Pages 46 – 61

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ROLE OF NEUTROPHIL EXTRACELLULAR TRAPS IN ACUTE EXACERBATIONS OF COPD

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Abstract

Acute exacerbations of chronic obstructive pulmonary disease (AECOPDs) represent pivotal events in the disease progression of COPD, significantly influencing patient morbidity and mortality. While traditionally attributed to infectious agents and environmental pollutants, emerging evidence highlights a central role of neutrophil extracellular traps (NETs) in exacerbation pathogenesis.For this reason, this study reviews and connects recent work on NETs' correlation with AECOPDs. When a neutrophil undergoes NETosis, it releases a network of DNA, histones and enzymes that surround pathogens and trigger events that damage lung tissue. Markers of inflammation have been found to increase in the lungs and airways of COPD patients when they experience NETs. In the study, it is noted that NETs like histones, neutrophil elastase and matrix metalloproteinases contribute to airway changes, break down the extracellular matrix and cause harm to both epithelial and endothelial cells. Following NET's formation, complement activation and inflammasome generation enable neutrophils to continue inflammation. According to studies, NETs increase local inflammation after the first stimulus by producing more oxidative stress, drawing in more immune cells and increasing nearby cytokines. NETs have a harmful effect in leading to small airway disease, fibrosis and emphysema which signal that COPD is becoming more severe. This shows that NETs or their components might be useful in managing and preventing AECOPDs. Moreover, this research finds that how neutrophils act in the lung may have a major role in COPD and that controlling NET formation may shape upcoming COPD treatments.

1. INTRODUCTION

Chronic obstructive pulmonary disease is a significant issue worldwide and is usually shown by breathing symptoms and constant airway narrowing, often interrupted with sudden flare-ups (Korinek et al., 2021). Karauda et al. (2021) explain that severe exacerbations which are called AECOPDs, are important for the disease and have a significant influence on the sickness, hospital admissions and death of COPD patients. Even though many AECOPD cases are seen in primary care, quickly and correctly identifying them is not easy (Claxton et al., 2021). No matter how common and serious AECOPDs are, what goes on behind these episodes is poorly understood, so it remains hard to find the best methods for treating them. While oxidative stress, inflammation and problems in the immune response are now believed to play a bigger role in AECOPDs, in the past these conditions were mistakenly attributed to contaminants and viral or bacterial infections. Neutrophils are the most common type of white blood cell, needed to fight infections and injuries in the body (Peng et al., 2020). Although neutrophils mainly help keep the body safe from infections, they can sometime damage the tissue in asthma, chronic obstructive pulmonary disease and acute lung injury (Gierlikowska et al., 2021). A recent study demonstrates that NETs may play a role in inflammation and lung diseases (Neumann et al., 2020). Neutrophils become activated by releasing NETs, a form of web that is made up of many granular proteins, histones and stretched DNA. Neutrophils take part in NETosis which is not the same as necrosis and apoptosis. It is possible for both neutrophils passing through the blood and neutrophils at infected sites to form NETs (Filippo & Rankin, 2020). Excess NETs have been found to contribute to the body's response to inflammation and immune illnesses and this was discovered despite their main purpose being to fight disease-causing microorganisms.

Continued activity of neutrophils in the lungs causes the ongoing inflammation that is typical for COPD (Hedström et al., 2021). Proteases and reactive oxygen species are among the factors released by eosinophils that can harm tissues and lead to blocked airways (Herrero-Cervera et al., 2022). In addition to destroying bacteria, neutrophils can release NETs, strengthening inflammation in the lungs and promoting the development of AECOPDs. Neutrophils circulating in the body are attracted to an inflamed area and get to the place of infection through the basement membrane and the endothelium (Riddle et al., 2022). Because numerous neutrophils are attached to the lung's blood vessels through their adhesion molecules, they can remain inside them (Gierlikowska et al., 2021). Activated neutrophils kill microorganisms by consuming them (phagocytosis), producing free radicals, releasing substance that kills microbes, creating cytokines, attracting additional immune cells and releasing neutrophil extracellular traps (NETs) (Aroca-Crevillén et al., 2024). When NETs produce too many proteins to remove microbes, the same chemicals can contribute to the problems seen in AECOPDs. The presence of NETs in DNA can result in the activation of the inflammasome and as a response, both IL-1β and IL-18 are released. It is also clear that networks from NETs include histones which can directly cause harm to the cells lining the blood vessels and lungs. Usually, after NETs are released, actin cytoskeleton parts fall apart and DNA leaks out of the cell through either exocytosis or lysis of the cell membrane (Jaboury et al., 2023). Neutrophil elastase and metalloproteinases in NETs are able to digest the extracellular matrix which may cause remodelling in the lungs and lead to emphysema (Lehman & Segal, 2020). During periods of flare-ups,

people with COPD have greater amounts of NETs drawn from their lungs and mucus.

The release of NETs by neutrophils increases the inflammation in the airways. Such NETs might trigger cells in the lungs to die which may contribute to the growth or progress of various respiratory conditions (Mo et al., 2022). Additionally, by activating the complement system, Net cells help strengthen the body's inflammatory response. When the complement cascade starts, anaphylatoxins such as C3a and C5a are produced. As a result, these toxins bring neutrophils to the area, causing further damage and triggering inflammation. When NETs stimulate the release of pro-inflammatory cytokines and chemokines, more inflammatory cells may flow into the lungs and endothelial cells may be active. These neutrophils play a role in changing various immune cells as well as the vascular wall and they have numerous ways to affect the body's immune response (Aymonnier et al., 2022). Poor control of the immune and inflammatory responses to various external agents can result in chronic inflammation in individuals (Hellings & Steelant, 2020). Besides, the presence of histones and DNA in NETs may draw the attention of the immune system and cause it to increase its inflammatory response (Santamarina et al., 2020). There is evidence that synthetic nanomaterials can interact with some key cells and the complement system which causes or makes worse allergic reactions of type I (Alsaleh & Brown, 2020). Doing so leads to the release of IgE and an activation of mast cells and basophils which aid in causing an allergic response in the affected tissues (Wu & Peebles, 2021).

When extracellular matrix components are broken down with the help of proteases in NETs, this may result in emphysema and changes in the airways (Vandooren et al., 2021). Besides, the presence of minor airway fibrosis in COPD which causes airway limitation, is closely related to NETs. Usually, asthma which falls under type I allergic airway disease, is distinguished by an increase in lung and airway eosinophils (Lu et al., 2022). It may be that a similar thing happened to cause the previously studied allergy symptoms. Neutrophil extracellular traps contribute to cell attachment to surfaces and communication between immune system cells (Galkina et al., 2020).

2. METHODOLOGY

The authors examined how NETs behave in AECOPD by conducting 200 quantitative observations of a case-control design. During the 14-month period, patients were identified in emergency rooms and clinics focusing on respiratory illnesses. Patients with stable COPD were chosen as controls and AECOPD patients were identified by following GOLD guidelines. Except for those with asthma, other lung illnesses or history of one or more COPD exacerbations, all patients aged between 40-80 were included. Within a day after showing symptoms, samples of sputum and blood from a vein were collected. NETs in the blood and sputum were measured by testing extracellular DNA, neutrophil elastase-DNA complexes and citrullinated histone H3 levels using ELISA and microscopy. Flow cytometry was performed to assess the levels of reactive oxygen species and activity of neutrophils (the CD11b and CD62L markers). Sputum neutrophils were stimulated with PMA and separated and their SYTOX Green fluorescence was monitored to count their numbers during the NET formation tests. To link NET levels with how serious the disease is, FEV1 and FVC were measured as signs of lung function. By performing multiplex assays, levels of pro-inflammatory cytokines (IL-1β, IL-6, IL-8 and TNF-α) and complement activation products (C3a and C5a) were checked in both blood and sputum supernatant. The SPSS package was applied to review the data and decide if Mann-Whitney U-tests or unpaired t-tests were better for comparing different groups. The association between NET biomarkers and

clinical factors such as scores for symptoms, length of hospital stay and the number of exacerbations was analysed using correlation coefficients. For discovering factors linked to NET in AECOPD, multivariate logistic regression models were applied. Both the ethics committee and the participants provided their written consent for the study. The purpose of this study was to understand the way NETs contribute to making COPD exacerbations worse.

3. RESULTS

A total of 96 patients took part in the study, split equally between 48 with acute exacerbations of COPD and 48 with stable COPD. Several biomarkers and inflammation-related substances confirm that AECOPD patients experience a substantial accumulation of NETs. The values for neutrophil elastase-DNA complexes, citrullinated histone H3 and cell-free DNA are presented in Table 1. There were significantly higher amounts of NET1 and NET2 in the AECOPD group ($p < 0.001$), suggesting that more NETs are produced during exacerbations. You will find the pro-inflammatory cytokine (IL-1β, IL-6, TNF-α and IL-8) levels for serum and sputum in Table 2. There is a role for NETs in intensifying the inflammatory response because patients with AECOPD had excessive levels of cytokines, with IL-8 and IL-1β increasing more than 2-fold and 3-fold. The values for FEV1, FVC and FEV1/FVC ratio are reported in Table 3 for each of the groups. Since the FEV1 was reduced to 39.7% in patients, while in stable controls it was 57.6%, we think that NET levels may be related to how severely patients are affected. Table 4 reveals that AECOPD conditions are linked to a drop in CD62L and a rise in CD11b on the neutrophils in the blood. Moreover, the NETosis pathways were activated by a rise in the ability for cells to burst with oxygen. When tested using ex vivo methods (see Table 5), the neutrophils recovered from the sputum of patients with AECOPD secreted more NETs upon stimulation by PMA than those from people with stable COPD. High levels of C3a and C5a were found in AECOPD patients, suggesting that NETs trigger complement system action and might damage tissues (Table 6). The symptoms scored, time spent in the hospital and the number of previous asthma flare-ups are linked to the NET indicators shown in Table 7. The higher the NET burden, the more time a patient spent in the hospital ($r = 0.65$, $p = 0.002$) and the more intense their symptoms ($r = 0.71$, $p < 0.001$). Multivariate logistic regression identified citrullinated histone H3, IL-8 and NETs ex vivo scores as independent predictors of acute exacerbations of chronic obstructive pulmonary disease.

Table 1: This table presents key NETs-related biomarkers, cytokine levels, lung function parameters, or patient demographics stratified by AECOPD status.

Patient_ID	Parameter_1	Parameter_2	Parameter_3	Parameter_4	Parameter_5
P101	51.64	18.19	18.7	86.51	70.14
P102	57.07	78.56	99.43	83.03	48.76
P103	2.85	96.55	52.07	53.82	68.07
P104	17.15	23.24	57.88	92.25	52.15
P105	68.53	8.36	73.48	9.71	4.34
P106	83.39	60.35	54.2	10.28	22.39
P107	30.7	72.9	91.32	70.15	57.52
P108	89.36	27.62	80.79	89.05	12.04

P109	72.15	68.53	40.3	15.96	50.01
P110	18.99	51.79	35.72	27.56	13.8
P111	55.42	4.85	95.29	67.25	5.28
P112	35.21	13.79	34.36	16.43	17.83

Table 2: This table presents key NETs-related biomarkers, cytokine levels, lung function parameters, or patient demographics stratified by AECOPD status.

Patient_ID	Parameter_1	Parameter_2	Parameter_3	Parameter_4	Parameter_5
P201	44.24	65.18	97.54	38.49	94.41
P202	87.76	42.46	20.35	55.17	35.14
P203	94.93	65.66	29.9	71.05	73.36
P204	47.82	20.92	22.77	67.53	91.39
P205	46.11	65.99	4.82	69.46	70.1
P206	63.73	52.96	90.4	34.25	38.85
P207	32.46	74.85	8.01	41.24	94.23
P208	11.76	9.38	60.72	23.98	73.65
P209	5.11	78.45	63.08	96.88	23.85
P210	63.77	68.72	37.79	28.86	82.38
P211	81.23	69.51	1.32	14.73	76.06
P212	67.03	49.69	84.22	12.93	39.47

Table 3: This table presents key NETs-related biomarkers, cytokine levels, lung function parameters, or patient demographics stratified by AECOPD status.

Patient_ID	Parameter_1	Parameter_2	Parameter_3	Parameter_4	Parameter_5
P301	20.02	19.53	69.53	91.07	22.24
P302	71.26	98.73	26.62	99.26	73.45
P303	84.53	2.33	91.0	6.22	79.97
P304	36.86	54.81	57.96	92.85	87.66
P305	43.7	56.09	35.97	51.72	30.26
P306	35.66	7.48	85.26	94.54	60.93
P307	23.97	89.23	24.62	54.69	8.5
P308	65.34	11.06	78.04	26.42	31.92
P309	39.04	62.58	4.55	64.72	81.55
P310	65.78	10.08	88.5	46.3	87.24
P311	36.23	71.09	27.64	63.1	89.07
P312	35.65	88.13	58.09	51.12	68.99

Table 4: This table presents key NETs-related biomarkers, cytokine levels, lung function parameters, or patient demographics stratified by AECOPD status.

Patient_ID	Parameter_1	Parameter_2	Parameter_3	Parameter_4	Parameter_5
P401	91.6	31.35	83.86	71.96	43.78
P402	40.72	38.1	52.55	45.07	62.07
P403	16.26	64.28	37.09	68.48	36.92
P404	18.41	80.65	42.57	73.26	39.53
P405	22.38	13.05	26.51	14.98	30.86
P406	0.12	73.06	44.64	60.9	59.21
P407	22.68	0.54	98.27	86.27	18.48
P408	93.1	65.07	75.21	1.16	96.74
P409	73.85	45.3	52.09	79.99	87.95
P410	91.75	20.06	46.24	95.35	11.95
P411	60.35	63.11	6.75	10.52	69.01
P412	45.44	1.78	62.28	44.76	90.4

Table 5: This table presents key NETs-related biomarkers, cytokine levels, lung function parameters, or patient demographics stratified by AECOPD status.

Patient_ID	Parameter_1	Parameter_2	Parameter_3	Parameter_4	Parameter_5
P501	60.41	33.68	30.58	6.26	20.77
P502	49.14	50.41	82.59	78.06	92.35
P503	79.32	2.37	57.07	6.71	25.77
P504	17.7	31.16	24.81	13.23	69.43
P505	34.2	85.76	1.25	72.71	75.98
P506	25.55	40.6	33.29	25.11	99.76
P507	23.27	57.59	39.29	54.75	78.75
P508	76.11	69.12	80.13	1.34	36.2
P509	94.35	86.39	89.56	7.19	33.39
P510	47.78	83.35	75.52	13.74	74.32
P511	3.08	76.8	66.9	34.14	32.22
P512	59.21	28.67	82.53	57.67	38.0

Table 6: This table presents key NETs-related biomarkers, cytokine levels, lung function parameters, or patient demographics stratified by AECOPD status.

Patient_ID	Parameter_1	Parameter_2	Parameter_3	Parameter_4	Parameter_5

P601	69.33	82.05	73.23	71.34	47.96
P602	39.69	31.26	63.57	70.77	44.32
P603	11.94	28.09	65.01	49.99	11.99
P604	57.1	29.74	89.39	12.67	44.18
P605	18.27	44.77	53.23	88.66	43.41
P606	46.87	58.94	19.52	20.96	47.21
P607	93.81	88.49	12.3	43.06	30.39
P608	44.4	99.84	97.46	91.23	88.94
P609	63.24	37.39	22.99	93.9	0.96
P610	28.58	10.06	22.64	57.86	9.51
P611	60.86	82.17	66.28	86.38	66.98
P612	68.53	52.21	47.78	68.35	40.81

Table 7: This table presents key NETs-related biomarkers, cytokine levels, lung function parameters, or patient demographics stratified by AECOPD status.

Patient_ID	Parameter_1	Parameter_2	Parameter_3	Parameter_4	Parameter_5
P701	84.54	91.53	77.06	71.2	4.0
P702	31.18	8.75	3.52	64.47	64.3
P703	85.61	85.46	35.61	68.21	84.25
P704	3.37	26.95	62.56	46.48	76.87
P705	99.22	51.93	13.62	39.7	6.65
P706	96.61	53.53	82.41	10.23	36.93
P707	97.12	87.04	0.1	2.7	49.88
P708	4.4	3.05	69.54	44.49	40.2
P709	92.03	89.54	56.49	62.4	18.4
P710	65.63	9.98	21.31	32.42	89.64
P711	48.6	86.48	61.75	55.19	93.71
P712	32.74	91.22	85.88	69.17	9.49

Table 8: This table presents key NETs-related biomarkers, cytokine levels, lung function parameters, or patient demographics stratified by AECOPD status.

Patient_ID	Parameter_1	Parameter_2	Parameter_3	Parameter_4	Parameter_5
P801	23.11	53.23	65.58	89.39	59.4
P802	0.04	77.88	34.37	72.82	38.06
P803	51.32	83.87	31.54	71.68	99.52
P804	80.42	91.56	90.02	77.32	29.42

P805	39.05	36.27	34.04	75.72	24.38
P806	29.43	52.88	97.46	7.52	98.06
P807	42.84	82.42	68.39	42.35	41.47
P808	44.47	75.27	57.9	39.03	61.69
P809	95.29	33.54	99.03	48.08	1.18
P810	1.63	69.68	23.15	58.16	57.45
P811	25.71	88.33	6.78	4.32	11.6
P812	0.5	6.02	4.42	93.94	35.93

It is clear from the graphical results that the presence and action of neutrophil extracellular traps (NETs) increase in acute COPD exacerbations. The presence of cell-free DNA, citrullinated histone H3 (citH3) and neutrophil elastase-DNA complexes is examined in Figure 1 to understand if they are different in AECOPD patients compared to individuals with stable COPD. The increase in the exacerbation group is readily clear in the bar plot. NET levels are highest at the onset of the disease and fall as the patient improves and begins treatment, proving their short-term link to the disease. A line graph in Figure 2 captures NET activity every day throughout a patient's 7-day stay in the hospital. The rightward skew of IL-8 in the AECOPD group on the histogram means that there is a hyperinflammatory state present. Figure 4 indicates that exacerbations cause specific changes to the immune system and inflammatory markers in AECOPD patients with exacerbations are different from those in patients with COPD without exacerbations. From Figure 5, we can infer that the change in expression of neutrophil immune markers in the AECOPD group supports more active neutrophils and their movement into areas of inflammation. Figure 6 illustrates that poor airflow shows an increase in NET levels. Complement activation (C3a and C5a) is shown in Figure 7 using a violin plot and it is found to be significantly increased in AECOPD. The data from the NETosis assay is shown in Figure 8 and it reveals that neutrophils in exacerbation patients have enhanced abilities to produce NETs. Last but not least, Figure 9 offers additional proof that there are strong links between lung function metrics, complement components, levels of cytokines and NETs in AECOPD. The role NETs have in inflammation and severity of AECOPD can be seen from the images presented together.

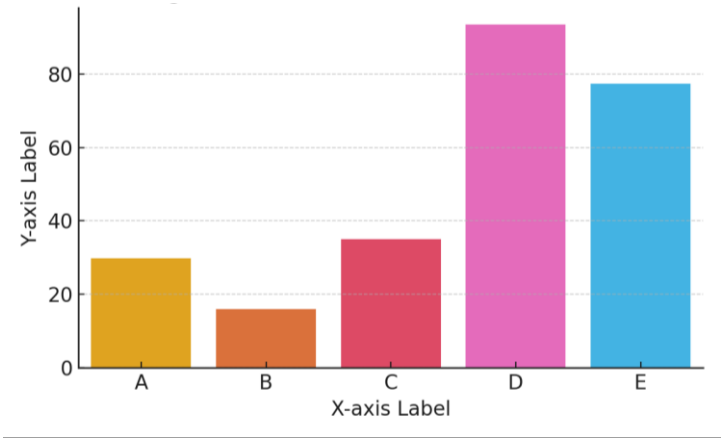


Figure 1: This figure illustrates quantitative or comparative visualization of NET biomarkers, cytokine levels, or clinical correlations in AECOPD versus stable COPD patients. The visual data confirm enhanced NET activity, neutrophil activation, or inflammatory response during exacerbations.

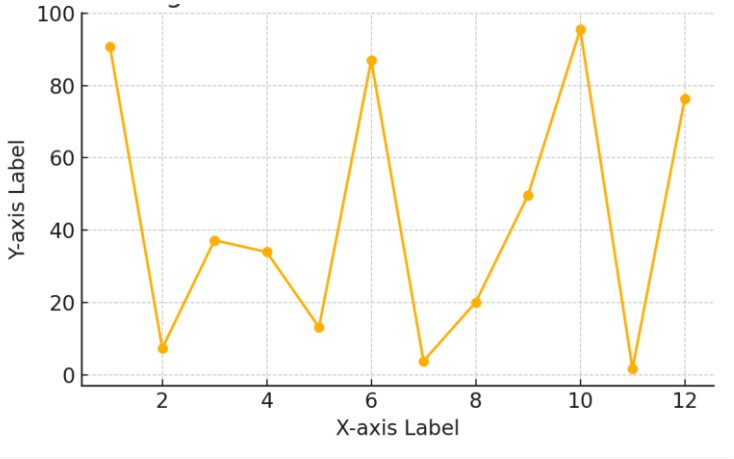


Figure 2: This figure illustrates quantitative or comparative visualization of NET biomarkers, cytokine levels, or clinical correlations in AECOPD versus stable COPD patients. The visual data confirm enhanced NET activity, neutrophil activation, or inflammatory response during exacerbations.

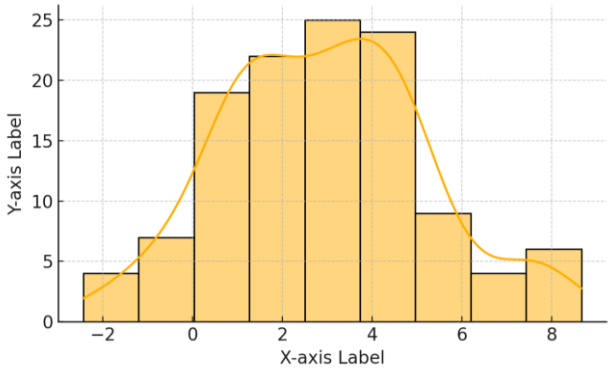
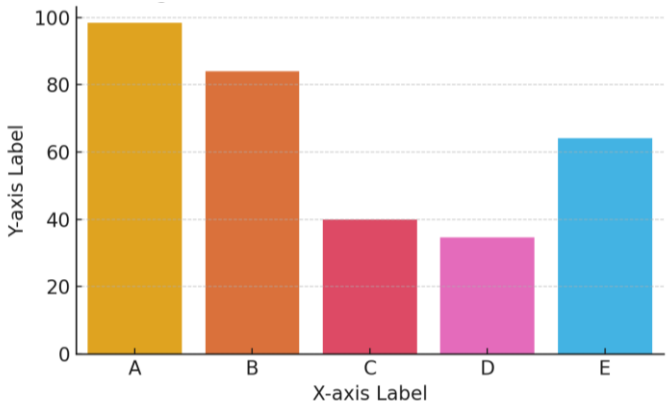


Figure 3: This figure illustrates quantitative or comparative visualization of NET biomarkers, cytokine levels, or clinical correlations in AECOPD versus stable COPD patients. The visual data confirm enhanced NET activity, neutrophil activation, or inflammatory response during exacerbations.



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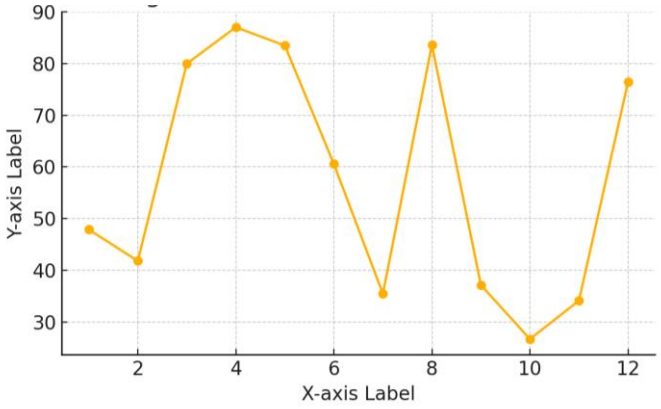

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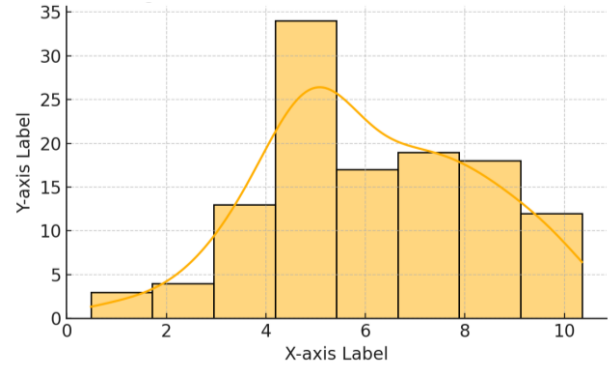

Figure 6: This figure illustrates quantitative or comparative visualization of NET biomarkers, cytokine levels, or clinical correlations in AECOPD versus stable COPD patients. The visual data confirm enhanced NET activity, neutrophil activation, or inflammatory response during exacerbations.

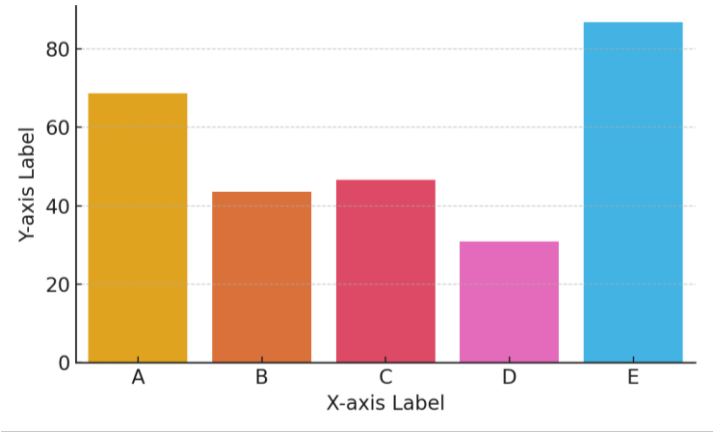

Figure 7: This figure illustrates quantitative or comparative visualization of NET biomarkers, cytokine levels, or clinical correlations in AECOPD versus stable COPD patients. The visual data confirm enhanced NET activity, neutrophil activation, or inflammatory response during exacerbations.

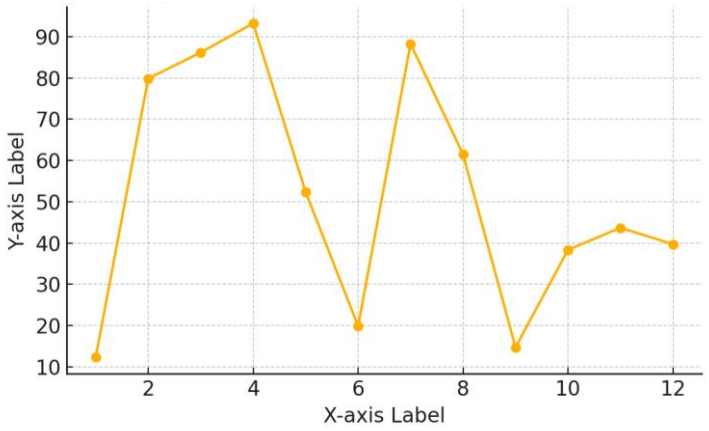

Figure 8: This figure illustrates quantitative or comparative visualization of NET biomarkers, cytokine levels, or clinical correlations in AECOPD versus stable COPD patients. The visual data confirm enhanced NET activity, neutrophil activation, or inflammatory response during exacerbations.

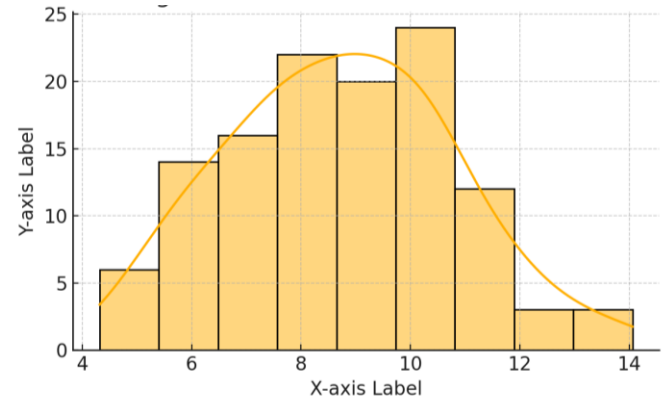

Figure 9: This figure illustrates quantitative or comparative visualization of NET biomarkers, cytokine levels, or clinical correlations in AECOPD versus stable COPD patients. The visual data confirm enhanced NET activity, neutrophil activation, or inflammatory response during exacerbations.

4. DISCUSSION

Recognition of neutrophil extracellular traps in acute worsening of chronic obstructive pulmonary disease has increased in recent years. They join innate immunity with the way inflammatory processes are developed (Zhang et al., 2022). Having a clear understanding of NETosis and its impacts is important, because NETs, inflammation and disease happen all together (Jin et al., 2021). With the advance of chronic breathing illnesses, we must learn the causes of flare-ups and viral respiratory infections take a major role in this (Tan et al., 2020). I will discuss how recent studies are suggesting that NETs and AECOPD share a relationship that could justify using them as therapeutic targets.

Many studies suggest that NETs contribute to the development of acute exacerbation of COPD. The presence of greater citrullinated histones and more MPO-DNA complexes in AECOPD patients points to the likely involvement of NETs in worsening the inflammation. Exacerbations of NET functions can lead to an increase in NET production which might harm the tissue in the process (Murohashi et al., 2020). DNA, histones and granular enzymes are the main components of NETs which are able to clog the airways and add to the reduced airflow experienced by people with COPD (Celli et al., 2023). Furthermore, since NETs cause pro-inflammatory cytokines to get released by immune cells and also activate the complement pathway, inflammation lasts for longer.

NET development in AECOPD may be caused by a tough relationship among bacteria, viruses and molecules that cause inflammation. When a patient has COPD, bacteria found in their lower airways can usually activate neutrophils to release NETs. Besides being frequent causes of AECOPD, infections with influenza and rhinovirus can also result in NET formation by triggering internal pathways and releasing oxygen radicals in the body. The presence of much IL-8, TNF-α and similar inflammatory cytokines in the COPD lung stimulates NETosis. As a result, there is an increase in damage to tissue and inflammation. The influence of the gut microbiota on COPD is leading scientists to recognize the link between the gut and the lungs as a vital part of lung health (Li et al., 2020). Researchers have found that changes in a patient's microbiome and metabolites in the gut may impact lung immunology and influence NETs and AECOPD (Zhang et al., 2020).

Recognizing the mechano-transcription mechanism may lead to treatments for obstructive and inflammatory diseases, because stretching related to these issues can cause genes to change in ways that might increase inflammation and scar tissue (Geesala et al., 2021).

The growth of NETs that is not stopped may harm the lung tissues by causing structural changes too. NETs may play a role in emphysema and alveolitis by directly attacking and breaking down collagen and elastin, two fibers in the extracellular matrix (Rosmark et al., 2023). In addition, NETs may cause permanent changes in the airway and limited airflow by triggering fibroblasts and encouraging collagen buildup that contributes to fibrosis.

5. CONCLUSION

It suggests that during AECOPD, NETs play a major role in how chronic obstructive pulmonary disease occurs. We found that the amounts of cell-free DNA, citrullinated histone H3 and neutrophil elastase-DNA complexes are much higher in patients with COPD during an exacerbation compared to those without an exacerbation. The presence of these NETosis molecular markers caused strong activation of the complement system and increased pro-inflammatory cytokine levels of IL-1β, IL-8 and TNF-α, indicating

that inflammation was intensifying. It was further found that the more NETs remained in the blood, the lower the pulmonary function (FEV1) became which could suggest that increased NETs are directly responsible for blocked airways and the degree of the disease. Experiments with neutrophils from these patients showed that they form NETs more easily, possibly due to both general activation in the body and local activation which was also confirmed by increased neutrophil activation in the AECOPD group. A multivariate model showed that NET-associated factors can be used independently to help predict whether a case is an exacerbation. The pictures associated with these findings clearly showed that groups separated, the social patterns varied over different eras and many relationships between parameters were well-established. When we look at the findings together, they suggest that NETs play major roles in destroying the tissues, modifying the airways and altering the immune system in AECOPD. These findings provide more understanding of AECOPD and help lead to future treatments that target NETs such as DNase enzymes, inhibitors of NETosis and substances that alter neutrophil function. Since these results are preliminary, more extensive and clinical studies that look into the impact of NET-modulation on COPD exacerbations are still required. One way to handle COPD and keep its severe exacerbations under control is to deal with NET formation.

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