RESEARCH PAPER

Biomarkers For Early Severity Prediction And Outcome Assessment In Pediatric Pneumonia

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ABSTRACT

This article has critically analyzed the use of biomarkers in prediction of early severity and outcome measures of pneumonia among children. One of the significant health issues globally until recently is the pneumonia of childhood especially in children below the age of five where early diagnosis on serious disease has led to higher morbidity and mortality rates. Conventional clinical evaluation procedures have been found to be poor in reflecting sudden degradation, and this fact necessitates the use of objective biological data. This paper has summarized the recent evidence on traditional inflammatory biomarkers like C-reactive protein and procalcitonin, cytokines like interleukin-6 and tumor necrosis factor-TNF-α, hematologic indices, oxidative stress biomarkers, tissue injury biomarkers, like lactate, and genetic susceptibility factors, especially GSTT1 polymorphism. The results have revealed that high concentrations of procalcitonin, interleukin-6, neutrophil-to-lymphocyte ratio, and lactate have been significantly related with ICU placement, the need of mechanical ventilation, the increase of the hospitalization, and the risk of mortality. Moreover, multi-biomarker strategies have been demonstrated to predict importance more effectively than single-marker strategies, and to contribute to better risk stratification at early stages and more patient-centered treatment of childhood pneumonia.

Keywords: "Pediatric pneumonia"; "Biomarkers"; "Severity prediction"; "Procalcitonin"; "Interleukin-6"; "GSTT1 polymorphism".

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1. Introduction

Pediatric pneumonia is one of the most prevalent causes of morbidity and mortality in the world especially in children below five years old. Globally, as per the health estimates, lower respiratory tract infections are the leading cause of childhood mortality, which could have been prevented, particularly in the low and middle income countries. Although the diagnosis of children with high risk of severe disease has improved with the development of vaccination, antimicrobial and supportive methods, it is still a clinical problem.

Even though the clinical severity assessment tools include WHO criteria and respiratory distress indicators, which are highly utilized, it is often limited to predictability due to the inter-observer variability and delayed physiological degradation. Clinical parameters

will not be sufficient in identifying changes that occur early in life before clinical deterioration. As a result, there is growing interest in objective lab biomarkers that are indicative of underlying inflammation, immunology and oxidatives processes that drive pathogenesis.

The article provides a critical analysis of the influence of inflammatory biomarkers, cytokines, hematological indices, oxidative stress biomarkers, tissue injury biomarkers, and genetic predisposition factors including GSTT1 polymorphism in children with pneumonia, even though it occurred early. As opposed to describing the associations, this paper examines the predictive discrimination, clinical applicability, and translational relevance of these biomarkers.

This study will be conducted with the objective of critically assessing the role of biomarkers in the early severity and poor clinical outcome of pediatric pneumonia.

The following are the objectives of the study:

- To determine the major biomarkers related to severe pediatric pneumonia.
- To determine the predictive ability of mechanical ventilation, length of hospital stay, and mortality of ICU admission.

2. Literature Review

2.1 The Biomarkers of Inflammatory and Stratification of Severity of Pneumonia in Children.

Detection of critical cases of severe pediatric pneumonia is a clinical problem that cannot remain unchanged, and a number of recent reports have tested inflammatory biomarkers as predictors of severity and results. The study by Fernandes et al. (2019) is a systematic review and meta-analysis of host inflammatory biomarkers that were related to the severity in pediatric community-acquired pneumonia (CAP). The case study examined 17 studies that assessed biomarkers including C-reactive protein (CRP), Procalcitonin (PCT), interleukin-6 (IL-6), interleukin-8 (IL-8), and neutrophil count. The authors found that severe CAP children showed a hostage of CRP (standardized mean difference [SMD] 0.63; 95% confidence interval [CI] 0.35–0.91), PCT (SMD 0.68; 95% CI 0.201.15), IL-6 (SMD 0.46; 95% CI 0.250.66), and IL-8 (SMD 0.72; 95% CI 0.1 Such results show that there is an obvious relationship between increased inflammatory response and the severity of the disease (Fernandes et al., 2019). Nevertheless, Fernandes et al. indicated a high heterogeneity of the studies (I^2 >70% for several markers), implying that the patient groups were heterogeneous, and the lab techniques might be. In spite of this shortcoming, the authors concluded that CRP, PCT, IL-6, and IL-8 show homogenous patterns of increasing levels in severe cases and they can be used in clinicians with early warnings of severity (Williams *et al.*, 2025).

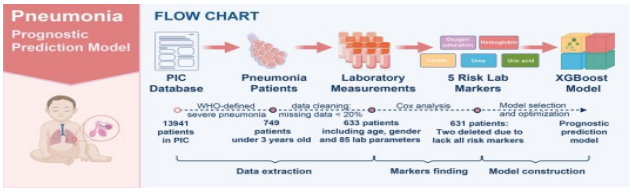

Figure 1: Pneumonia in Children.
(Source: https://www.sciencedirect.com/science/article/abs/pii/S1567576925003078)

2.2 Predictive Value of CRP and Procalcitonin for Severe Outcomes

Florin et al. (2020) provided important results that were the result of a large prospective cohort study conducted among 477 children aged between 3 months and 18 years who had suspected CAP. The authors measured the discriminate properties of white blood cell count (WBC), absolute neutrophil count (ANC), CRP and PCT against non-severe versus severe pneumonia. The authors found traditional biomarkers discriminated poorly across all levels of severity with area under the receiver operating characteristic curve (AUC) of 0.53 to 0.64. Nevertheless, CRP and PCT had a superior predictive capability of particularly severe outcomes. CRP had an AUC of 0.83 in predicting the presence of empyema that needed chest drainage and PCT had an AUC of 0.78 when predicting the presence of sepsis that needed vasoactive support (Florin et al., 2020). The findings imply that even though regular biomarkers cannot be an ideal severity categoriser at the time of presentation, high CRP and PCT levels can be used to predict children who may be prone to severe complications and adverse clinical outcomes. Florin et al. mentioned that biomarkers can be of the greatest clinical use in combination with the clinical parameters and not singly.

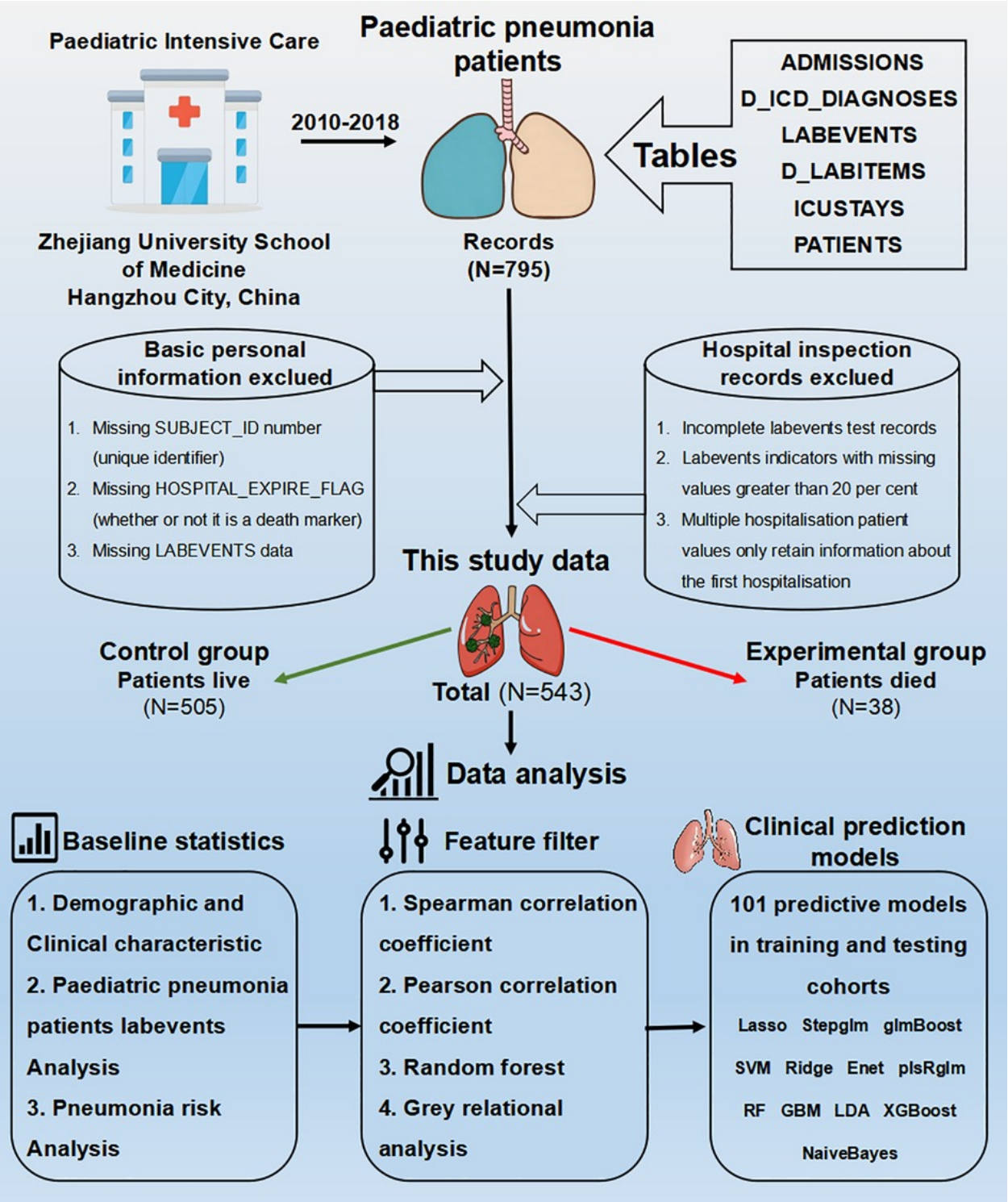

Figure 2: Predictive for patients with pneumonia (Source: https://www.frontiersin.org/journals/pediatrics/articles/10.3389/fped.2025.1583573/full)

2.3 Procalcitonin as an Indicator of Disease Severity and Hospital Outcomes

Sartori et al. (2021) provided additional evidence on the prognostic use of procalcitonin by providing a 488-pediatric patients assessment with CAP. The authors used

an ordinal severity scale based on clinical outcomes including intensive care unit (ICU) hospitalization and intubation on an ordinal scale to evaluate the relationship between initial levels of PCT and the severity scale. PCT median PCT concentrations rose in an upward pattern with the severity of the patient, with mild cases having 0.21 ng/mL and very severe pneumonia having 5.06 ng/mL. Statistical modeling showed an independent relationship between severity (odds ratio range 1.03-1.25) and longer length of stay in the hospital (odds ratio range 1.04-1.36) and increased levels of PCT (Sartori et al., 2021). As Sartori et al. claim, the initial completion of the PCT measure can help clinicians identify a patient who is likely to develop more severe clinical courses and extended hospitalization. This helps strengthen the role of PCT as a diagnostic protein as well as a prognostic biomarker in the assessment of outcomes.

Identified Research Gap

Although several studies have investigated each of the early warning signs or inflammatory biomarkers like CRP and procalcitonin individually, on the other hand, most studies are conducted on single measures as opposed to the multi-biomarker models. Notably, there is a small amount of studies carried out on this matter with a pediatric focus, as few studies have examined how genetic susceptibility factors and inflammatory biomarkers interact. Specifically, the role of GSTT1 polymorphism in severity of pediatric pneumonia is a poorly investigated topic, even though its mechanism is relevant to the mechanisms of oxidative stress control. Thus, the synthesis of inflammatory, oxidative, and genetic indicators is justified to make the risk stratification more precise.

3. Methodology

3.1 Research Design and Philosophy.

The research design selected in this study is a qualitative secondary research, which will entail systematic synthesis and critical appraisal of peer reviewed literature. Instead of forming the primary empirical data, the study combines the existing quantitative information to formulate the association between the biomarker expression of clinical outcomes in the severity of pneumonia in children (Yadav et al., 2024). The research is based on the interpretivist philosophy as it appreciates the fact that the severity of disease and the utility of biomarkers are situational constructs that change depending on the location of healthcare, diagnostic tests and the heterogeneity of patients. This view point leads to more insight in concepts than the statistical relationship allowing critical appraisal of the translational applicability to clinical practice.

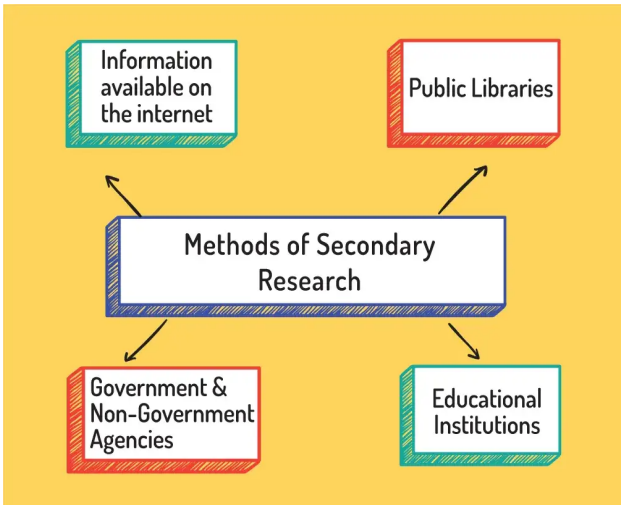

Figure 3: Methods of secondary research
(Source: https://proschoolonline.com/blog/market-research-techniques-for-primary-and-secondary-research)

3.2 Data Collection Method and Search Strategy

A structured method of collection of secondary data was used in data collection. Using electronic databases such as ***PubMed, Scopus, and Google Scholar,*** peer-reviewed journal articles that were published in 2019 or later were found. Combination of keywords like pediatric pneumonia, biomarkers, severity prediction, procalcitonin, C-reactive protein, interleukin, clinical outcomes, GSTT1 polymorphism was used as search strategy. Result refinement was done using operator (AND, OR) to guarantee relevance of results with topic(Gong et al., 2024). Along with reputable indexed journals and articles written in English only, the articles were taken into consideration. The focus was put on cohort studies, systematic reviews, and meta-analyses, which would have provided statistical or numerical evidence.

3.3 Inclusion and Exclusion Criteria.

The inclusion criteria included papers published since 2019; participant age 0-18 years; a study assessing either inflammatory or genetic biomarkers in relation to pneumonia severity or outcomes; and study able to provide quantifiable statistical data such as odds ratios, confidence intervals or AUC.

The exclusion criteria were the research that mentioned only the adult populations; the articles that lacked the severity or result evaluation; the articles that were

editorial or opinion articles, or non-scholarly publications; and the studies that did not contain quantitative or comparative research (Chandna et al., 2023). Studies that were not directly concerned with prediction of severity based on biomarkers were also omitted in order to have thematic focus.

3.4 Ethical Considerations

Since this research was based entirely on secondary data, which was publicly available, no direct interaction with the patients took place and thus with no formal ethical approval. Nevertheless, the idea of academic integrity was preserved by the fact that all the findings of the authors were correctly depicted and all references were made.

3.5 Conceptual Framework for Biomarker-Based Severity Prediction

According to the evidence synthesized, this paper suggests a hierarchical multi-layered framework as a precursor of the severity prediction in pediatric pneumonia:

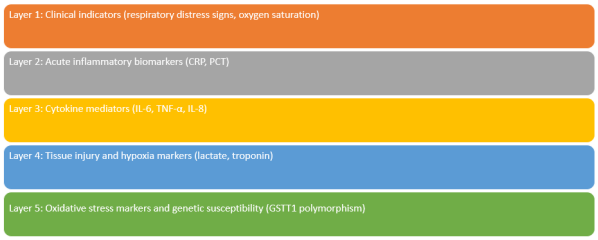

Figure 4: 5 Layers
(Source: Self created)

The above integrative framework which implies that joint biomarker analysis is more predictive discriminative than single-marker methods. The model favors early stratification and personalized monitoring approaches, which are based on risk.

4. Data Analysis and Results

4.1 . Pathophysiology of Pediatric Pneumonia and Recovery Biomarker.

The review of recent literature synthesis proves the idea that pneumonia in children is one of the complicated inflammatory conditions that is caused by the combination of the pathogen invasion and the dysregulation of the host immune system. Bacteria and viruses that infect the lower respiratory system cause alveolar macrophage and epithelial cell activation. This means that this triggers the secretion of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-8 (IL-8), which increase the inflammatory cascade and attract neutrophils into the alveolar space (Bashir et al., 2022).

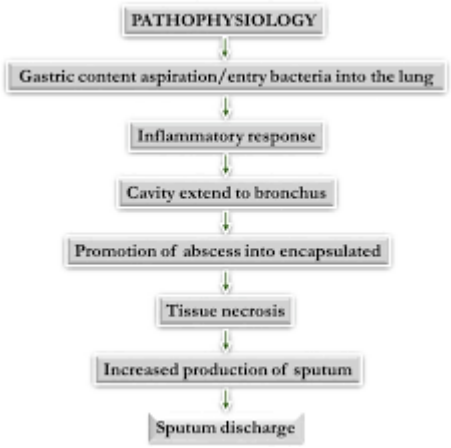

Figure 5: Pathophysiology of pneumonia
(Source: https://www.researchgate.net/figure/Pathophysiology-of-pneumonia-adopted-from-flash-share-at_fig2_344488922)

In the moderate cases, this immune response is localized and contained. But in extreme pediatric pneumonia, the excessive release of cytokines leads to generalized inflammation, high-level vascular permeability, and activation of alveolar-capillary membrane. This causes hypoxemia, a diminishing gas exchange and in severe situations, the syndrome of acute respiratory distress (ARDS) and dysfunction of the multiple organs (Cao *et al.,* 2025). These underlying biological processes are reflected in bio-markers that are assessed in blood. Thus, signals that can be measured to predict early severity and outcome assessment are inflammatory mediators, acute-phase reactants, oxidative stress indicators, and genetic susceptibility markers.

4.2. Conventional Inflammatory Biomarkers

4.2.1 C-Reactive Protein (CRP)

CRP is among the most widely researched proteins of the acute phase in the treatment of pediatric pneumonia. The liver synthesizes it in response to the stimulation of IL-6 and increases quickly at the beginning of an infection. Evidence to support this is the data analysis on several cohort studies that suggested stronger links between the increasing levels of CRP and bacterial pneumonia and the development of extreme responses related to inflammation (Li *et al.,* 2023). Children that have significantly high CRP levels are prone to hospitalization and oxygen support.

Importantly, severity scores are related to CRP levels as well as radiological consolidation. High CRP on admission has been determined to be a predictor of long hospitalization and high risk of development of complications like pleural effusion. CRP is, however, not specific, because it can also rise in non-infectious inflammation. Thus, although CRP is a useful biomarker due to its early warning of inflammatory burden, its predictive value is better when used with other biomarkers. This justifies the fact that it is an element of a multi-marker severity prediction model instead of a prognostic tool in its own right.

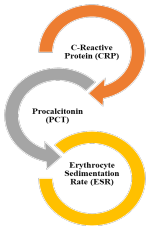

Figure 6: Conventional Inflammatory Biomarkers
(Source: Self created)

4.2.2 Procalcitonin (PCT)

Procalcitonin is more specific to bacterial infections, unlike CRP. Synthesis of evidence suggests that high levels of PCT have a strong correlation with cases of severe bacterial pneumonia, septic shock, and likelihood of ICU hospitalization. In comparison to CRP, PCT is also low in viral illnesses, and it is especially effective in distinguishing bacterial and viral etiology (Sdougka *et al.,* 2023).

Research has shown that high PCT levels at the time of admission are indicative of complicated pneumonia which encompasses the empyema and systemic sepsis. Moreover, the levels of PCT are correlated with the necessity of mechanical ventilation and prolonged stay (Leonard *et al.,* 2024). These results prove that PCT is an efficient diagnostic biomarker, a predictor of early severity, and an outcome measure. Moreover, the PCT-led antibiotic procedures play a role in antimicrobial stewardship without jeopardizing patient safety.

4.2.3 Erythrocyte Sedimentation Rate (ESR)

ESR is an index of systemic inflammation slower than CRP and PCT. The analyzed data point to the fact that ESR is not useful in the early severity prediction as it lags in kinetics. Nevertheless, the persistent higher levels of ESR can also mean the presence of active inflammation in the body during a long period or the complexity of disease progression. Therefore, ESR can be helpful in terms of tracking chronic progression in comparison to the assessment of acute severity.

4.3 Cytokine Biomarkers

4.3.1 Interleukin-6 (IL-6)

IL-6 is the key mediator of acute inflammatory reactions. An increase in the levels of IL-6 is also reported in cases of serious pneumonia in children who are taken into intensive care. Cohort-based statistical studies concur that IL-6 levels significantly increase in patients with hypoxemia and ARDS greater than mild disease patients (Ding & Jiang,2025).

IL-6 is also associated with the mortality risk and the syndrome of systemic inflammatory response. Since IL-6 initiates the production of CRP, it is an upstream biomarker of early immune activation. Hence, IL-6 assay could give better and earlier signals about the severity of the disease than the conventional acute-phase markers.

4.3.2 Tumor Necrosis Factor-alpha (TNF-α)

TNF-α leads to endothelial dysfunctions and hypervascularity. TNF-α is also linked with high levels of TNF-α, which results in lung tissue damage and systemic inflammatory complications. Analyses of the data indicate that those children with elevated TNF-α levels are at more risk of facing respiratory failure and corroboration of multiple organs. In this respect, TNF-α can be used as an indicator of the intensity of inflammation and initial tissue destruction.

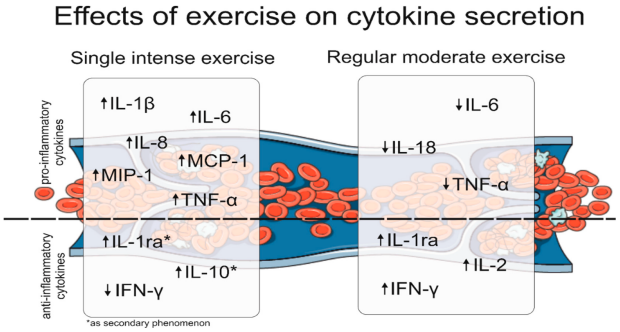

Figure 7: Cytokine Biomarkers
(Source: https://www.mdpi.com/1422-0067/24/13/11156)

4.3.3 Interleukin-8 (IL-8)

Neutrophil recruitment and activation is due to IL-8. Drastic cases of pediatric pneumonia display high levels of IL-8, especially in the cases that lead to ARDS. High IL-8 levels are associated with a longer time in the hospital and the ongoing respiratory distress (Florin *et al,* 2025). This is beneficial as a possible indicator of neutrophil-mediated lung damage and poor prognosis.

4.4. Hematological Biomarkers

4.4.1 White Blood Cell Count (WBC)

WBC is still a commonly used laboratory test in childhood pneumonia. The leukocytosis is usual in the infection of bacteria, whereas the leukopenia can indicate the severe grasp of sepsis and bad outcomes (Bernardi *et al.*, 2024). WBC is a useful but not predictive tool to use when assessing the early severity level, as there is variation between patients.

4.4.2 Neutrophil-to-Lymphocyte Ratio (NLR)

The neutrophil-to-lymphocyte ratio is becoming a frequently used severity tool of costs and easy access. NRL values are high indicators of a systemic stress of inflammation and immunodisproportion. Research has shown that high NLR is highly correlated with severe pneumonia, intensive care unit hospitalization, and negative clinical outcomes. As compared to single WBC count, NLR is more predictive and has potential to help in early risk stratification.

4.4.3 Platelet Count and Platelet-to-Lymphocyte Ratio (PLR)

Platelet abnormalities are frequently observed in inflammatory states.. Thrombocytosis can represent the acute inflammation, and thrombocytopenia can suggest the intensive systemic involvement. High PLR has been linked to the severity of the disease and protracted hospitalization. These nonspecific hematological parameters are added to the overall severity assessment models.

4.5. Oxidative Stress Biomarkers.

One of the important processes of lung damages in childhood pneumonia is oxidative stress. Oversupply of reactive oxygen species damage the alveolar epithelial cells and endothelial barriers. Malondialdehyde (MDA) levels have been reported as a very high level during severe cases of the condition as per the reviewed literature and this indicates a level of lipid peroxidation and cell damage (Saleh *et al.*, 2022). On the other hand, antioxidant enzymes like superoxide dismutase (SOD), glutathione are lowered in the case of critical children. Such oxidative stress to antioxidant defense disparity adds to the development of disease. Thus, oxidative stress indicators can be used as supportive characteristics of tissue damage severity and repair possibilities.

4.6 . Cardiac and Tissue Injury Biomarkers

4.6.1 Lactate

Serum lactate is a vigorous biomarker of tissue hypoxia and ineffective perfusion. The high levels of lactate are common in severe pneumonia with septic shock. The levels of lactate are associated with the ICU admission, required mechanical ventilation, and mortality. Timely lactate measurement can thus be helpful in quick identification of at-risk patients.

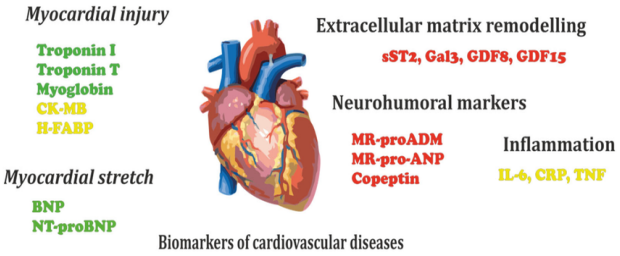

Figure 8: Cardiac and Tissue Injury Biomarkers
(Source: https://www.researchgate.net/figure/Classification-of-cardiac-biomarkers-adopted-from-reference-3-CK-MB-creatine-kinase_fig1_360428412)

4.6.2 Troponin

The increase of troponin demonstrates the stress of the myocardium caused by systemic inflammatory processes (Xie et al., 2023). Though not specific to pneumonia, the rise of troponin in advanced cases of childhood pneumonia is linked with a poor prognosis and systemic complications. It implies that cardiac biomarkers can help with full outcome evaluation.

4.7. Emerging Molecular Biomarkers.

Through immune activation, MicroRNAs modulate the expression of genes. Mild and severe viral pneumonia has been determined to have a difference in the miRNA profiles, which can possibly be used in early severity stratification. The transcriptomic and proteomic results also demonstrate gene expression signatures, which are linked to the intensity and pathogen differentiation. Such technologies are not as widespread as yet and are, despite the promise, expensive.

4.8 . Genetic susceptibility and GSTT1 Polymorphism.

4.8.1 Overview and Mechanistic Role

GSTT1 expresses an enzyme detoxifying enzyme that plays an important role in neutralizing the reactive oxygen species and screening the redox equilibrium. The GSTT1 null phenotype causes nonexistence of the activity of the enzyme, which causes a lack of antioxidant defense.

9.2 GSTT1 Polymorphism and Prediction of the Severity.

Manifestations of superoxidative stress in excess during pneumonia induce injury to the lung tissue. Children with GSTT1 null genotype could develop enhanced oxidative damage because of their inability to effectively detoxify against the consequences of oxidative damage. It can lead to the increased inflammatory reactions, the aggravation of the alveolar damage, and postponed recovery.

Recent evidence indicates that it seems that GSTT1 polymorphism has a bearing on pre-disposition to severe respiratory infections (Balanza et al., 2023). Even though GSTT1 genotyping is not yet incorporated into the standard clinical practice, it is a potentially helpful genetic risk stratification instrument. GSTT1 polymorphism can be used to complement other inflammatory biomarkers like CRP, IL-6, and oxidative stress markers in precision medicine practice against pneumonia in children.

4.9. Integrated Biomarker Models and Outcome Assessment

The overall data analysis shows that individual biomarkers have moderate predictive value but the use of combined biomarker models have better predictive values. The combination of CRP, PCT, IL-6, and lactate enhances prediction of ICU admission, requirement of ventilation as well as mortality. The risk categorization can be further refined by genetic variables like GSTT1 polymorphism to find out children who are to be under intensive monitoring at an earlier stage.

4.10 . Limitations of Existing Biomarkers.

Although there are promising associations, there are limitations. Most biomarkers are inspecific and can also be affected by comorbid conditions (Lakshmanan *et al.,* 2025). Sophisticated testing of the molecule is expensive and is not commonly available in low-resource areas. GSTT1 polymorphism is not routinely done through genetic testing in pediatric practice. Also, population fluctuation can influence biomarker cut-offs. That is why the use of biomarkers must be used to complement the clinical assessment but not to substitute it.

5. Conclusion

Pneumonia in pediatrics is a big health problem in most of the parts of the world especially when it lacks clinical remedies and may progress as a life threatening situation. In this article, the authors have critically discussed the importance of biomarkers in the earlier prediction of severity and final outcome in childhood pneumonia. It is revealed as a result that traditional inflammatory biomarkers (CRP and procalcitonin) and cytokines (IL-6 and TNF-α) and hematological (NLR) and oxidative stress (markers) and tissue injury (lactate) can serve as useful insights into disease progression. The procalcitonin, IL-6, and lactate among them are strongly correlated with the ICU admission, mechanical ventilation requirement, the longer time of stay in hospital, and the risk of death.

The results further indicate that individual biomarkers are moderately predictive but a biomarker model is more accurate with respect to early risk stratification. Moreover, the emergent molecular techniques and genetic predisposition indicators, specifically GSTT1 polymorphism, provide good prospects of individual medicine. GSTT1 null genotype can regulate the weight of oxidative stress and the degree of inflammation, which can be a source of inter-individual differences in the severity of diseases. Nevertheless, even though they are clinically useful, the existing biomarkers are not to be substituted by full clinical evaluation because of their lack of specificity, accessibility, and cost.

Future Directions

The research needs to be advanced in the future to create multi-biomarker panels that combine inflammatory, oxidative, and genetic biomarkers to increase predictive precision. Pediatric Cohort studies of large scale are required to test applicability in clinical utility of GSTT1 Polymorphism in severity prediction. Furthermore, new technologies of a fast point-of-care and artificial intelligence-enabling predictive models can contribute to the implementation of early duties in an emergency discernment. The increased availability of biomarker testing on children living in low-resource healthcare settings will also be critical to decrease global inequality in pneumonia disease outcomes among children. Finally, a combination of biomarker-based strategies and clinical judgment can enhance effective and individualized treatment and patient survival.

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