**Table 2: Netosis and its association with the disease characteristics**

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study author and Title** | **NET markers in COVID-19 patients' serum compared to controls** | **NETs biomarkers associated with clinical biomarkers** | **NETs biomarkers associated with disease severity** | **NETs biomarkers association with thrombosis** | **Neutrophil and NETs infiltration in lungs of COVID-19 patients** | **Fluctuation of NET biomarkers with oxygenation** | **NETs biomarkers in those requiring respiratory support** | **COVID-19 patient’s serum** | **Effect of Treatment on NETs biomarkers** |
| 1. Wang, Li, Yin et al(3) | - | - | - Neutrophilia occurred in 6 of 8 severe patients  -Increased NLR associated with poorer prognosis.  -Neutrophilia-induced lung injury was suggested by higher CT value of lesions in those with higher neutrophilia | - | - | - | - | - | - |
| 2. Liu et al  (8) | - | - | -NLR > 3.7 was associated with severe COVID-19  -Neutrophil counts were higher in severe COVID-19 patients. | - | - | - | - | - | - |
| 3. Mutinelli-Szymanski  (9) | Increased anti-NET IgG and IgM in patients hospitalized with COVID-19 | Anti-NET IgG and IgM showed a positive correlation with D-dimer, Neutrophil count and Platelet count. | Anti-NET IgG and IgM were related to disease ease severity and the need for mechanical ventilation. | - | - | Anti-NET IgG and IgM showed a negative correlation with oxygen efficiency | Patients requiring mechanical ventilation had higher anti-NET IgG and IgM than those breathing room air. | Anti NET IgG and IgM from COVID-19 patients' serum prevented NET degradation in control serum on 90 mins of incubation. IgG from healthy donors was used as controls | - |
| 4. Yu Zuo et al(12) | Increased anti-NET IgG and IgM in patients hospitalized with COVID-19 | Anti-NET IgG and IgM showed a positive correlation with D-dimer, Neutrophil count and Platelet count. | Anti-NET IgG and IgM were related to disease ease severity and the need for mechanical ventilation. | - | - | Anti-NET IgG and IgM showed a negative correlation with oxygen efficiency | Patients requiring mechanical ventilation had higher anti-NET IgG and IgM than those breathing room air. | Anti NET IgG and IgM from COVID-19 patient's serum prevented NET degradation in control serum on 90 mins of incubation. IgG from healthy donors was used as controls | - |
| 5. Obermaye, Jakob et al(13) | -Increased NETs in Serum  - circulating platelet-neutrophil aggregates in COVID-19 patients compared to controls |  | Plasma NETs levels directly correlated with SOFA score which indicates the severity of illness | -Lung autopsy samples showed early-stage NETosis and Neutrophil-platelet aggregates in Blood vessels  -Increased levels of platelet-derived factors that trigger NETosis in COVID-19 patients' serum | -Robust PMNL infiltration seen in autopsies from lungs of patients who dies of COVID-19  -PMNs from lung autopsy specimens stains positive for NET markers indicating NETosis occurrence. | The ratio of PaO2/FiO2(a marker of the severity of respiratory failure) is inversely related to plasma NETs levels. | The level of NETs in intubated and non-intubated patients increased in both wrt HD  Plasma MPO-DNA complexes increased in those intubated and those who died | Triggers NETosis in healthy adults’ PMNs when incubated.  While healthy adults’ serum could not | As patients recovered from COVID-19, the level of NETs declined to come to match those in healthy adults. |
| 6. Middleton, He, Denorma et al  (19) | -Increased NETs in Serum  - circulating platelet-neutrophil aggregates in COVID-19 patients compared to controls |  | Plasma NETs levels directly correlated with SOFA score which indicates the severity of illness | -Lung autopsy samples showed early-stage NETosis and Neutrophil-platelet aggregates in Blood vessels  -Increased levels of platelet-derived factors that trigger NETosis in COVID-19 patients' serum | -Robust PMNL infiltration seen in autopsies from lungs of patients who dies of COVID-19  -PMNs from lung autopsy specimens stains positive for NET markers indicating NETosis occurrence. | The ratio of PaO2/FiO2(a marker of the severity of respiratory failure) is inversely related to plasma NETs levels. | The level of NETs in intubated and non-intubated patients increased in both wrt HD  Plasma MPO-DNA complexes increased in those intubated and those who died | Triggers NETosis in healthy adults’ PMNs when incubated.  While healthy adults’ serum could not | As patients recovered from COVID-19, the level of NETs declined to come to match those in healthy adults. |
| 7. Blasco, Coronado, Terciado et a(39) | - | - | Poorer prognosis in patients with NETs-derived thrombus of STEMI  (hypothesized) | -All coronary aspirates from COVID-19 patients with STEMI detected NETs compared to 68% of those with STEMI but without COVID-19.  -NETs density was higher in COVID-19 than in non COVID-19 STEMI patients | - | - | - | - | - |
| 8. Radermecker et al(40) | - | - | - | NET-prone primed neutrophils in the arteriolar microthrombi | Postmortem lung specimens from COVID-19 patients showed NETs infiltration in the airway and interstitium compared to no NETs in those who died of non-COVID-19 causes.  No NETs infiltration in postmortem specimens from COVID-19 patients’ liver, kidney, pancreas and heart | - | - | - | - |
| 9. Petito, Falcinella et al(41) | Increased  Higher in males than females |  | NETs biomarkers, and not platelet activation, correlated with disease severity and SOFA scores, and were higher in patients admitted to ICU. | NETs biomarkers and not platelet activation were increased and associated with Thrombosis in COVID-19 19 patients | - |  | NETs biomarkers were higher in ICU patients and those requiring mechanical ventilation – but not platelet activation parameters. | COVID-19 19 patients’ serum caused platelet and neutrophil activation and NET formation in vitro.  Was blocked by LMWH dose-dependently but not by aspirin and dipyridamole. | No difference in NETs levels in COVID-19 patients treated with LMWH vs those who were’  Platelet P selectin, PMPs, Platelet leukocyte and Platelet-neutrophil complexes and MMP-9 normalized on recovery from COVID-19, but not of the NET biomarkers. |
| 10. Ng, Haverall et al  (42) | Increased | NETs biomarkers correlated with TLC, Neutrophil count, NLR, CRP and inflammatory cytokine TNF-a and IL-6 levels  Correlated with levels of in vivo coagulation markers and markers of fibrinolysis and endothelial damage-D dimer, PAP, TAT,vWF, ADAM-TS-13 | Higher NET markers at the time of admission were associated with poor prognosis, ICU admissions and even mortality. | - | - | - | NET biomarker levels were associated with respiratory support requirement and short-term mortality | - | NETs biomarkers declined 4 months post-infection. |
| 12. Matthias H. Busch et al(44) | - | - | - | - | - | - | - | Serum from severe COVID-19 patients induced extensive NETosis in healthy donors' neutrophils  While moderate and mildly diseased patients did not. |  |
| 13 Vera et al  (45) | Increased NETs and neutrophilia. | - | NETs were found to be released in the lung tissue and were associated with lung damage in COVID-19 patients. | - | Increased NETs in COVID-19 patients lung autopsies and tracheal aspirates compared to healthy controls. | - | - | -Release of NETs by healthy neutrophils induced by SARS-CoV-2  -NETs promote lung epithelial cell death in vitro | - |
| 14. Zuo et al  (47) | Increased | MPO-DNA strong positive correlation with ANC  -Cit-H3levels positively correlated with platelet count | - | - | - | Increased with decreased oxygenation | Patients on mechanical ventilation had higher cell-free DNA and MPO-DNA (but not Cit-H3) levels compared to those breathing room air. | Trigger control neutrophils to release NETs | No difference in NETs markers in those treated with hydroxychloro  quine for days vs those who weren’t |
| 15. Yu Zuo et al(48) | Elevated NETs and Neutrophils | - | - | Increased NETs biomarkers are associated with morbid thrombotic events even when patients are on prophylactic anticoagulants.  COVID-19 thrombotic group had higher platelets but not higher peak neutrophils compared to COVID-19 non-thrombotic group. | - | Calprotectin and cell-free DNA was associated with worse oxygen efficiency. | No significant difference in SpO2 of COVID-19 thrombotic and non-thrombotic groups, but those in the thrombosis group required mechanical ventilation more. | - | - | - |

SARS-CoV 2-Severe acute respiratory syndrome virus-2

EETs -Eosinophil extracellular traps

EETosis - Eosinophil extracellular trap cell death.

NETs -Neutrophil extracellular traps NETs

ARDS -Acute respiratory distress syndrome

MPO-Myeloperoxidase

NETosis - Neutrophil extracellular trap

DAMPs -Danger-associated molecular patterns

PAD4-peptidyl arginine deiminase 4

ROS -reactive oxygen species

SIRS -inflammatory response syndrome

PRR -pattern recognition receptor

TLR -Toll-like receptors

CBC -Complete blood cell

IL-Interleukin

TNF: Tumor necrosis factor

TLC: Total leukocyte count

GGT: Gamma‑glutamyl transpepatientidase

COVID‑19: Coronavirus disease 2019

USG: Ultrasonography

CT: Computed tomography

IHC: Immunohistochemistry

N/A: Not available

ARDS: Acute respiratory distress syndrome

Hb: Hemoglobin

HbA1c: Glycated Hb

WBC: White blood cell

RBC: Red blood cell

ALT: Alanine aminotransferase

CRP: C‑reactive protein

LDH: Lactate dehydrogenase

RV: Right ventricle

LV: Left ventricle hypertrophy

RA: Right atrium

BMI: Body mass index

CAD: Coronary artery disease

MI: Myocardial infarction

ESR: Erythrocyte sedimentation rate

MF: Myocardial ischemia

MH: Myocardial hypertrophy

PMI: Postmortem interval

McH: Myocyte hypertrophy

IF: Interstitial fibrosis

RT‑PCR: Real‑time reverse transcription–polymerase chain reaction

AST: Aspartate aminotransferase

GFR: Glomerular filtration rate

FFPE: Formalin fixed paraffin embedded

EM: -Electron Microscopy

PM: post mortem BNP: Brain natriuretic peptide

INR: international normalised ratio,

NTproBNP: N-terminal pro-B type natriuretic peptide

CK: creatine kinase

IHD: ischaemic heart disease

PCT: procalcitonin

DAD: diffuse alveolar damage