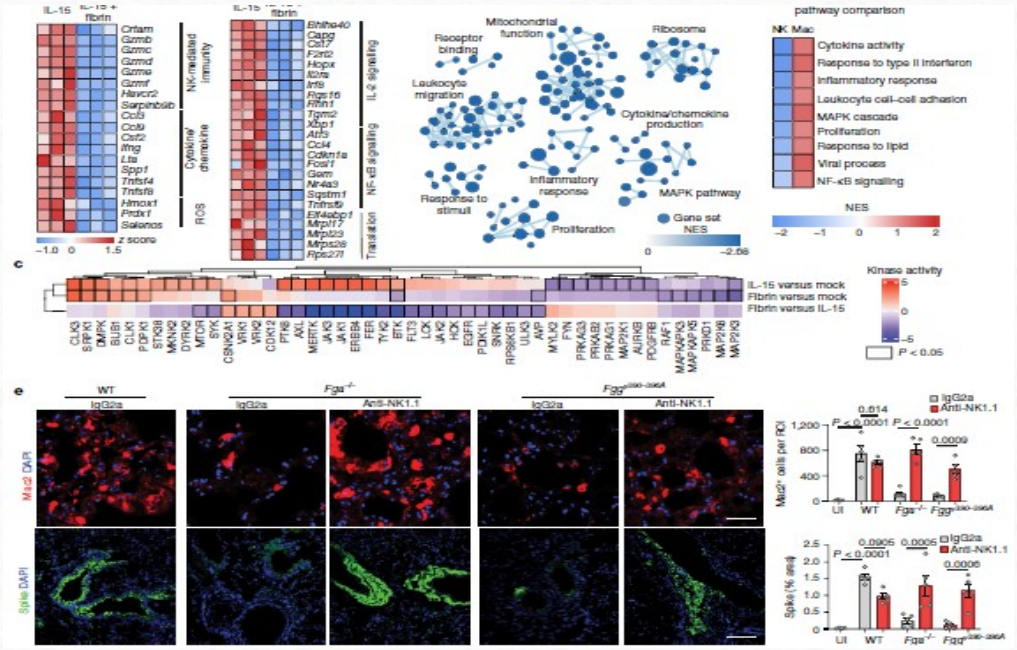
Arterial Thrombi From COVID-19+Patients Contain SARS-CoV-2 Spike Protein But Not Nucleocapsid Protein.



Cureus 2023

Fibrin drives thromboinflammation and neuropathology in COVID-19





Nature, 2024

viruses

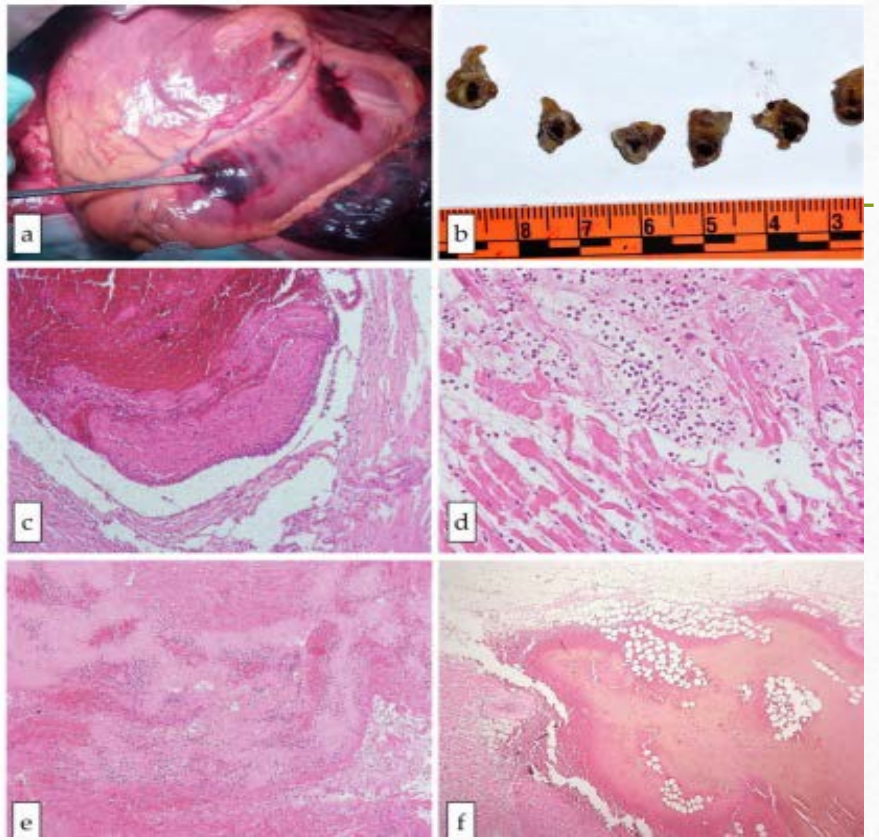
MDPI

Case Report

Myocardial Infarction Following COVID-19 Vaccine Administration: *Post Hoc, Ergo Propter Hoc*?

Arianna Baronti [1,†], Francesco Gentile [2,†], Alice Chiara Manetti [1], Andrea Scatena [1], Silvia Pellegrini [3], Angela Pucci [4], Maria Franzini [5], Vincenzo Castiglione [2,6], Aniello Maiese [1], Alberto Giannoni [2,6], Mauro Pistello [7], Michele Emdin [2,6,*], Giovanni Donato Aquaro [2] and Marco Di Paolo [1]

Abstract: Vaccination against coronavirus disease 2019 (COVID-19) is the safest and most effective strategy for controlling the pandemic. However, some cases of acute cardiac events following vaccine administration have been reported, including myocarditis and myocardial infarction (MI). While post-vaccine myocarditis has been widely discussed, information about post-vaccine MI is scarce and heterogenous, often lacking in histopathological and pathophysiological details. We hereby present five cases (four men, mean age 64 years, range 50–76) of sudden death secondary to MI and tightly temporally related to COVID-19 vaccination. In each case, comprehensive macro- and microscopic pathological analyses were performed, including *post-mortem* cardiac magnetic resonance, to ascertain the cause of death. To investigate the pathophysiological determinants of MI, toxicological and tryptase analyses were performed, yielding negative results, while the absence of anti-platelet factor 4 antibodies ruled out vaccine-induced thrombotic thrombocytopenia. Finally, genetic testing disclosed that all subjects were carriers of at least one pro-thrombotic mutation. Although the presented cases do not allow us to establish any causative relation, they should foster further research to investigate the possible link between COVID-19 vaccination, pro-thrombotic genotypes, and acute cardiovascular events.



Mutazione MTHFR e patologia emocoagulativa nell'infezione naturale e nella vaccinazione anti SARS-COV-2

La diffusione del COVID-19 in tutto il mondo è correlata all'allele C677T della prevalenza del gene della metilentetraidrofolato reduttasi (MTHFR)

Giovanni Ponti [1], Lorenza Pastorino [2], Marco Manfredini [3], Tomris Ozben [4], Gabriella Oliva [5], Shaniko Kaleci [6], Raffaele Iannella [1], Aldo Tomasi [1]

affiliazioni + espandere

PMID: 34061414 PMCID: PMC8209953 DOI: 10.1002/jcla.23798

Articolo PMC gratuito

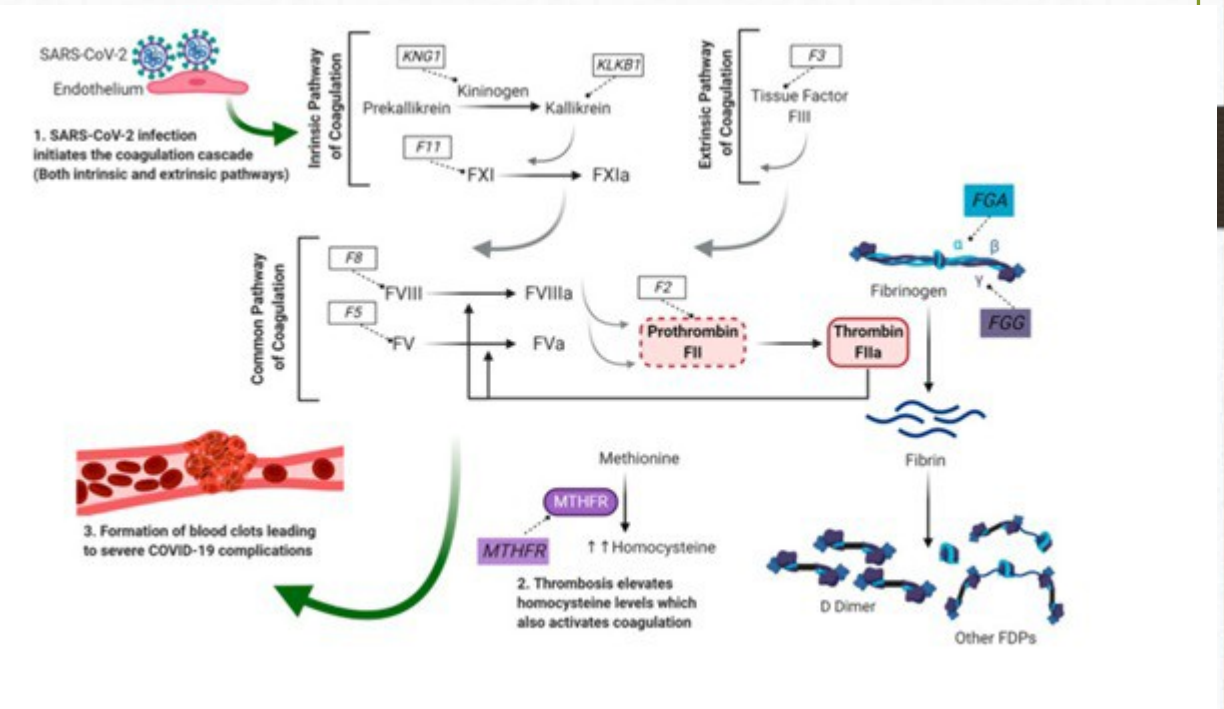
Astratto

Contesto: la valutazione dell'omocisteina è stata proposta come potenziale biomarcatore predittivo per la gravità dell'infezione da COVID-19. Lo scopo di questa revisione era analizzare la correlazione tra la prevalenza del polimorfismo del gene MTHFR C677 T e l'incidenza e la mortalità di COVID-19 in tutto il mondo.

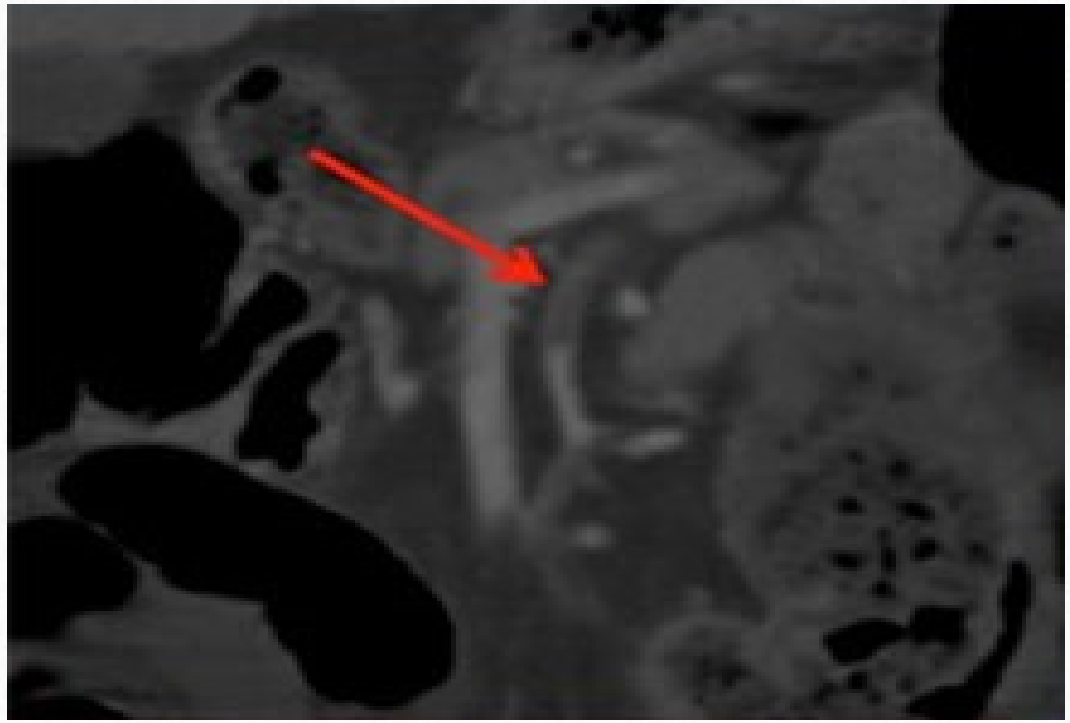
Metodi: i dati relativi alla mutazione del gene MTHFR C677 T sono stati ottenuti dall'interrogazione del Genome Aggregation Database (genomAD), che è pubblicamente disponibile sul web "https://gnomad.broadinstitute.org." I casi di COVID-19, inclusi prevalenza e mortalità, sono stati ottenuti da "https://www.worldometers.info/coronavirus" 27 agosto 2020.

Risultati: esiste una chiara tendenza verso la prevalenza mondiale di MTHFR 677 T e l'incidenza e la mortalità di COVID-19. La prevalenza dell'allele MTHFR 677 T nella popolazione latina e l'incidenza e la mortalità per COVID-19 erano più elevate per questo gruppo etnico rispetto a quelle riportate per la maggior parte delle altre popolazioni a livello globale. L'analisi statistica ha mostrato una correlazione relativamente forte tra C677 T e morte per coronavirus.

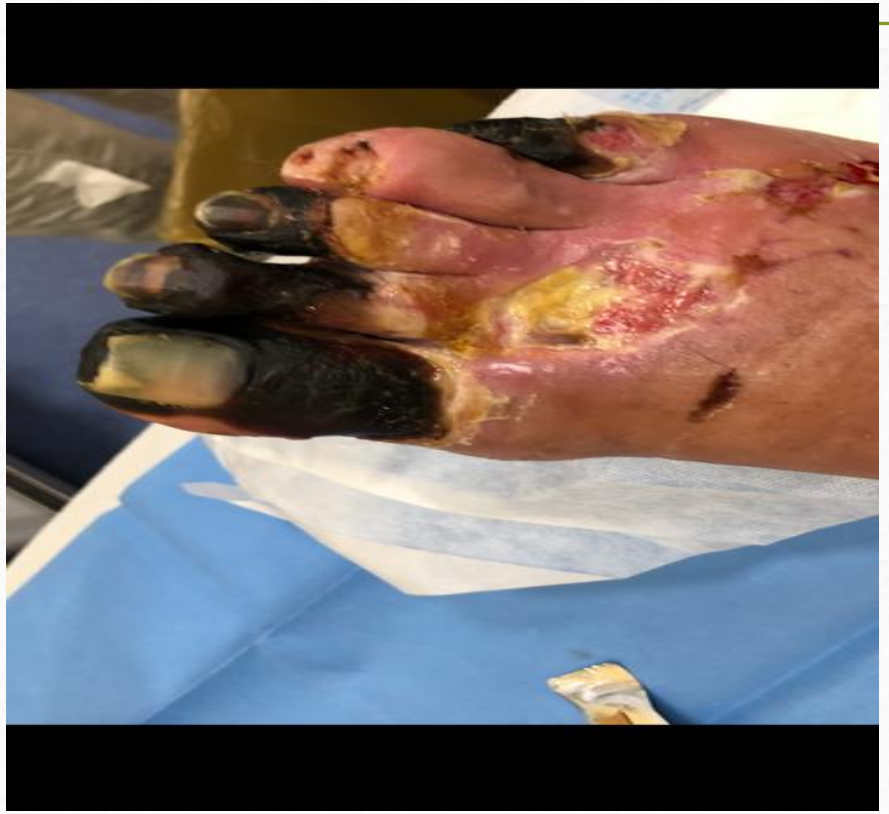
Conclusioni: il polimorfismo genetico di MTHFR C677 T può modulare l'incidenza e la gravità dell'infezione pandemica da COVID-19.

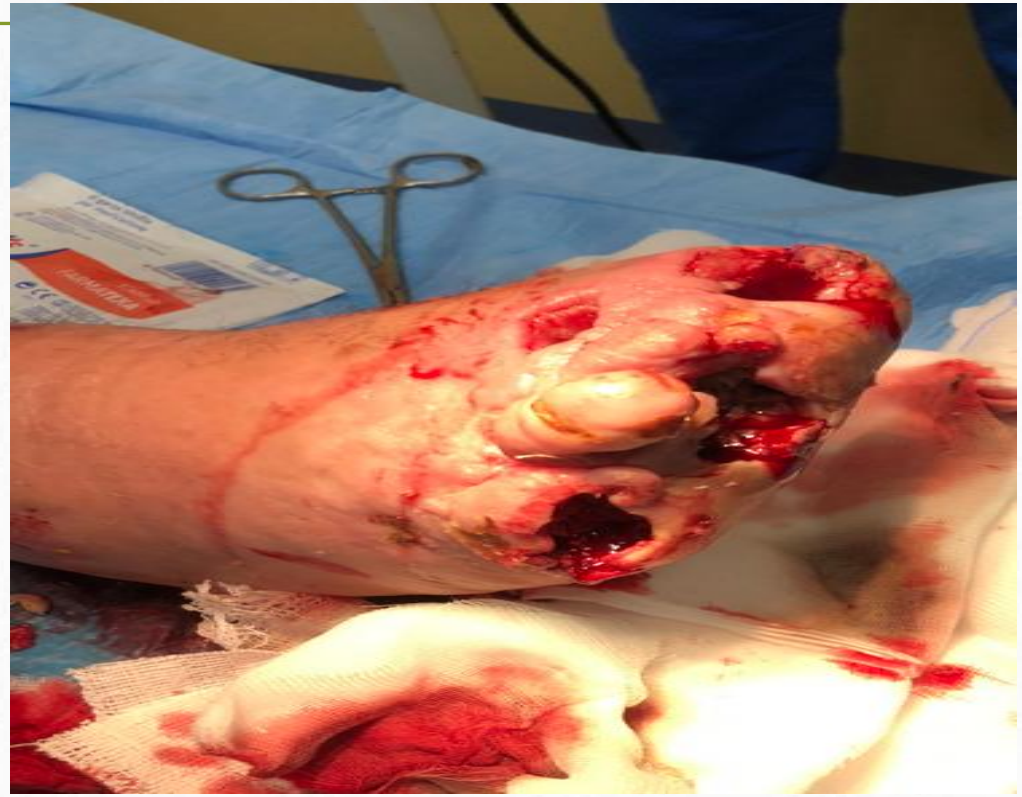


Angina abdominis per trombosi della mesenterica in paziente di 56 anni dopo terza dose Pfizer con mutazione in eterozigosi del fattore II e del fattore V di Leiden e in omozigosi di MTHFR C677T

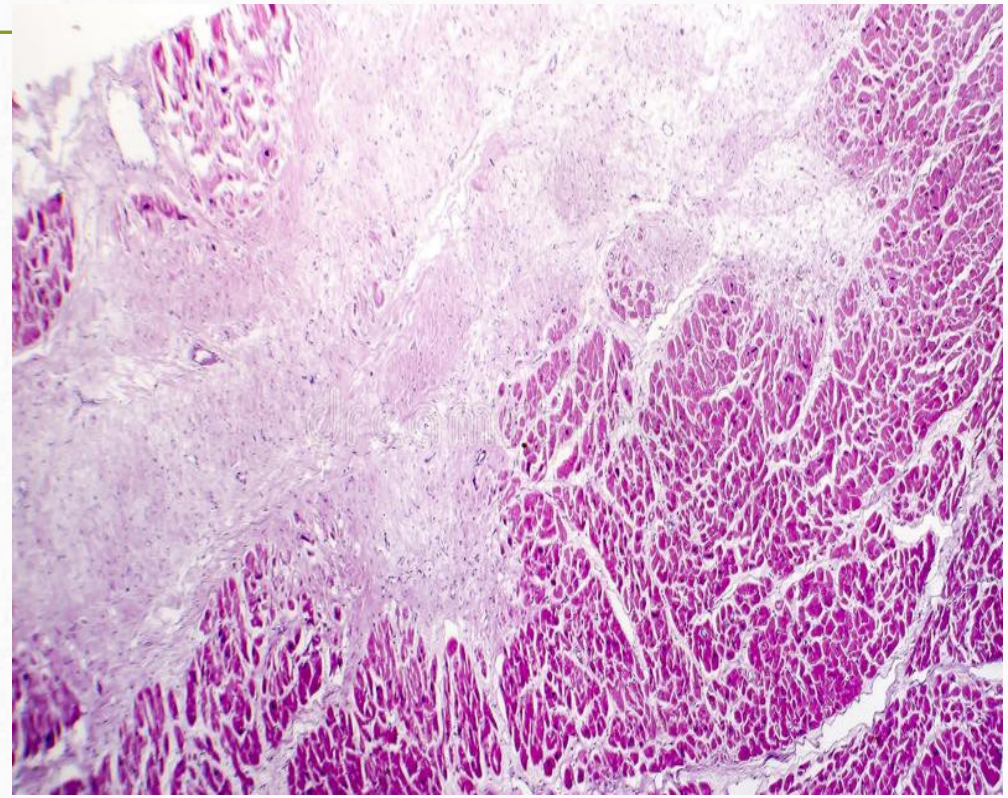


Ischemia del piccolo circolo agli arti inferiori in pazienti giovani senza alcuna comorbilità ma con mutazioni genetiche del sistema emocoaglulativo. Caso di mutazione in omozogosi di PAI1 (4G/4G) e omozigosi MTHFR (C677T) con livelli elevati di omocisteina e D-Dimero. Gangrena delle dita del piede dopo seconda dose Pfizer

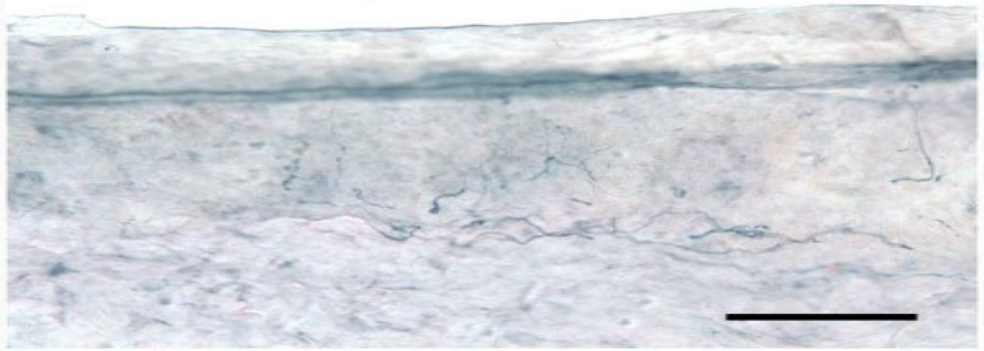




Infarto del miocardio in paziente di 42 anni dopo seconda dose Pfizer con mutazione PAI1 4G/4G e doppia mutazione in eterozigosi MTHFR (C677T e A1298C)



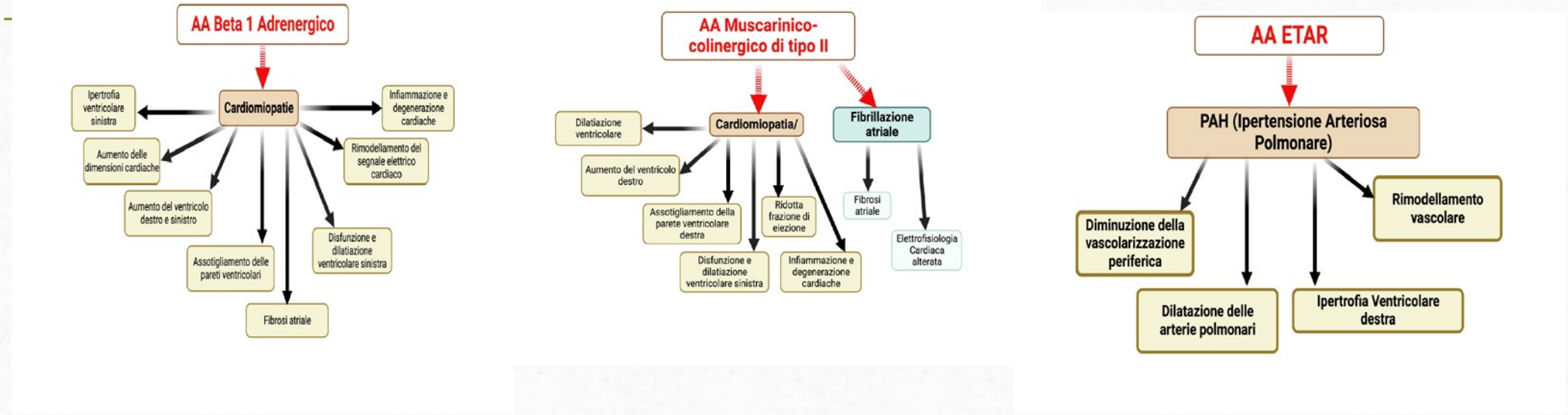
Neuropatia delle piccole fibre nervose



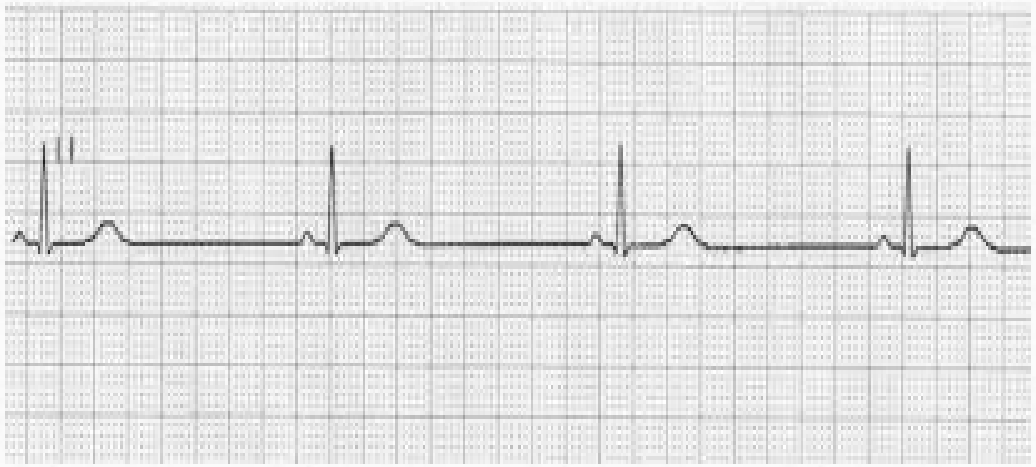
Manifestazioni cardiovascolari associate neuropatia delle piccole fibre nervose con interessamento del sistema nervoso autonomico con meccanismo immuno-mediato (anticorpi FGT3,TSHDS) o per ischemia dei vasa nervorum.

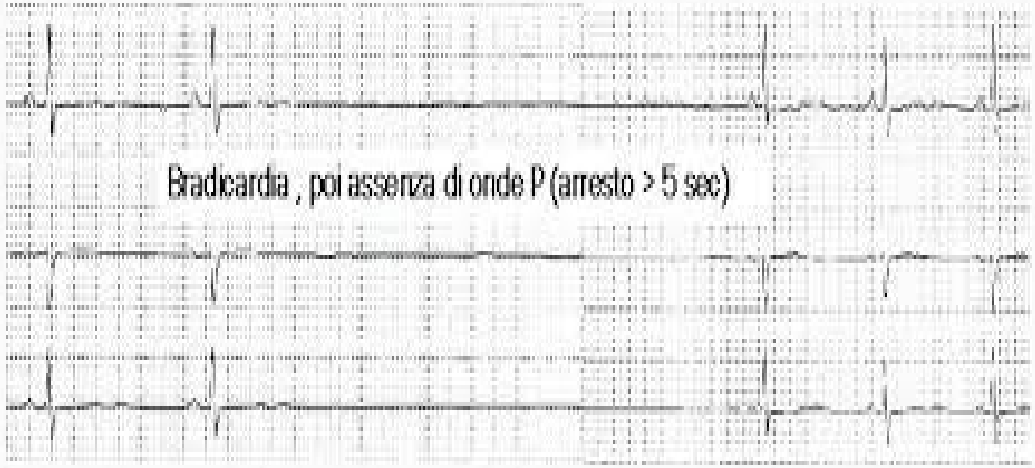
- **Frequente alterazione (>60%) dell'HVR (variabilità respiratoria della frequenza cardiaca con fissità degli intervalli R-R all'ecg basale indice di disfunzione autonomica)**
- **Tachicardia sinusale inappropriata**
- **Tachicardia posturale ortostatica (POTS)**
- **Bradicardia ed ipotensione (possibile asistolia).**

Anticorpi anti-recettori cardiovascolari e rischio di morte improvvisa



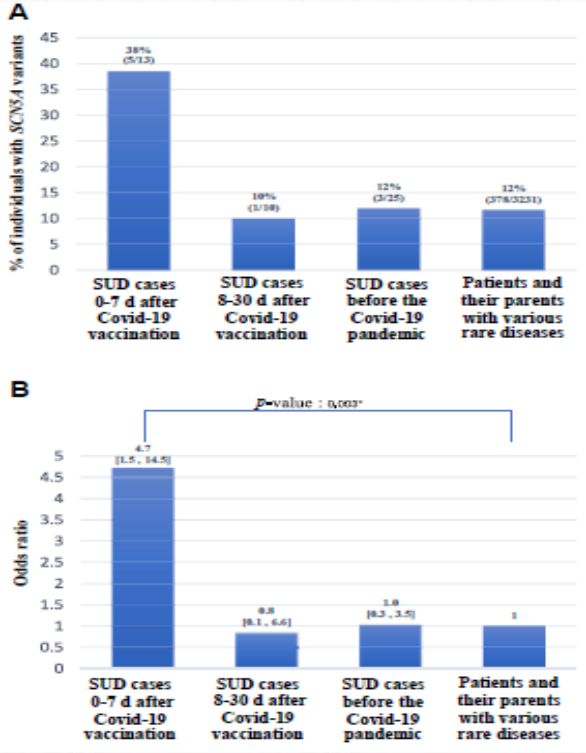
Paziente di 32 anni dopo terza dose Pfizer ed episodi lipotimici recidivanti (possibile disautonomia secondaria a neuropatia delle piccole fibre)





Genetic basis of sudden death after COVID-19 vaccination in Thailand (Heart Rhythm 2022; 19:1874-9)

Chupong Ittiwut,PhD,*† Surakameth Mahasirimongkol,MD,‡ Smith Srisont,MD,x Rungnapa Ittiwut,PhD,*† Manoch Chockjamsai,MD,k Piya Durongkadech,MD,{ Waritta Sawaengdee,PhD,# Athiwat Khunphon,MD,# Kanidsorn Larpadisorn,PharmD,‡ Sukanya Wattanapokayakit,PhD,# Suppachok Wetchaphanphesat,MD,** Surachet Arunotong,MD,†† Suphot Srimahachota,MD,‡‡ Chakrarat Pittayawonganon,MD,xx Panithee Thammawijaya,MD,xx Derek Sutdan,MD,** Pawinee Doungngern,MD,xx Apichai Khongphatthanayothin,MD,kk StephenJ.Kerr,PhD,{{ Vorasuk Shotelersuk,



Conclusion

Our study suggests that *SCN5A* variants could be associated with SUD within 7 days of COVID-19 vaccination, regardless of vaccine type, number of vaccine dose, and presence of underlying diseases or postvaccine fever. Given the observational nature of our study, these findings should be further explored and confirmed in surveillance programs in other settings. Until then, it seems prudent to closely monitor individuals who harbor variants in *SCN5A*, and possibly in other genes that predispose to cardiac arrhythmias or cardiomyopathies, for 7 days after the administration of COVID-19 vaccines, regardless of preexisting underlying diseases and the presence of vaccination-associated fever.

Meccanismi ipotizzabili nei casi di morte improvvisa associata alla vaccinazione anti SARS-COV-2

- Miocardite acuta (inclusa l'azione diretta a livello endomiocardico della proteina spike vaccinale e la riattivazione di infezioni endogene da parte di virus cardiotropi, come EBV e CMV nell'ambito della VAIDS). Una miocardite subclinica può esitare in una cicatrice fibrosa che rappresenta una condizione di instabilità elettrica capace di evocare aritmie ventricolari fatali in condizioni associate ad un incremento del livello delle catecocalamine.
- Infarto acuto del miocardio, con frequente interessamento dei piccoli vasi subepicardici, specialmente nei soggetti con trombofilia genetica.
- Sindrome ADE (intensificazione dell'infezione virale naturale anticorpo-mediata) con associata miocardite e/o attivazione del sistema di coagulazione.
- Reazione allergica acuta ad eccipienti del vaccino (PEG e polisorbato 80) con associata sindrome ipereosinofila, miocardite eosinofila e sindrome di Kounis: sindrome coronarica acuta associata a reazione allergica.
- Bradiaritmia (blocco seno-atriale o blocco atrio-ventricolare avanzato e asistolia) per neuropatia disautonomica nel contesto della neuropatia delle piccole fibre nervose.
- Mutazioni genetiche (es. varianti di SCN5A) associate all'insorgenza di aritmie ventricolari fatali ed anticorpi anti-alfa/beta recettori.

Screening consigliato pre- e post-vaccinale

- **PRIMA DELLA VACCINAZIONE:**
- Accurata anamnesi clinica e familiare (allergopatia, patologie sistemiche a carattere autoimmune, patologie cardiache congenite, storia di morte improvvisa in famiglia che richiederebbe la ricerca di mutazioni di geni associati ad arimie ventricolari maligne, es. SNC5A).
- Test sierologico quantitativo (valutazione di pregressa infezione naturale con sviluppo di anticorpi neutralizzanti), tampone molecolare e test allergologici (es. prick test per PEG e polisorbato 80)
- Visita cardiologica con elettrocardiogramma
- Screening trombofilico (con ricerca dei mutazioni del fattore II protrombinico, del fattore V di Leiden, del PAI1, di MTHFR (C677A e A1298C), dosaggio omocisteina, fibrinogeno e D-Dimero.
- **DOPO LA VACCINAZIONE (specialmente dopo 2 o 3 dosi)**
- Visita cardiologica (con ECG ed ecocardiogramma), specialmente nei soggetti <40 anni. Alterazioni elettrocardiografiche non presenti in fase pre-vaccinale impongono la richiesta di esami diagnostici di secondo livello (RMN cardiaca)
- Pannello MIT (per valutazione dell'immunità cellulo-mediata) con associata sierologia per herpesvirus (EBV,CMV e HVVZ) e parametri di autoimmunità (autoanticorpi)
- Valutazione della conta piastrinica (frequente piastrinopenia autoimmune), degli indici di flogosi e dei parametri di coagulazione (in particolare, fibrinogeno e D-Dimero e omocisteina)