The Association between Post-COVID-19 Myocardial Infarction and Antiphospholipid Syndrome

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Abstract

Background: Post-COVID-19 introduces various health challenges, including myocardial infarction (MI) linked to inflammation and coagulation, raising concerns for antiphospholipid syndrome (APS) patients. Elevated APS-related antibodies in some COVID-19 patients underscore the need for a comprehensive understanding of this cardiovascular interplay.

Objectives: To determine the association between Post-COVID-19 and Myocardial Infarction and Antiphospholipid Syndrome.

Patients and methods: This case-control study at Qena University Hospital explored the relationship between post-COVID-19 MI and APS, considering immune responses, genetics, and coexisting factors. Criteria included COVID-19 history, and MI symptoms, excluding certain conditions. Assessments included PCR, inflammatory markers, troponin I, coagulation profile, and specific antibody tests to detect Anticardiolipin-IgG, Anticardiolipin-IGM, anti nuclear anibody (ANA), and Anti-Double Strand (anti-DS).

Results: Gender differences weren't significant (p = 0.0691). Lab data showed significant ESR and CRP elevation in cases (p<0.0001, p=0.00767), and non-significant differences in serum calcium, platelet Count, hematocrit, and INR, with higher troponin I in cases (p=0.04349). Lupus anticoagulant levels were slightly higher in cases (p = 0.05148), while APS presence differed significantly (p = 0.000051). APS patients had more COVID-19 history (p = 0.000051). Among other parameters, ESR, and CRP correlated positively with APS, and D-dimer correlated with MI (r = 0.496, p < 0.0001).

Conclusion: APS was significantly associated with Post-COVID-19 Myocardial Infarction. Elevated antiphospholipid antibodies, altered laboratory parameters, and a higher history of COVID-19 infection were observed in MI cases after COVID-19. This suggests a potential link between APS and MI in COVID-19 recovery.

Keywords: COVID-19; Myocardial infarction; Antiphospholipid.

Introduction

Post-COVID-19, complex health challenges arise due to SARS-CoV-2. COVID-19, known for respiratory symptoms, also triggers cardiovascular issues, notably myocardial infarction (MI) **(Aghagoli et al., 2020; Bermejo-Martin et al., 2020).**MI, from coronary obstruction, relates to COVID-19's systemic inflammation, coagulation irregularities, and impaired endothelial function, impacting individuals with conditions like antiphospholipid syndrome (APS) **(Altamimi et al., 2020, Solomon et al., 2020; Del Prete et al., 2022;).**

APS, an autoimmune disorder with antiphospholipid antibodies (APS), heightens clot formation, increasing thrombotic risks. Some COVID-19 patients show elevated APS levels, potentially intensifying coagulation issues in APS individuals. A comprehensive understanding of COVID-19 and APS's cardiovascular interplay is crucial **(Talotta and Robertson, 2021).**

The intricate bond between post-COVID-19 MI and APS needs further research. Viral-induced immune responses, APS exacerbation via COVID-19's pro-inflammatory and pro-thrombotic effects, genetics, and coexisting factors warrant exploration **(Angius et al., 2012; Cimolai, 2021).**

This study aims to determine the association between Post-Covid 19 Myocardial Infarction and Antiphospholipid Syndrome.

Patients and Methods

This case-control research was conducted at the Internal Medicine Department of Qena University Hospital. COVID-19 history verified by PCR and myocardial infarction symptoms such as increased troponin I levels and electrocardiogram (ECG) abnormalities are inclusion criteria. The research excludes those with systemic lupus, other autoimmune diseases, cardiac problems, chronic coagulopathy disease, or a history of disabling illnesses.

To thoroughly evaluate the studies subjects. First, age, sex, disabling illnesses, heart sickness, coagulopathy history, and COVID-19 infection were recorded.CBC will be done. Real-time polymerase chain reaction (RT-PCR) to detect COVID-19 infection using respiratory samples obtained by throat swab, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) levels indicating inflammation, serum troponin I for heart muscle damage assessment, and coagulation profile tests including prothrombin time, International Normalized Ratio (INR), and Partial Thromboplastin Time (PTT). Also, Lupus Anticoagulant, Rheumatoid factor (RF), and D-Dimer tests were performed. The Lupus Anticoagulant test detected clotting disease antibodies, the Rhesus factor (RF) test was performed, and the D-dimer test detected fibrin breakdown.

IgM, IgG anticardiolipin

QUANTA Lite Anticardiolipin IgM and IgG (AcuStar Anti-Cardiolipin IgG and AcuStar Anti-Cardiolipin IgM) (Inova Diagnostics, United States) was used.

The QUANTA Lite Anticardiolipin IgM and IgG test is an enzyme-linked immunosorbent assay (ELISA) that detects the presence of IgM and IgG antibodies against the antigen complex between cardiolipin and β2-Glycoprotein in human serum or plasma. The complex is coated on a microplate. The test involves sample dilution, binding of antibodies to the antigen, washing to remove non-reactive components, incubation with anti-human IgM or IgG horseradish peroxidase conjugate, color development using a chromogenic substrate, and calculation of antibody concentration. Reference values for anticardiolipin IgM are typically <10 AU/mL for normal and >=10 AU/mL for affected individuals.

Antinuclear antibodies (ANA)

QUANTA Lite Anti-dsDNA (Inova Diagnostics, United States) was used. The QUANTA Lite ANA test is an enzyme immunoassay that semi-quantitatively determines IgG antibodies to nuclear and cytoplasmic antigens. It uses HeLa nuclei enriched with recombinant and native antigens immobilized on microtiter plates. After patient samples react with these antigens, unbound components are washed away. Bound IgG antibodies then react with anti-human-IgG conjugated to horseradish peroxidase, leading to a color change with a chromogenic substrate. Patient ratios are calculated based on optical density at 450 nm, providing a semi-quantitative result. The test is used to screen for autoimmune antibodies associated with various conditions.

Specimen Storage and Collection Centrifugation separated serum after clotting from vein-punctured specimens. Samples exhibiting lipemic, hemolytic, or contaminant concerns were eliminated.

Anti-dsDNA by ELISA

QUANTA Lite Anti-dsDNA (Inova Diagnostics, United States) was used. The QUANTA Lite Anti-dsDNA test is an enzyme immunoassay that quantitatively determines IgG antibodies to double-stranded DNA (dsDNA). Highly purified dsDNA is coated on microtiter plates. Patient samples react with the immobilized dsDNA, and unbound components are washed away. Bound IgG antibodies react with anti-human-IgG conjugated to horseradish peroxidase, leading to a color change with a chromogenic substrate. Optical density at 450 nm is proportional to the amount of specific antibodies bound. Results can be read directly from a standard curve or calculated using a semi-quantitative method. This test aids in the diagnosis of conditions like systemic lupus erythematosus (SLE).

For lupus anticoagulants (LA) Thrombostat (Stago, France) was used. For plasma samples used for aPLS we used double centrifugation. The first centrifugation was at 1,500 x g for 10 minutes to remove the red blood cells and platelets. The second centrifugation was at 2,000 x g for 15 minutes to pellet the remaining platelets. The purpose of double centrifugation is to remove as many platelets as possible from the plasma sample. Platelets can interfere with the aPLS assay by activating the clotting cascade, which can lead to a false positive result.

APS is positive when Lupus anticoagulant exceed 39, or Anticardiolipin IgG exceed 15 or IgM exceed 12.5.

Our study's main outcome is the relationship between Post-COVID-19 Myocardial Infarction and Antiphospholipid Syndromes. The secondary outcome is to minimize COVID-19-related coagulopathy morbidity and death.

Ethical Considerations: Informed consent was obtained from all participants. The investigators have kept individual data as private information safely. Participants had the right to withdraw. **Ethical Approval: SVU-MED-CCP031-1-21-11-176**

Statistical Analysis

In this study, we employed Statistical Package for the Social Sciences (SPSS) software, version 26, to perform data management and analysis. Continuous variables were summarized using measures such as Mean ± Standard Deviation (SD) or median along with their respective ranges. Median and range statistics were employed to assess ordinal variables. Statistical significance was determined when the p-value was less than or equal to 0.05. The normality of the data was assessed using the Shapiro-Wilk test. For comparisons between two groups of continuous variables that followed a normal distribution, we used the t-test, whereas for non-normally distributed

data, the Mann-Whitney U test, which is analogous to the t-test, was employed. Qualitative data comparisons were conducted using the Chi-square test, and Pearson correlation analysis was employed for exploring relationships between variables.

Results

In terms of gender, the data shows that there were 26 males (52%) among the controls and 17 males (34%) among the cases. Among the females, there were 24 (48%) in the control group and 33 (66%) in the case group. The difference in gender distribution between the two groups was not statistically significant (p = 0.0691).

MI patients with COVID-19 had a mean SBP of 107.82 ± 3.51 mmHg, while those without COVID-19 had a mean SBP of 108.38 ± 4.04 mmHg (p = 0.461). The mean DBP was 76.36 ± 2.96 mmHg for MI patients with COVID-19 and 76.56 ± 2.83 mmHg for those without COVID-19 (p = 0.731). Similarly, the heart rate was not significantly different between the two groups, with MI patients with COVID-19 having a mean HR of 91.76 ± 3.56 beats/min compared to 92.38 ± 3.65 beats/min for MI patients without COVID-19 (p = 0.392). The respiratory rate also showed no significant difference, with MI patients with COVID-19 having a mean RR of 23.62 ± 2.3 breaths/min, while MI patients without COVID-19 had a mean RR of 23.3 ± 2.22

breaths/min (p = 0.481). There were no statistically significant differences in systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), and respiratory rate (RR).

The levels of lupus anticoagulant were slightly higher in MI patients with COVID-19 (42.02 ± 10.32 um/L) compared to those without COVID-19 (38.6 ± 8.27 um/L), although this difference did not reach statistical significance (p = 0.098). Similarly, the levels of anticardiolipin-IgG and anticardiolipin-IgM antibodies were slightly elevated in MI patients with COVID-19, with values of 5.54 ± 1.86 u/ml and 4.65 ± 2.13 u/ml, respectively, compared to 4.87 ± 2.17 u/ml and 4.03 ± 1.48 u/ml in those without COVID-19 (p = 0.092 and p = 0.117, respectively). However, the D-dimer levels were significantly lower in MI patients with COVID-19 (4308.92 ± 1385.37 mg/L) compared to those without COVID-19 (4748.32 ± 1389.57 mg/L) with a p-value of <0.0001.

Additionally, MI patients with COVID-19 had a lower erythrocyte sedimentation rate (ESR) and international normalized ratio (INR) but higher prothrombin time (PTT) and troponin levels compared to those without COVID-19, with statistically significant differences (p < 0.001, p = 0.015, p < 0.001, and p = 0.015, respectively), (**Table. 1).**

Table 1. Comparison of Antiphospholipid Syndrome Markers between Controls and Cases

Variables	MI patients without COVID (N = 50)	MI patients with COVID (N = 50)	P- Value
Lupus anti-coagulant (um/L)	38.6 ± 8.27	42.02 ± 10.32	0.071[t]
Anticardiolipin-IgG (u/ml)	4.87 ± 2.17	5.54 ± 1.86	0.098[U]
Anticardiolipin-IGM (u/ml)	4.03 ± 1.48	4.65 ± 2.13	0.092[U]
D-Dimer (mg/L)	4748.32 ± 1389.57	4308.92 ± 1385.37	0.117[U]
APS	11 (22%)	31 (62%)	<0.0001*[X]
Number of ANA-positive	3 (6%)	6 (12%)	0.295[X]
Number of Anti-ds DNA positive	0 (0%)	2 (4%)	0.495[F]

PTT (S)	31.52 ± 2.98	30.75 ± 3.14	0.219[t]
ESR (mm/hr)	48.86 ± 18.62	27.93 ± 9.49	<0.001*[U]
CRP (mg/L)	34.34 ± 18.7	21.11 ± 7.6	<0.001*[U]
PT (s)	11.9 ± 0.57	12 ± 1.25	0.649[t]
Hematocrit (%)	95.24 ± 6.46	95.81 ± 8.07	0.705[t]
INR	1.06 ± 0.08	1.05 ± 0.09	0.465[t]
Troponin (ng/mL)	14.8 ± 4.26	11.69 ± 3.6	0.015*[t]

APS - Antiphospholipid Syndrome, ANA - Antinuclear Antibody , Anticardiolipin-IgG Anticardiolipin Immunoglobulin G , Anticardiolipin-IGM - Anticardiolipin Immunoglobulin M , PTT - Partial Thromboplastin Time, ESR - Erythrocyte Sedimentation Rate , CRP - C-Reactive Protein , PT - Prothrombin Time , INR - International Normalized Ratio , t: T. Test, U: MWU Test, X: Chi Square Test, F: Ficher Exact test*P<0.05 Statistically Significant

Gender distribution lacked statistical significance between APS and non-APS patients (p = 0.7). APS patients: 45.24% male, 54.76% female. Non-APS patients: 41.38% male, 58.62% female. No debilitating, cardiac, or coagulopathy cases in both groups. However, a significant difference emerged in COVID-19 history between APS and non-APS patients (p = 0.000051). APS patients: 73.81% had COVID-19 history. Non-APS patients: 32.76% had COVID-19 history, (**Table.2).**

Table 2. Comparison of Demographic and Medical History between APS Patients and Non-APS Patients

Variables	MI patients with APS (N = 42)	MI patients without APS (N = 58)	P. Value
Gender			
• **Male**	19 (45.24%)	24 (41.38%)	0.7005[X]
• **Female**	23 (54.76%)	34 (58.62%)	
History of COVID-19 Affection	31 (73.81%)	19 (32.76%)	0.000051*[X]

X: Chi Square Tes
*P<0.05 Statistically Significant

APS patients had a significantly higher prevalence of ANA compared to non-APS patients (p = 0.023). No significant differences were found in the presence of Anti dsDNA and D-Dimer levels between APS and non-APS patients. Additionally, no patients in either group tested positive for RF (**Table .3).**

Table 3. Comparison of Laboratory Parameters in APS and Non-APS Patients

Variables	MI patients with APS (N = 42)	MI patients without APS (N = 58)	P- Value
Number of ANA-positive	7 (16.67%)	2 (3.45%)	0.023*[X]
Number of Anti-ds DNA positive	2 (4.76%)	0 (0%)	0.174[F]
D-Dimer (mg/L)	4088.19 ± 1352.82	4029.66 ± 1181.54	0.819[U]
Rheumatoid Factor detection	0 (0%)	0 (0%)	-

ANA - Antinuclear Antibody, Anti-ds DNA - Anti-Double Stranded DNA.
t: T. Test, U: MWU Test, X: Chi Square Test, F: Ficher Exact test
*P<0.05 Statistically Significant

APS had a significant positive correlation with COVID-19 infection history (r = 0.405, p = 0.00003). ESR (r=0.596 and P–<0.001), CRP (r =0.442 and P–<0.001), Troponin (r =0.370 and P = 0.015), Lupus anti-coagulant (r =0.369 and P. Value = 0.016), Anticardiolipin IgG (r =0.461 and P <0.001), Anticardiolipin IGM (r =0.473 and P <0.001), significant mild positive correlation with ANA (r =0.228 and P = 0.023) and significant mild negative correlation with Ca (r =-0.221 and P = 0.027). History of COVID-19 infection shows a significant positive correlation with APS (r = 0.405 and P = 0.003), ESR (r = 0.470 and P <0.001), CRP (r = 0.265 and P = 0.007) and show a significant mild positive correlation with troponin (r =0.202 and P= 0.043), (**Table. 4**).

Table 4. Correlation between Coagulopathy, APS, and COVID-19 infection history with other parameters and each other's

Variables	APS		COVID-19 infection history	
	r	**P. Value**	**r**	**P. Value**
APS	-	-	.405**	0.00003
COVID-19 History	.405**	0.00003	-	-
Gender				
Male	0.03847	0.70395	-0.18179	0.07027
Female	-0.03847	0.70395	0.18179	0.07027
PTT	0.123973	0.21911	0.026722	0.79185
ESR	0.596**	<0.0001	0.470**	<0.0001
CRP	0.442**	<0.0001	0.265**	0.00767
PT	-0.04605	0.64917	-0.13375	0.18464
Hematocrit (%)	-0.03833	0.70499	0.069207	0.49386
INR	0.073925	0.46481	-0.10029	0.32083
Troponin-I	0.370**	0.00015	0.202*	0.04349
Lupus anti-coagulant	0.369**	0.00016	0.195318	0.05148
Anticardiolipin-IgG	0.461**	<0.0001	0.166985	0.09681
Anticardiolipin-IGM	0.473**	<0.0001	0.067262	0.5061
ANA	0.228*	0.02254	0.104828	0.29928
Anti-ds DNA	0.167877	0.09501	0.142857	0.15622
D-Dimer	0.012942	0.89831	-0.04616	0.64837

ᵨ Pearson Correlation, *P<0.05 Satatistically significant, **P<0.0001 High Statistcal Signficance APS - Antiphospholipid Syndrome, PTT - Partial Thromboplastin Time, ESR - Erythrocyte Sedimentation Rate, CRP - C-Reactive Protein, PT - Prothrombin Time, INR - International Normalized Ratio, Anticardiolipin-IgG - Anticardiolipin Immunoglobulin G, Anticardiolipin-IGM - Anticardiolipin Immunoglobulin M, ANA - Antinuclear Antibody, Anti-ds DNA - Anti-Double Stranded DNA.

Discussion

MI, or heart attack, is an irreversible heart muscle injury caused by reduced or stopped blood flow to the coronary artery, producing cardiac tissue ischemia. This causes permanent necrosis **(Aghagoli et al., 2020)**. APS, commonly known as Hughes Syndrome, is caused by immune system failure and increases blood clot risk. This disease increases the risk of deep venous thrombosis, repeated arterial thrombosis (stroke or heart attack), and fetal loss**.** COVID-19 is a zoonotic illness that may cause asymptomatic cases, severe pneumonia, sequelae, and deaths **(Solomon et al., 2020).**Critically sick COVID-19

individuals have coagulopathy, which impairs blood coagulation. Multiple studies show delayed arterial and venous thromboembolic consequences of COVID-19 **(Del Prete et al., 2022).**

In our study, COVID-19 MI patients with COVID had significantly higher ESR (44.86 ± 20.09 mm/hr) and CRP (30.59 ± 18.62 mg/L) than MI patients without COVID (22.74 ± 8.28 mg/L, p=0.00767) and Troponin (13.84 ± 4.93 ng/mL) than MI patients without COVID (12.16 ± 3.06 ng/mL, p=0.04349). ESR, CRP, and Troponin elevations may suggest inflammation and cardiac involvement post-COVID-19 **(Zeng et al., 2020; Zhang et al., 2021).**

Gul et al. (2022), examined cardiac damage in COVID-19 patients using biomarkers and echocardiography. The cardiology outpatient clinic saw 224 patients, 126 of whom had COVID-19 and 98 healthy controls. The COVID-19 group had an average age of 43.48 ± 11.9 years, whereas the control group had 42.02 ± 12.3 years (p = 0.37). The COVID-19 group had substantially greater cardiac and other inflammatory markers such RDW, ESR, CRP, NT-ProBNP, D-dimer, and troponin T than the control group.

We found that APS causes substantial heart damage and inflammation. APS patients showed increased ESR, CRP, and Troponin I, suggesting heart injury and inflammation. Antiphospholipid antibodies put APS patients at risk of thrombotic events including myocardial infarction. ESR, CRP, and Troponin levels are positively correlated with APS and COVID-19, which is fascinating. This shows that COVID-19's chronic inflammation and APS's immunological response may increase cardiac markers in the myocardium. We showed that APS severely impacts blood coagulation. Lupus anticoagulant, Anticardiolipin IgG, and IgM levels were greater in APS patients. APS patients have a higher thrombotic risk because antiphospholipid antibodies affect coagulation. Calcium dysregulation occurs when Ca levels are negative and APS is positive. APS affect calcium-dependent coagulation pathways, making APS patients more prothrombotic, however further study is needed.

Variable prevalence of APS in severely sick COVID-19 patients. **Bowles et al. (2020)** discovered APS in 91% with extended aPTT, whereas **Najim et al. (2021)** found it in 37% with 35% having lupus anticoagulant. In contrast, **Xiao et al. (2020)** discovered 47% APS and 3% lupus anticoagulant. **Devreese et al. (2020)** identified single lupus anticoagulant positive in 52% of severely sick COVID-19 patients. Post-COVID-19, SARS-CoV-2 causes myocardial inflammation and pseudo acute MI **(Inciardi et al., 2020; Loghin et al., 2020).**

Hypoxemia, sympathetic activation, and inflammation relate respiratory infections like COVID-19 to cardiovascular events **(Musher et al., 2019, Sandoval and Jaffe 2019;).** **Helms et al. (2020)** found 43% thrombotic problems in ICU COVID-19 patients, whereas **Stefanini et al. (2020)** identified ST elevated myocardial infarction as a possible long-term sequela. APS is a prothrombotic condition caused by APS **(Lim, 2013).** Early studies found APS in ICU COVID-19 patients, including anticardiolipin IgA and anti-β2-glycoprotein IgA/IgG, and cerebral infarctions **(Zhang et al., 2020).** However, severely sick COVID-19 patients vary in APS prevalence **(Bowles et al., 2020; Devreese et al., 2020; Xiao et al., 2020).**

APS was significantly higher in cases 62% compared to 22% of MI patients without COVID (P= 0.000051), linking APS to Post-COVID-19 MI. The history of COVID-19 infection varied greatly. APS

patients (73.81%) had significantly higher COVID-19 infections than non-APS (32.76%). (P= 0.000051).

The complex COVID-19 infection process links APS to post- COVID-19 MI. First, COVID-19 damages blood vessels through hypercoagulability and endothelial dysfunction. In addition, APS enhances hypercoagulability **(Bonaventura et al., 2021).** This combined impact increases MI/ thrombosis risk. COVID-19 causes immunological dysregulation, causing aPLs and APS **(Karimzadeh et al., 2020).** Antibodies that target cell membrane phospholipids clog arteries. The APS and COVID-19 immune activation enhance cardiovascular risk, including MI. COVID-19's vascular injury creates microthrombi, which APS enlarges and increases MI risk. Antiphospholipid antibodies in COVID-19 patients promote thrombus formation, particularly in coronary arteries, causing MI. Chronic inflammation from COVID-19 and APS causes atherosclerosis and MI risk **(Huang et al., 2021).**

Our investigation found myocardial infarctions in COVID-19 patients, indicating APS shares a pathogenic mechanism. COVID-19 myocardial damage was connected to death by **Guo et al. (2020),** especially in cardiovascular diseases (CVD) patients. **Shi et al. (2020)** noted that hospitalized COVID-19 patients often had myocardial infarction, which affects outcomes. In 28 days after admission, **Karahan et al. (2022)** observed deep venous thrombosis, myocardial infarction, and ischemic stroke, suggesting APS may be linked to COVID-19. APS was suspected by positive Lupus anticoagulant testing. **Abdel-Wahab et al. (2018)** linked thromboembolic events, notably myocardial infarction, to specific antiphospholipid antibodies (e.g., Anti-cardiolipin antibodies (aCL)) but not anti-b2-GPI. This shows greater antiphospholipid antibody interactions.

Contrary to **Najim et al. (202),** severely sick COVID-19 patients had reduced thrombosis rates (8%, 5/60). Methodological differences likely caused this mismatch.

Conclusion

Our study reveals a significant association between APS and Post-COVID-19 MI. APS was found to be more prevalent in cases of MI after COVID-19 infection, along with higher levels of aPLs and altered laboratory parameters such as ESR, CRP, Troponin, and Calcium levels. Additionally, a history of COVID-19 infection was more common among APS patients. These findings suggest a potential link between APS and the occurrence of MI in individuals recovering from COVID-19.

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