**Table 1:Clinical and laboratory manifestations of the effect of Netosis in COVID-19 patients**

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| Study author and Title | Study Name | Participants no. Age and sex BMI | Comorbidities | Management  a.)Medications | b.)Respiratory support | Thrombotic complications | NETs findings | Laboratory findings | Outcome |
| 1. Wang, Li, Yin et al(3) | Excessive Neutrophils and Neutrophil Extracellular Traps in COVID-19 | n = 55  45 yrs  49.1% males | Diabetes 9.1%  Heart disease 1.8%  Thyroid disease 3.6%  Cancer 3.6%  HTN 23.6%  H/O surgery 14.5% | - | - | - | 1 Neutrophilia occurred in 6 of 8 severe patients  2 Increased NLR associated with poorer prognosis.  3 Neutrophilia-induced lung injury was suggested by higher CT value of lesions in those with higher neutrophilia | |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | | White blood cell (×109/L)- Normal range (3.5–9.5)  Mild -5.3  Mod- 4.8  Severe-5.4  Neutrophil-normal range (1.8-6.3)  Mild-2.9  mod-3.0  severe- 3.4   |  |  |  | | --- | --- | --- | | Lymphocyte Normal range (11.3.2)  Mild-1.9  Mod-.1.3  Severe-1.0  Monocyte Normal range (0.1-0.6)  Mild-0.5  Mod-0.5  Severe-0.4  Platelets Normal range (125.0-135.0)  Mild-194.5  Mod-191.0  Severe-154.0  NLR  Mild-1.8  Mod-2.3  Severe-2.4  Mono/lymphocyte ratio-  Mild-0.3  Mod-0.4  Severe-0.3 | 1.1–3.2 | 1.0 (0.7–1.6) | |  |  |  |  |  | |  |
| 2. Liu et al  (8) | Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19 | n = 245  53.95 +- 16.90  46.53% males  BMI 23.67 +- 3.34 | Diabetes 9.39%  Heart disease 7.35%  Lung disease 3.27%  CLD 2.86%  Cancer 3.67%  HTN 21.22%  Immunodeficiency  H/O smoking 4.08% | - | - | - | With every unit rise in NLR, the risk of death increased by 8%  Neutrophil count was also correlated with the risk of death in the hospital. | Neutrophils 4.09 +- 3.97  Lymphocytes 0.98 +- 0.57  Platelet 181.56 +- 70.01  Hb 127.52 +- 18.78  PT 12.88 +- 1.34  Serum creatinineinine 86.46 +- 109.60  D-dimer 1102.17 +-4050.14 | Mortality 13.47% |
| 3. Mutinelli-Szymanski  (9) | Neutrophil: Lymphocyte ratio predicts short-term outcomes in COVID-19 in haemodialysis patients | n = 62  62.5 6 17 yrs  61% males | Diabetes 50%  Heart disease 32%  Lung disease 6%  Autoimmune 5%  Cancer 6%  H/O stroke 13%  HTN 84%  Immunodeficiency  H/O smoking  Dyslipidemia  H/O surgery | Antibiotic therapy 37%  Chloroquine 10%  Ritonavir/lopinavir 6%  Immunomodulatory therapy 19%  Oral steroids 16%  Anakinra 10%  Tocilizumab 2%  Anti-platelet therapy 52%  Vitamin K antagonist 10%  Steroid 11% | Oxygen therapy length (days) 6 +- 4 | Pulmonary Embolism 2% | Neutrophil counts, NLR, CRP, ferritin, and fibrinogen were significantly higher in severe COVID-19 patients. | Haemoglobin (g/dL) 11 +- 1.3  TLC (/mm3) 5099 +- 1633  Neutrophil count (/mm3) 3575 +- 1527  Platelet count (/mm3) Ferritin (ng/mL) 181 +- 65  CRP (mg/L) 18 +- 9  Creatinineine kinase (UI/L) 125 +- 135  LDH (UI/L) 264 +- 64 | ICU admission, 8%  Hospitalization length (days) 12+- 9  Recovery, n (%) 87%  Mean recovery time (days) 14 +- 6  Death, n (%) 10% |
| 4. Yu Zuo et al(12) | Autoantibodies stabilize neutrophil extracellular traps in COVID-19 | n = 328  59 ± 17 yrs  57.2% males | Diabetes 40%  Heart disease 42%  Renal disease 36%  Lung disease 41%  Autoimmune 4%  Cancer 13%  H/O stroke 7%  Obesity 52%  HTN 59%  Immunodeficiency 18%  H/O smoking 25% | - | - | Thrombus:  Arterial 0.6%  Venous: 6% | 1 Increased anti-NET IgG and IgM in patients hospitalized with COVID-19  2 Anti-NET IgG and IgM showed a positive correlation with D-dimer, Neutrophil count and Platelet count.  3 Anti-NET IgG and IgM were related to disease severity, oxygen efficiency and the need for mechanical ventilation.  4 Anti-NET IgG and IgM from COVID-19 patients sera prevented NET degradation in control sera on 90 mins of incubation | - | Mortality 20% |
| 5. Obermaye, Jakob et al(13) | Neutrophil Extracellular Traps in Fatal COVID-19 associated Lung Injury | n = 7  78 (66-96) | Diabetes 43%  Heart disease 71%  Lung disease 14%  Cancer 29%  Obesity 14%  H/O smoking 57% | - | - | The increased presence of NETs and NETs generating neutrophils in COVID-19 patients' sites of intravascular clotting. | 1. Increased presence of NETs and NETs generating neutrophils in COVID-19 patient's lungs, sites of alveolar damage and intravascular clotting  2. Higher prevalence of microthrombi in COVID-19-associated DAD than in DAD in general. | CRP (mg/l) 262.4 (82.1–512.3)  LDH 605.1 (236–1605) Hemoglobin (g/l) 108.3 (73–132) Anemia, n (%)6/7 (86)  Total white blood cell count 10.8 (1.75–27.08)  Neutrophilic granulocytes 9.6 (2.86–25.32)  Lymphocytes 0.6 (0.24–0.96) Lymphopenia, n (%)7 (100)  Neutrophilia, n (%)4 (57)  Platelets ) 222.9 (16–400) | Hospital time(days)  5.1(3-9) |
| 6. Middleton, He, Denorma et al  (19) | Neutrophil Extracellular Traps contribute to immune  thrombosis in COVID-19 acute respiratory disease stress syndrome | **non ICU** 19 Age 48.2 +- 13.6, 53% male, BMI 33.9 +- 9.6  **ICU** 14 Age 64.5+-13.7, 57.1% male, BMI 30.5+-9.4 | Diabetes 31.6% non ICU, 57.1% ICU  Lung disease 26.3% non ICU , 42.9% ICU  HTN 36.8%, non-ICU, 42.9% ICU | - | Mechanical Ventilation  0% non-ICU  50% ICU | - | 1. Lungs of COVID-19 patients had robust PML and NETs infiltration 2. Higher levels of NETs were found in the plasma of COVID-19 patients compared with healthy controls 3. NETs were significantly high in the plasma of both intubated and non-intubated patients compared to HD | TLC : 6.1 +-2.4 non ICU, 8.3 +- 2.3 ICU  Platelet: 245+-107 non ICU, 244+-56 ICU | 28-day survival  100% non-ICU  71.4% ICU |
| 7. Blasco, Coronado, Terciado et a(39) | Association of Neutrophil Extracellular traps in Coronary Thrombus of a Case Series of Patients with COVID-19 and myocardial infarction | n = 5  62 +- 14  80% male | Diabetes 0%  HTN 80%  H/O smoking 40%  Dyslipidemia 0% | - | - | Occlusion of. 1. RCA 80% 2. CCA 20%  All thrombi in COVID-19 patients are composed of Fibrin and PMNs, and none of the atherosclerotic plaque fragments or iron | 1. All thrombi in STEMI COVID-19 patients were detected to have NETs(median density 61%)   The number of NETs in these patients was higher than found in STEMI patients without COVID-19 in historic studies | TLC = 18,300(11,500-19,400)  Platelet 346(322-419)  CRP 2.9(1.9) |  |
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| 8. Radermecker et al(40) | Neutrophil Extracellular Traps infiltrate the lung airway, interstitial, and vascular compartment in severe COVID-19 | n = 4  60.75 yrs  75% male | Diabetes 50%  Lung disease 25%  Obesity 25%  HTN 25% | Hydroxychloroquine 100%  Antibiotic 100%  Any anticoagulant 25% | Mechanical ventilation 50% | Arteriolar thrombi found in the lungs of 3 out of 4 patients  NET-prone primed neutrophils in the arteriolar microthrombi | 1 Postmortem lung specimens from COVID-19 patients showed NETs infiltration compared to no NETs in those who died of non-COVID-19 causes.  2 NET infiltration in the airway compartment and interstitium.  3 NET-prone primed neutrophils in the arteriolar microthrombi  4 No NETs infiltration in postmortem specimens from COVID-19 patients’ liver, kidney, pancreas and heart | TLC 16.265  Platelet 80  CRP 272.75  D dimer 5813.5 | Hospitalization time(days) : 20  Mortality: 100% |
|  |  |  |  |  |  |  |  |  | - |
| 9. Petito, Falcinella et al(41) | Neutrophil more than platelet activation associated with Thrombotic complication in COVID-19 patients | n = 36  70.6 +-2.8  55.5% males | Diabetes 16.6%  Obesity 13.8%  HTN 41.6%  H/O smoking 8%  Cirrhosis 2.7%  Renal Failure 8.3%  Stroke 5.5%  PAD 5.5%  A fib 13.8% | Antihypertensives 19.4%  Statins 11.11%  Aspirin 13.88  Anti P2Y12 5.55%  LMWH 80%  Apixaban 8.33%  Hydroxychloroquine 13.8%  Darunavir/Cobicistat 5.55%  Tocilizumab 2.77% | - | Thrombotic events in 25% of patients | 1.Net biomarkers correlated with disease severity and thrombosis.  2. COVID-19 patients’ sera caused platelet and neutrophil activation and NET formation in vitro. | Platelets (x 103/uL) 209.1±22.3  Neutrophils (x 103/uL) 4.3±0.8  NLR (neutrophil to lymphocyte ratio) 6.0±1.2  D-dimer (ng/mL) 1634±325.3  Fibrinogen (mg/dL) 371.6±30.4  VWF Ag (%) 297.8±26.3  VWF RCo (%) 319.2±27.8  Procalcitonin (ng/ml) 1.5±1.2  CRP (mg/dL) 5.1±1.5  LDH (U/L) 251.2±28.3 |  |
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| 10. Ng, Haverall et al  (42) | Circulating Markers of Neutrophil Extracellular Traps are of prognostic value in patients with COVID-19 | n = 106  60(50-69) yrs  64% males | Diabetes 25%  Heart disease 18%  Renal disease 9.4%  Lung disease 4.7%  Cancer 1.9%  Obesity 32%  HTN 40% | Antibiotic 24%  Corticosteroids 13%  LMWH preventive dose (%) 57%  LMWH double preventive dose (%) 24%  LMWH treatment dose (%)0.94%  OAC (%)3.8%  Any anticoagulant (%)85% | Mechanical ventilation 1.9%  Nasal cannula 62% | - | 1.NET biomarkers were increased in COVID-19 patients compared to controls.  2.NET biomarker levels were associated with respiratory support requirement and short-term mortality  3.NET biomarker levels also correlated with WBC, neutrophil, circulatory cytokines and CRP levels and to markers of in vivo coagulation. | H3Cit-DNA, ng/mL; median (IQR) 191 (136–294)  cfDNA, ng/mL; median (IQR) 551 (476–661  NE, ng/mL; median (IQR) 144 (84–248) | - |
| 11. L Staats et al( (43) | IgA2 Antibodies against SARS-CoV-2 Correlate with NET Formation and Fatal Outcome in Severely Diseaseeased COVID-19 Patients. | Mild 34, 39(19-65) yrs, 82% males  Mod 3, 68(34-96) 55% males  Severe 17, 68(37-78) yrs, 76% males | Diabetes 6%, 26%, 29%  Heart disease 0%, 26%, 29%  Lung disease 0%, 3%, 24%  HTN 3%, 58%, 76% | - | - | - | 1 Anti SARS-CoV2 IgA2 but not IgG was a marker for NETs formation, severe disease and poor prognosis  2 Patients with moderate and severe disease had a higher level of NETs biomarkers | - | Hospitalization time 0(0-14) mild, 8(1-64) moderate, 31(2-50) severe  Mortality: 0 mild, 0 moderates, 4(24%) severe |
| 12. Matthias H. Busch et al(44) | Neutrophil and Contact Activation of Coagulation as Potential Drivers of COVID-19 | Mild 54, 62 +-16 yrs, 53% males  Moderate 68, 69+-13 yrs, 62%  Severe 106, 69+-12, 74% | Diabetes 22%, 15%, 24%  Heart disease 28%, 34%, 30%  Renal disease  Lung disease 17%, 24%, 12%  H/O stroke 13%, 12%, 14%  HTN 30%, 40%, 33% | - | - | Thrombotic events:  Mild: 2/54  Moderate: 3/68  Severe: 23/106  Hypercoagulability (i.e. increased thrombin: antithrombin):131/217 (60%) | 1 Sera from severe COVID-19 patients induced extensive NETosis in healthy donors' neutrophils  2 While that from moderate and mildly diseased patients did not. | TLC 5.9 (5.1–8.5), 6.6 (4.7–9.0), 7.5 (5.8–10.1  Neutrophils 4.5 (3.5–6.3), 5.0 (3.4–7.4), 5.9 (4.6–8.1)  Lymphocyte 1.2(0.7-1.5), 0.8(0.6-1.2), 0.7(0.5-1.1)  Platelet 225 (±97), 213 (±88), 209 (±66)  CRP 57 (17–96), 66 (39–123), 101 (56–179)  LDH 273 (±91), 362 (±142), 480 (±191)  AST 38 (27–55), 49 (36–64), 54 (39–79)  Albumin 34 (31–38), 34 (30–36), 29 (26–32)  Creatinine 83 (61–110), 86 (71–112), 92 (71–121)  High C5a 63%, 89%, 74%  Extracellular histone H3, n/N : 0/44, 8/65, 14/102  In vitro NETosis, n/N : 0/5, 0/5, 9/9 | Hospitalization days: 7(5-11) mild, 7(5-14) moderate, 7(5-14) severe |
| 13. Vera et al  (45) | SARS-CoV-2-triggered neutrophil extracellular traps mediate COVID-19 pathology | n = 32  58.9 +- 18.2 yrs  53% males | Diabetes 50%  Heart disease 19%  Renal disease 12.5%  Lung disease 28%  Autoimmune 3%  Cancer 6%  H/O stroke 9.5%  Obesity 44%  HTN 59%  Immunodeficiency 3%  H/O smoking 25% | Antibiotic 88%  Antiviral 50%  Heparin 88% | Mechanical ventilation 53%  Nasal cannula 47% | - | 1 Neutrophilia and increased NETs in serum, tracheal aspirates and lung autopsy specimens, when compared to controls  2 Increased ability of neutrophils from COVID-19 patients to release NETs | Neutrophils 7294 +- 4983  Platelet 274892 +- 125497  CRP 13.8 +- 10.1  LDH 513.5 +- 285.8  D Dimer 3.6+-3.2  Ferritin 2591.1 +- 4047.8 | Hospitalization time(days): 9.4+-5.5  Mortality 19% |
| 14. Chen et al  (46) | Clinical characteristics of 113 deceased patients with Coronavirus disease 2019 – a retrospective study | N = 274  62(44-70)yrs  62% males | Diabetes 17%  Heart disease 8%  Renal disease 1%  GI disease 1%  Lung disease 7%  Thyroid disease  HBsAg + 4%  Autoimmune 1%  Cancer 3%  H/O stroke 1%  HTN 34%  H/O smoking 7%  Pregnancy 1% | Antiviral therapy 86%  Glucocorticoid therapy 79%  Antibiotics 91%  Intravenous immunoglobulin therapy 20%  Interferon inhalation 32% | Oxygen treatment92%  High flow nasal cannula 31%  Mechanical ventilation 43% |  | - | white blood cell count, ×109/L 5.9 (4.3-9.2)  neutrophil count,×109/L 4.4 (2.8-8.0)  haemoglobin, g/L 128.0 (116.0-140.0)  platelet count, ×109/L 179.0 (133.0-235.0)  ferritin, μg/L (30-400) 669.7 (388.8-1494.6)  CRP 53.4 (18.6-113.0)  LDH 321.5 (249.8-510.5)  Serum creatinineinine μmol/L 76.0 (58.0-94.0)  D dimer 1.1(0.5-2.2) | Deaths = 113  Recovered = 161 |
| 15. Zuo et al  (47) | Neutrophil Extracellular Traps in COVID-19 | n = 50  Mean age and range = 61 + 15  66% males  BMI : 3.7 +- 4.1 | Diabetes 32%  Heart disease 24%  Renal disease 32%  Lung disease 34%  Autoimmune 8%  Cancer 20%  H/O stroke 6%  Obesity 46%  HTN 74%  Immunodeficiency 6%  H/O smoking 36% | Hydroxychloroquine 48%  Anti IL-6 receptor 4%  ACEi 2%  Antibiotic 44% | Mechanical ventilation 32%  High flow oxygen 4%  Nasal cannula 34%  Room air 30% | - | 1. NET remnants markers were increased in COVID-19 patients sera compared to controls  2. Nets markers increased with deceased oxygenation  3. COVID-19 sera trigger control neutrophils to release NETs | - | - |
| 16. Yu Zuo et al(48) | Neutrophil extracellular traps and Thrombosis in COVID-19 | n = 11  56 ± 12 (38–77) yrs  81.9% males | Diabetes 36.4%  Heart disease 45.5%  Renal disease 36.4%  Lung disease 9%  Autoimmune 9%  Cancer 9%  H/O stroke 9%  Obesity 54.5%  HTN 54.5%  Immunodeficiency 0  H/O smoking 36.4%  Dyslipidemia  H/O surgery | 9 out of 11(82.2%) were receiving prophylactic heparinoids at the time the thrombotic events were diagnosed  2 who weren't on prophylactic heparinoids had PE at the time of admission. | Mechanical ventilation 82%  The nasal cannula is 9%  Room air 9% | 11 patients with COVID-19 who developed thrombosis were studied | 1 Increased NETs and neutrophils in COVID-19 patients  2 NETs remnants and neutrophil-derived S100A8/A9 in COVID-19 patients’ sera were associated with a higher risk of morbid thrombotic events despite prophylactic anticoagulation.  3 Increased NET biomarkers associated with poor oxygen efficiency | Troponin T: 39 (6–285)PEAK  Platelet 416 (234–619) PEAK  CRP 29 (14–54)PEAK  LDH 661 (494–5295)PEAK  D dimer 18 (1.5–35) PEAK  Ferritin 2370 (149–7730) PEAK | Mortality: 18.1% |

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