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Liver Damage in Pediatric

Strategy for Prevention of Diabetes

Highlights

Global Aircraft Noise Metrics

Pneumomediastinum in COVID-19 Patients

Discovering Thoughts, Inventing Future

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Liver Damage in Pediatric Critically Ill COVID-19 Patients: Brazilian Case-Series

By Michele Luglio, MD, UenisTannuri, MD, PhD, WertherBrunow de Carvalho, MD, PhD, Maria Fernanda Badue Pereira, MD, PhD, Isadora Souza Rodrigues, MD, Cintia Johnston, PhD & Artur Figueiredo Delgado, MD, PhD

Abstract- Coronavirus disease 2019 (COVID-19) has become an important cause critical care admission worldwide. In the context of newly described multisystem inflammatory syndrome temporally related to SARS-CoV-2 (PIM-TS), the question of liver compromise came into evidence. Our group summarized a case series of 6 critically ill COVID-19 pediatric patients that presented some degree of liver damage, as demonstrated by liver and/or canalicular enzymes elevation, a yet not fully explored characteristic of the infection in the pediatric patient, that may indicate a more severe progression. Observations regarding the role of systemic inflammatory response can be taken from the described cases.

Keywords: *hepatic, intensive care, coronavirus.*

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Liver Damage in Pediatric Critically Ill COVID-19 Patients: Brazilian Case-Series

Michele Luglio, MD [α], UenisTannuri, MD, PhD [σ], WertherBrunow de Carvalho, MD, PhD [ρ], Maria Fernanda Badue Pereira, MD, PhD [ω], Isadora Souza Rodrigues, MD [¥], Cintia Johnston, PhD [§] & Artur Figueiredo Delgado, MD, PhD [χ]

Abstract- **Coronavirus disease 2019 (COVID-19) has become an important cause critical care admission worldwide. In the context of newly described multisystem inflammatory syndrome temporally related to SARS-CoV-2 (PIM-TS), the question of liver compromise came into evidence. Our group summarized a case series of 6 critically ill COVID-19 pediatric patients that presented some degree of liver damage, as demonstrated by liver and/or canalicular enzymes elevation, a yet not fully explored characteristic of the infection in the pediatric patient, that may indicate a more severe progression. Observations regarding the role of systemic inflammatory response can be taken from the described cases.**

Keywords: hepatic, intensive care, coronavirus.

I. Introduction

Coronavirus disease 2019 (COVID-19) has increasingly become an important cause of critical care admission. Some adult studies and case series have focused on the important aspect of extra-pulmonary commitment by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), with attention to potential liver damage[1]. Between 14 and 53% of adult patients with COVID-19 showed alanine aminotransferase (ALT) and/or aspartate aminotransferase elevations[1].

In the context of the recently described multisystem inflammatory syndrome temporally related to SARS-CoV-2 infection (PIM-TS), Whittaker *et al*[2] compiled data of 58 individuals, showing that ALT median levels on the different phenotypic groups varied from 26 (12-141) to 86 (34-129) U/L.

Our group summarized a series of critically ill COVID-19 pediatric patients with hepatic damage (as demonstrated by liver and/or canalicular enzymes elevation), admitted to a Brazilian tertiary hospital Pediatric Intensive Care Unit (PICU), dedicated to cases of SARS-CoV-2 infection.

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II. Methods

From March to June 2020, 35 patients were admitted to Pediatric COVID-19 dedicated wards and PICU in a single tertiary center in São Paulo. Of those patients, 15 needed intensive care support. All the patients had a confirmed diagnosis of SARS-CoV-2 infection performed by nasopharyngeal reverse-transcriptase polymerase chain reaction (RT-PCR), serological tests (IgM and IgG) and/or diagnosis of PIM-TS, following the World Health Organization (WHO) criteria[2].

Demographic, clinical and laboratory data were obtained from medical records by two independent investigators (ML and ISR). After retrospective analysis of 15 critical patients' records, 6 patients without previous hepatic illnesses showed some degree of liver damage and were included in the case series, after thorough discussion among experts and all authors' agreement. As COVID-19 is a new disease, consensus towards the precise definition of liver damage is still lacking[3]. On this case series, the authors defined liver damage by the presence of new elevations of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gama-glutamyl transferase (GGT), alkaline phosphatase (ALP) and/or Total Bilirubin in relation to the patient's baseline values (when available) or the institution's laboratory references, through the hospitalization for critical COVID-19.

Patients consented at the time of hospital admission for the inclusion in a case series, and approval was obtained from the hospital ethics committee for the report of these cases.

III. Results

On table 1, main demographic, clinical and liver enzymes characteristics of those included patients are summarized. On Figure 1, the temporal evolution of AST/ALT and GGT levels, during PICU stay, is shown:

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Table 1: Main Clinical and Laboratorial Description of Pediatric COVID-19 patients with Liver Damage

Patient	Age at admission	BMI (z-score) kg/m²	Sex	Comorbidities	ICU Admission Diagnosis and Clinical Presentation	Main Drugs Used During Hospitalization	Shock?	Hypoxic Respiratory Failure?	Basal ALT/AST (U/L)	Highest ALT/AST (U/L)	Basal GGT/ALP (U/L)	Highest GGT/ALP (U/L)	Basal Total Bilirubin (mg/dL)	Highest Total Bilirubin (mg/dL)	PICU Length of Stay (days)	Deceased?
1	12 years	15.0 (-0.93)	Male	Metastatic Teratoma, Hydrocephalus	Septic Shock - Fever, Tachycardia, Hypotension and Respiratory Distress	Azithromycin, Ceftriaxone, Meropenem, Oseltamivir, Vancomycin	Yes	Yes	13/20	38/65	133/133	143/194	0.93	0.44	26	No
2	13 years	14.2 (-2.78)	Male	Neurofibromatosis, High Degree Sarcoma, Congestive Cardiac Insufficiency	Cardiogenic Shock and Pneumonia - Fever, Coryza, Coughing, Tachycardia and Hypotension	Azithromycin, Ceftriaxone, Oseltamivir	Yes	Yes	121/92	1842/5908	NA	356/316	0.25	0.82	5	Yes
3	15 years	29.3 (1.75)	Female	Asthma, Autism	Respiratory Failure - Progressive Respiratory Distress with no coryza nor fever	Azithromycin, Ceftriaxone, Oseltamivir, Risperidone	No	Yes	NA	42/81	NA	59/NA	NA	0.33	11	No
4	12 years	22.1 (1.17)	Male	Non-Hodgkin's Lymphoma	Hypokalemia and Sepsis - low potassium levels with cardiac rhythm disturbances (U wave and QT interval prolongation) and fever without other symptoms	Amphotericin B, Azithromycin, Meropenem, Oseltamivir, Teicoplanin, Voriconazole	No	No	45/42	254/249	313/357	488/382	1.04	1.57	14	No
5	8 years	23.4 (2.10)	Female	No	Refractory Status Epilepticus - Patient with fever and newly onset refractory status epilepticus	Acyclovir, Azithromycin, Ceftriaxone, Levetiracetam, Oseltamivir, Pentobarbital, Phenytoin, Piperacilin-Tazobactam	Yes	No	NA	112/73	NA	646/NA	NA	0.38	22	Yes
6	11 years	21.1 (0.97)	Female	Acute Lymphoblastic Leukemia	Sepsis and Respiratory Failure - Fever, coughing and progressive respiratory distress	Amphotericin B, Azithromycin, Cefepime, Oseltamivir, Sulfamethoxazole-trimethropin, Teicoplanin, Vancomycin	Yes	Yes	21/20	107/28	39/206	237/206	0.40	0.40	5	Yes

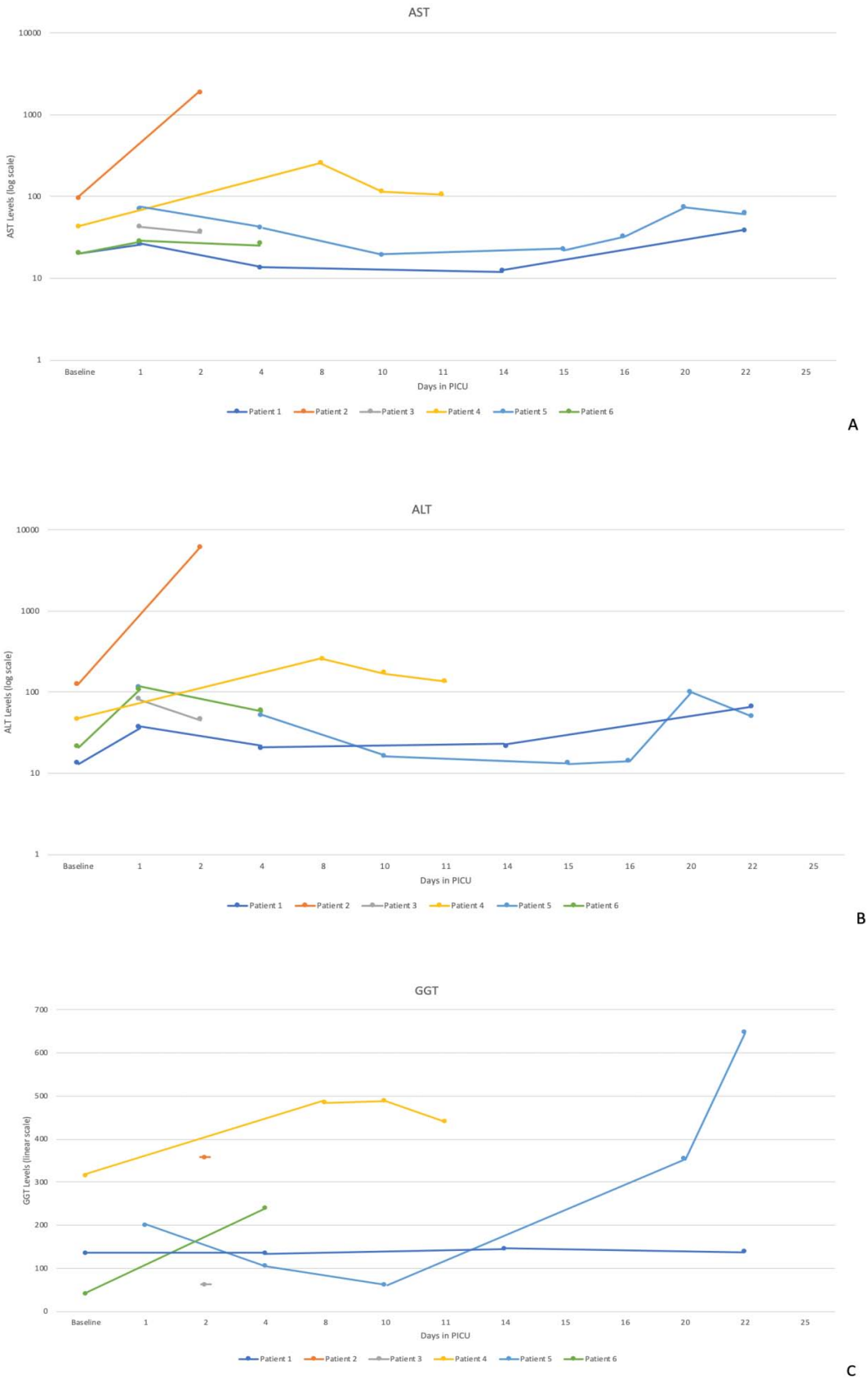


Figure 1: AST, ALT and GGT temporal evolution during PICU stay:

Figure 1: AST, ALT and GGT levels during PICU stay (A: AST levels on log scale vs days in PICU; B: ALT levels on log scale vs days in PICU; C: GGT levels on linear scale vs days in PICU).

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Patient 1:

Admitted at Pediatric Emergency Department (PED) with 5 days of cough and 2 days of progressive respiratory distress and fever. Patient evolved with hypoperfusion and hypotension, managed with the administration of continuous epinephrine. The patient presented no gastrointestinal symptoms. SARS-CoV-2 nasopharyngeal polymerase chain reaction (PCR) was positive, and all other etiologic exams (blood cultures, respiratory virus panel) were negative. Abdominal ultrasound (US) showed normal-sized, regular shaped liver with no intrahepatic biliary channel dilation. Echocardiography showed dilated Left Coronary Artery (z-score = +2.0) and left ventricular systolic and diastolic dysfunction. CRP (318.1 mg/L), Troponin-t (0.092 ng/mL), CK-MB (6.23 ng/mL), ferritin (1,017 ng/mL) and D-dimer (19,514 ng/mL) were elevated at admission and during PICU stay. Prothrombin time (PT) and Activated Partial Thromboplastin time (aPTT) showed elevations, with values of 20.6s and 38.2s (INR = 1.69 and R = 1.33), respectively. The AST/ALT alterations shown completely resolved after discharge.

Patient 2:

Admitted to PED with 2 days of weakness and inappetence, followed by cough and progressive respiratory distress. The only gastrointestinal symptoms present during hospitalization were sporadic vomits. The patient showed signs of hypoperfusion and hypotension, with point-of-care ultrasound (POCUS) showing turgid inferior vena cava, right atrium dilation and compromised global systolic function, and Dobutamine infusion was started. SARS-CoV-2 nasopharyngeal PCR was positive, with all other etiologic exams (blood cultures, respiratory virus panel) negative. CRP was elevated on admission (111.0 mg/dL). The patient was transferred to PICU, where evolved with worsening respiratory failure and the need of invasive mechanical ventilation. Echocardiography showed Left Coronary Artery dilation (z-score = +2.7) and left ventricular systolic and diastolic dysfunction (LVEF = 24% with Milrinone and Adrenaline). Due to the diagnosis of incomplete Kawasaki disease, two doses of IVIG (total 2 g/kg) were administered and high dose aspirin was started. PT and aPTT showed elevations, with values of 34.9s and 34.2s (INR = 2.86 and R = 1.19), respectively. After 5 days in critical care, the patient died.

Patient 3:

Admitted to PED with 4 days of progressive respiratory distress with no fever or other symptoms. No gastrointestinal symptoms were present during hospitalization. Patient was intubated and mechanically ventilated due to hypoxic respiratory failure. SARS-CoV-2 nasopharyngeal RT-PCR was positive, with all other etiologic exams (blood cultures) negative. Echocardiography was normal. CRP (48.2 mg/L), Troponin-t (0.059 ng/mL), d-dimer (4,157 ng/mL) and LDH (892 U/L) were elevated at admission. PT (12.3s, INR = 1.01) and aPTT (26.7s, R = 0.98) were normal through PICU stay. The patient showed mild ALT/AST elevations, that resolved after hospital discharge. After 11 days on critical care, the patient was discharged to general pediatric ward.

Patient 4:

After 4 months of hospitalization following chemotherapy complications and acute renal failure, the patient began intermittent fever without other symptoms. Infectious screening exams were performed, including SARS-CoV-2 nasopharyngeal RT-PCR that came out positive. Galactomannan test was the only other etiologic test to be positive. Echocardiography, thoracic and cranio-facial CT-scans showed no new alterations. Abdominal CT-scan showed liver dimensions on the upper limit with regular shape and contour, without biliary dilation and mild colonic parietal thickening. In spite of the colonic findings, no gastrointestinal symptoms were present. Patient developed severe hypokalemia and worsening renal function, needing PICU transfer. During the course of SARS-CoV-2 infection, the patient showed a nearly 6-fold ALT/AST elevation, associated with moderate GGT/ALP elevations (in relation to the previous basal values, shown in table 1) and stable values of PT and aPTT, 14.4s (INR = 1.18) and 29.2s (R = 1.07) respectively. Alterations on liver enzymes resolved after discharge.

Patient 5:

Admitted to PICU after 4 days of odynophagia, fever and headache, evolving with vomits and episodes of convulsion. The diagnosis of refractory status epilepticus was made, and continuous midazolam and pentobarbital were started after orotracheal intubation. Multiple antimicrobial schemes were used through hospitalization (Table 1). Cerebral Spinal Fluid (CSF) showed mild alterations (3 cells, with normal glucose and protein levels). Cranial Computed Tomography scan (CT-scan) was normal and thoracic CT-scan showed bilateral ground-glass opacifications. SARS-CoV-2 PCR was negative, as were all other etiologic tests (CSF culture and viral PCRs, blood cultures, respiratory virus panel). Echocardiography showed right (z-score: +3.0) and anterior descendent (z-score: +2.6) coronary arteries dilation. CRP (318.1 mg/L) and D-dimer (19,514 ng/mL) were elevated at admission and during intensive care. IVIG and high-dose methylprednisolone pulse-therapy were administered, due to the diagnosis of PIM-TS. The patient presented episodes of melena and was submitted to endoscopic evaluation that showed two ulcerations on duodenal superior wall. PT also showed mild elevations, with a peak of 15.5s (INR = 1.27) while aPTT was normal throughout the PICU stay. The patient developed progressive metabolic disturbances and uncontrolled

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status epilepticus, dying of refractory shock after 22 days in PICU.

Patient 6:

Patient on the seventh day after chemotherapy (vincristine and doxorubicin) was admitted to the PED with 2 days of fever, cough and progressive respiratory distress. The patient was diagnosed with neutropenia and sepsis, starting empiric antimicrobial therapy, with association of Amphotericin B through the course of hospitalization. SARS-CoV-2 nasopharyngeal PCR was positive, with all other etiologic exams (blood cultures, respiratory virus panel) negative. The patient evolved with respiratory failure and hemodynamic instability, needing invasive ventilatory and inotropic support on the second day of hospital admission. No gastrointestinal symptoms appeared during PICU stay. D-dimer (1,932 ng/mL) and ferritin (3,295 ng/mL) showed elevations through hospitalization, with normal PT (13s, INR = 1.0) and aPTT (30s, R = 1.11). Echocardiography showed small pericardial effusion and thoracic CT-scan showed diffuse bilateral ground-glass opacifications. The patients deceased after 5 days in ICU due to refractory shock.

IV. Discussion

Important variations are found when evaluating ALT/AST levels in patients with COVID-19[3,4]. This case series corroborates previous findings, with AST elevations ranging from 65 to 5908 U/L.

Transaminase elevations seen in this series may be related to four mechanisms: (1) Drug induced liver injury (DILI); (2) Direct biliary injury by coronavirus; (3) inflammatory response in the context of cytokine storm; (4) Ischemia/Reperfusion and microthrombosis[7].

Abnormalities on liver enzymes seen can occur on either the initial viremia phase or during the subsequent inflammatory phase[7]. It was already reported that high ALT and bilirubin can be considered biomarkers of a more severe clinical course[7,8].

The potential for DILI in the context of critical COVID-19 cannot be neglected[9]. All patients included in our case series received at least one Category A or B hepatotoxic drug, as described by LiverTox®[10]. Drug induced liver damage may be an important contributing factor to a multifactorial condition.

Different from previous reports[4,5], patients included showed moderate elevations on GGT levels, consistent with experimental observations that cholangiocytes express ACE-2 receptors, a target for direct viral invasion and damage[6].

Three patients had features consistent with PIM-TS (patients 1, 2 and 5)[2], as defined by the WHO criteria. SARS-CoV-2 can be considered the trigger of an uncontrolled systemic inflammatory condition or cytokine "storm". In this context, cellular apoptosis and necrosis and the release of damage-related patterns may induce injuries to multiple organs, the liver included. Hepatic endothelial involvement in the inflammatory process, with consequent neutrophil extracellular traps (NETS) stimulation and microthrombi formation, in a process similar to the one happening in the lungs[11], needs to be further studied.

Effenberger*et al*[12] explored the connection between systemic inflammation and liver injury in COVID-19 hospitalized patients. IL-6 and CRP levels positively correlated with AST elevations (respectively, $r^2 = 0.481$, $p<0.001$ and $r^2 = 0.38$, $p<0.001$) in all 96 included patients with pronounced effects on critically ill patients. Those findings correlate with this case series, as high levels of CRP and PCT were seen in patients with liver enzyme elevations. This cytokine "storm" may play a vital role in the hepatic damage.

In the beginning of the pandemic, the main focus of intensivists was on the viral potential to induce hypoxia. Hypoxia-reperfusion injury to the liver can stimulate hepatocyte cell death and inflammation, marked by oxygen reactive species accumulation[13], another potential causative mechanism to liver damage.

PICU mortality among the described patients was 50% (3/6) with a length of stay of 12.5 (6.5-20) days, while the remainder of the pediatric COVID-19 critically ill patients experienced a mortality rate of 33.3% (3/9) and length of stay of 7 (3-10) days. Presence of liver enzyme alterations indicates a more severe disease course, with all patients but one (patient 4) needing ventilatory, hemodynamic support or both. Given the tertiary condition of our center, the population included is mainly composed of patients with chronic conditions, what have impacts on the outcomes seen. In regard of the liver enzyme elevations, special care was taken to compare previous individual baseline levels to the highest values seen towards disease course.

This study has limitations of a small case series, which needs confirmation on larger groups. Due to the retrospective nature of the study and to conditions inherent of a pandemic in a developing country, a complete evaluation of radiological and histological aspects of the hepatic compromise may be lacking. As the focus was on the clinical description of patients with liver abnormalities, comparison with the global data of all COVID-19 patients admitted to the hospital was not made and can be an important future step.

Reports from over the world[13] show slightly different outcomes and evolutions of clinical conditions associated with COVID-19 in children. In a recent report by Sadiq *et al*[14], Pakistani children with PIM-TS showed an incidence of coronary artery aneurism (62.5%), higher than European and North American numbers (9-36%). Some of the findings in our case series can be justified by regional differences, that may be better identified in future studies. Knowledge of those disparities are relevant to deepen the understanding of the clinical potential of SARS-CoV-2 infection.

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This may be the first pediatric COVID-19 case series focused on liver damage, an important start-point to raise clinical attention to this aspect of SARS-CoV-2 infection. Further characterization of this population of patients may elucidate some still obscure aspects of COVID-19 related hepatic physiopathology.

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Pneumomediastinum in COVID-19 Patients

By Sebastián Campbell-Quintero, Santiago Campbell-Quintero & Santiago Campbell-Silva

Introduction- Emerging infectious diseases, such as severe acute respiratory syndrome (SARS), present a major threat to public health. In December 2019, a novel coronavirus referred to as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as the causative agent of a respiratory syndrome named coronavirus disease 2019 (COVID-19). Since then, the pandemic has escalated. The spectrum of COVID-19 presentations ranges from mild self-limited flulike illness to severe viral pneumonia leading to acute respiratory distress syndrome that can be potentially fatal.

Within this context, other complications from COVID-19 pneumonia are expected, such as pneumomediastinum. Reports of cases of spontaneous pneumomediastinum have increased due to the current COVID-19 pandemic. To date, 43 articles on COVID-19 and pneumomediastinum have been published in PubMed.[1]

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Pneumomediastinum in COVID-19 Patients

Sebastián Campbell-Quintero [α], Santiago Campbell-Quintero [σ] & Santiago Campbell-Silva [ρ]

I. Introduction

Emerging infectious diseases, such as severe acute respiratory syndrome (SARS), present a major threat to public health. In December 2019, a novel coronavirus referred to as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as the causative agent of a respiratory syndrome named coronavirus disease 2019 (COVID-19). Since then, the pandemic has escalated. The spectrum of COVID-19 presentations ranges from mild self-limited flulike illness to severe viral pneumonia leading to acute respiratory distress syndrome that can be potentially fatal.

Within this context, other complications from COVID-19 pneumonia are expected, such as pneumomediastinum. Reports of cases of spontaneous pneumomediastinum have increased due to the current COVID-19 pandemic. To date, 43 articles on COVID-19 and pneumomediastinum have been published in PubMed.[1]

In general, the physiopathological basis of this disease is based on the existence of a pressure gradient between the alveolus and the pulmonary interstitium. Once the alveolar rupture occurs, air passes from the interstitium to the hilum and then to the mediastinum due to the pressure difference between the latter and the pulmonary periphery which is known as the Macklin effect.[2]

SARS-CoV-2 can affect the pulmonary terminal structure, causing alveolar exudation and lymphocytic infiltration of the pulmonary interstitium. In advanced stages, SARS-CoV-2 can cause diffuse alveolar damage, which may lead to alveolar rupture and, therefore, pneumomediastinum.

a) Confusion about terminology of spontaneous pneumomediastinum

The common use of “chaos” refers to a state of confusion and disorder. Hence, things associated with disorder and confusion are called "chaotic".

This is the perception we have when reading articles about pneumomediastinum and especially about spontaneous pneumomediastinum. Pneumomediastinum is the term used to characterize the presence of air in the mediastinum, and the expression spontaneous pneumomediastinum describes the presence of air in the mediastinum with no specific cause.[3,4] Despite numerous published reports on this condition, there is no consensus on its terminology and classification, and the term "spontaneous pneumomediastinum" does not correspond with the definition in most publications. Most reports consider cases with predisposing or triggering factors as "spontaneous". This should not be so because it leads to confusion and controversy in the literature.

Allows to the term "spontaneous pneumomediastinum" to be used even when a causal factor has been identified, causing further chaos, rather than clarification. The lack of clarification leads to disputes among authors, complications in teaching, and confusion to readers.

The adjective "spontaneous” means an event without apparent cause, or that which arises suddenly. If we define spontaneous pneumomediastinum correctly, that is, “the presence of air in the mediastinum of healthy individuals without a causal factor” (predisposing or precipitating) and later affirm that it can be caused by factors such as smoking, asthma, the use of recreational drugs,[3,4]and recently COVID-19 pneumonia, we contradict ourselves. Nor can it be said that spontaneous pneumomediastinum is associated with several lung diseases without specifying the type of association because it creates ambiguity.

Some authors consider a pneumomediastinum which occurs outside of trauma (iatrogenic or non-iatrogenic) to be spontaneous, regardless of whether there is a non-traumatic predisposing or precipitating factor. However, these factors contribute indirectly or directly to the development of a pneumomediastinum. These cases do not correspond with the definition of a spontaneous pneumomediastinum.

Pneumomediastinum that results from an exertional esophageal perforation (Boerhaave syndrome) or as a complication of an esophageal foreign body cannot be called spontaneous. This is because the immediate cause of esophageal perforation is exertion due to nausea and severe vomiting, and the presence of an esophageal foreign body results in asphyxiation (both are non-traumatic

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precipitating factors). Furthermore, this condition can occur in both healthy individuals and individuals with underlying lung disease. Likewise, a pneumomediastinum that occurs with anorexia nervosa, Marfan syndrome, Ehlers-Danlos syndrome, malnutrition, dermatomyositis, polymyositis, diabetic ketoacidosis, ulcerative colitis, or COVID-19 is not spontaneous.

If a patient has a previous condition such as asthma or another underlying lung disease such as COVID-19 pneumonia and a coughing fit causes a pneumomediastinum, should we call this condition spontaneous pneumomediastinum? Similarly, if a healthy person experiences intense vomiting for any reason and a pneumomediastinum occurs, should we call this condition spontaneous pneumomediastinum?

These cases have factors that increase the risk of developing a pneumomediastinum and should not be called spontaneous pneumomediastinum. In the former case, there is a predisposing factor, either congenital or acquired. If a patient develops COVID-19 pneumonia prior to the development of a pneumomediastinum, it is then the respiratory disease that contributes to the increased susceptibility to this disorder. In the latter case, a precipitating factor is present, which causes a sudden increase in intra-alveolar pressure resulting in rupture and appears just before the episode of pneumomediastinum. This can occur in patients with or without underlying lung disease. It is important to differentiate the two cases in order to classify pneumomediastinum properly through an adequate medical history.

Perhaps we are accustomed to referring to this type of pneumomediastinum as spontaneous. Keeping with customary terminology, the same could be said of other situations such as spontaneous abortion, spontaneous pneumothorax, or spontaneous esophageal perforation. However, custom is one thing, and the appropriate terminology is another.

II. Pneumomediastinum Classification

Pneumomediastinum can be divided into two groups: primary and secondary pneumomediastinum (Figure 1). We believe that this classification is more precise and explanatory than those published previously. [3,4]

The term "primary pneumomediastinum" should be used for cases of pneumomediastinum that occur in the absence of predisposing and precipitating factors. The term "secondary pneumomediastinum" should be used when there is a predisposing or precipitating factor or both.

The term "primary" usually refers to the fact that there is no known underlying disease, and the term "spontaneous" means that there is no known cause; however, several authors imply that predisposing and precipitating factors are present in both terms.

Many authors consider a primary pneumomediastinum to be a pneumomediastinum which occurs in previously healthy individuals and is triggered by a non-traumatic precipitating factor, such as a coughing fit or intense exercise. Others regard this as spontaneous. This pneumomediastinum is neither spontaneous nor primary, but secondary to an episode of coughing or intense exercise in a previously healthy person. The primary pneumomediastinum is itself spontaneous, idiopathic, or Hamman's syndrome.

If a primary pneumomediastinum is suspected, additional diagnostic procedures, such as bronchoscopy, esophagogram, or esophagoscopy, may be necessary to rule out a secondary cause. This would result in a diagnosis by exclusion, which is not clinically relevant for cases of secondary pneumomediastinum. In general, the treatment and prognosis of primary pneumomediastinum is similar, unlike secondary pneumomediastinum. Treatment and prognosis of this pneumomediastinum depends on complications from precipitating factors in the presence or absence of underlying lung disease, not the pneumomediastinum itself. Differentiating between primary and secondary pneumomediastinum thus impacts patient outcome.

Primary pneumomediastinum is exceptionally rare, but its existence cannot be denied.[5] For these exceedingly rare cases, the abnormal condition causing the air leak would remain unclear. Until a cause is determined, we must call it primary.

In the literature, there are many expressions, such as “primary spontaneous pneumomediastinum” and “idiopathic spontaneous pneumomediastinum”, which suggest that there are different terms for the same condition. Furthermore, stating that idiopathic pneumomediastinum is a form of spontaneous pneumomediastinum[5] is inappropriate because both terms are referring to the same condition.

When a precipitating factor for pneumomediastinum exists, it is not appropriate to use phrases such as “primary spontaneous pneumomediastinum” and “secondary spontaneous pneumomediastinum” to differentiate between a pneumomediastinum in which there is no underlying lung disease predisposing air leakage. Therefore, the word "spontaneous" should be omitted.

It is preferable to use the term primary pneumomediastinum and not spontaneous pneumomediastinum, although they refer to the same condition. From chaos must be born order.

III. Conclusion

Pneumomediastinum due to COVID-19 is not spontaneous because there is a pre-condition like SARS-CoV-2 pneumonia.

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In general, pneumomediastinum cannot be spontaneous when a predisposing or precipitating factor or both are identified.

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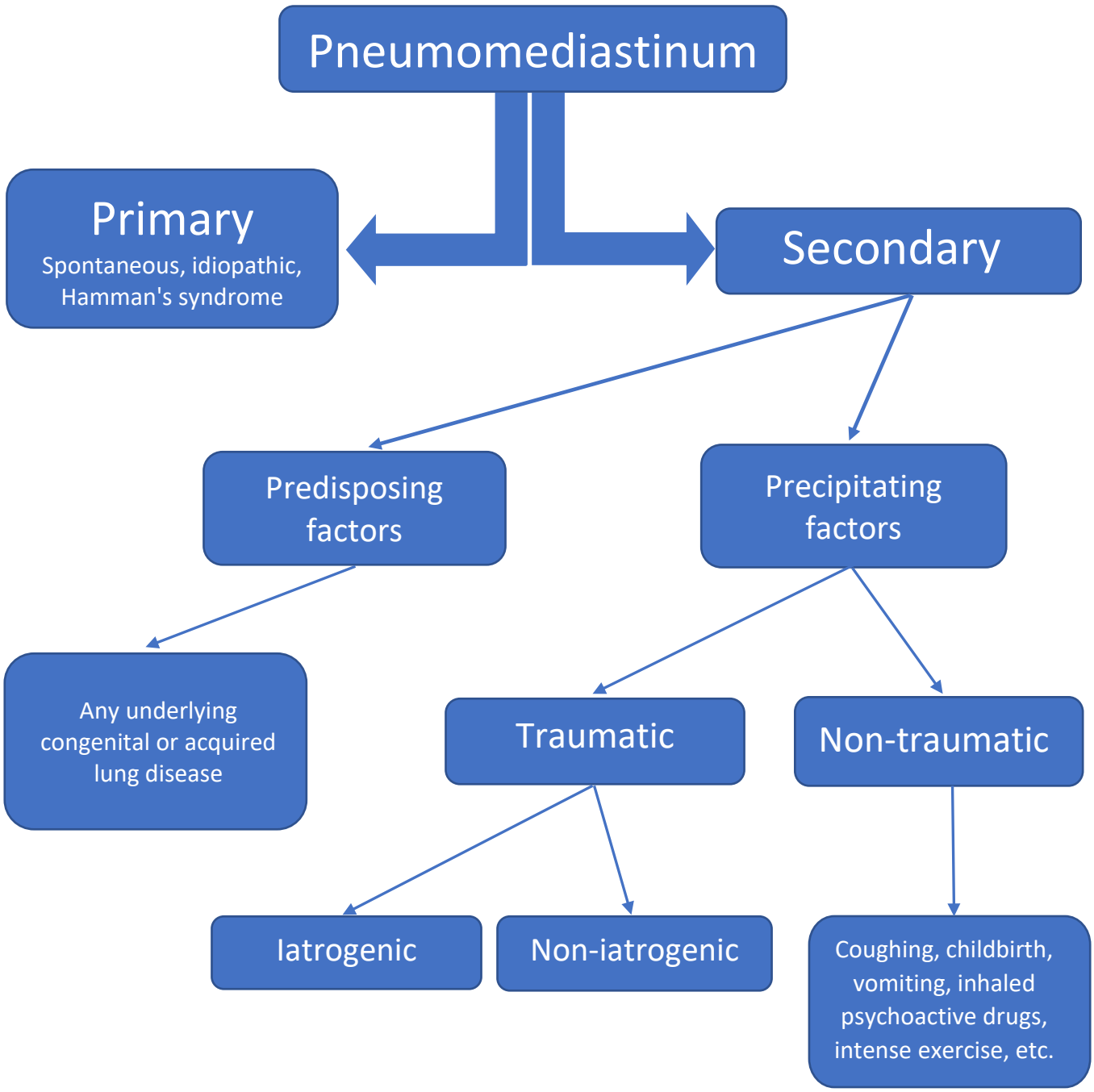


Figure 1: Pneumomediastinum classification

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A Critical Review of Global Aircraft Noise Metrics and their Applications

By OF Orikpete, TG Leton & O.L.Y. Momoh

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Abstract- Aircraft noise metrics are used to assess airport and heliport noise impacts on host communities. Airports and heliports host communities need to be carried along to contribute to deliberations, understand proposals, and have their views heard on aircraft noise reduction strategies. People can feel disillusioned by noise metrics that are too complex and do not express what residents experience. Selecting the best noise metric is essential if all aviation stakeholders are to engage meaningfully on modalities for aircraft noise reduction. A single global noise metric that would capture all the factors influencing people's perception of aircraft noise and produce a definitive measure of annoyance is highly desirable, but such does not exist. Some of these noise metrics are simple but do not include subjective factors in their analysis; others that capture both the objective and subjective aspects of aircraft noise effects are complex and difficult to interpret. In selecting a noise metric to use for the measurement of aircraft noise, it is necessary to strike a balance between precision and simplicity. This paper examines the various noise metrics currently used to assess aircraft noise exposure globally and makes a case for equivalent continuous sound level(L_{eq}) as the best based on the fact that it is easy to understand and communities can easily relate it to their experiences.

Keywords: heliport, noise metrics, aircraft noise, equivalent continuous sound level.

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A Critical Review of Global Aircraft Noise Metrics and their Applications

OF Orikpete [α], TG Leton [σ] & O.L.Y. Momoh [ρ]

Abstract- Aircraft noise metrics are used to assess airport and heliport noise impacts on host communities. Airports and heliports host communities need to be carried along to contribute to deliberations, understand proposals, and have their views heard on aircraft noise reduction strategies. People can feel disillusioned by noise metrics that are too complex and do not express what residents experience. Selecting the best noise metric is essential if all aviation stakeholders are to engage meaningfully on modalities for aircraft noise reduction. A single global noise metric that would capture all the factors influencing people's perception of aircraft noise and produce a definitive measure of annoyance is highly desirable, but such does not exist. Some of these noise metrics are simple but do not include subjective factors in their analysis; others that capture both the objective and subjective aspects of aircraft noise effects are complex and difficult to interpret. In selecting a noise metric to use for the measurement of aircraft noise, it is necessary to strike a balance between precision and simplicity. This paper examines the various noise metrics currently used to assess aircraft noise exposure globally and makes a case for equivalent continuous sound level(L_{eq}) as the best based on the fact that it is easy to understand and communities can easily relate it to their experiences.

Keywords: heliport, noise metrics, aircraft noise, equivalent continuous sound level.

I. Introduction

Noise is any sound perceived to be loud or unpleasant by the ear through any medium. It is a health hazard that causes discomfort, stress, lack of concentration, reduction in performance, and in extreme cases, loss of hearing. People get exposed to harmful noise levels through the use of machines, equipment at workplaces, and social gatherings, hence the need to evaluate noise and identify areas where people are prone to be exposed to harmful levels of noise to protect their health and safety.

An aircraft noise metric refers to the unit or quantity that quantitatively measures the effect of aircraft noise on the environment. Various aircraft noise metrics that are used to measure aircraft noise have evolved globally. These noise metrics were developed to capture different aspects of aircraft noise over time, and to understand the effects of aircraft noise on community residents living close to airports or heliports. Some of these noise metrics are simple but do not include subjective factors in their analysis; others that capture both the objective and subjective aspects of aircraft noise effects are complex and difficult to interpret. In selecting a noise metric to use for the measurement of aircraft noise, it is necessary to strike a balance between precision and simplicity. Selecting a metric for assessing aircraft noise is no simple task because it must reflect the impact on people and must be easy to understand. There is no single aircraft noise metric that can describe all responses in all situations. However, nowadays, the most used noise exposure measure for all sources is the L_{eq} and, for aircraft noise, this is in widespread use around the world. It is the aim of this paper to provide a critical review of the various noise metrics that are currently in use globally in the evaluation of aircraft noise and the associated effects.

II. Theoretical Framework

a) Noise Metrics: what are they?

Noise metrics are an attempt to emulate the way humans respond to sound (Lamancusa, 2000). Most sounds that occur in the environment are not constant, but their sound level varies over time. To characterize the magnitude of such sounds, various descriptors, or metrics, have been developed. In other words, noise metrics are the units or quantities that measure the effect of noise on the environment, and they fall into two groups (Plotkin et al., 2011). (Murphy and King, 2014)further, expatiate that noise metrics are used to reduce large volumes of information about a noise situation into a single number system. They further explained that noise metrics were designed to make acoustic information easier to handle while still providing accurate results about the noise environment. All noise metrics are used to help quantify various aspects of noise and depending on the type of noise and relevant legislation in a country, noise metrics can take many different forms. While they are all based on the decibel scale, there is no agreement on a single best measure (Lamancusa, 2000).Some noise metrics are used to describe a single flight phase, such as take-off or landing, while others describe the combined effect of the various phases of flight within a specified time. Both types of noise metrics help in understanding how people tend to respond to a given noise condition.

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Noise metrics are basically of two types: single event metrics and cumulative noise metrics.

Single event metrics describe the noise impact of a single aircraft movement or over-flight in terms of its intrusiveness, loudness, or noisiness. They quantify the impact of an event, and the duration and time are also considered. There are four single event metrics, which include: maximum sound level (L_{max}), Sound Exposure Level (*SEL*), Single Event Noise Equivalent Level (*SENEL*), and Effective Perceived Noise Level (*EPNL*).

Cumulative noise metrics refer to metrics that quantify the noise impact from multiple aircraft movements during a given time frame. They quantify noise over an extended period and cover several events. There are nineteen cumulative event metrics. Examples include Equivalent Sound Level (L_{eq}), Percentile Noise Levels or Statistical metrics (L_{10}, L_{50}, L_{90}), Time-Above a Specified Level (*TA*), Day-Night Average Sound Level (L_{dn}), Day-Evening-Night Average Sound Level (L_{den}), Noise and Number Index (*NNI*), Weighted Equivalent Continuous Perceived Noise Level (*WECPNL*), Community Equivalent Sound Level (*CNEL*), Composite Noise Rating (*CNR*), etc.

To adequately describe noise on a broadband spectrum, several metrics have been used. These metrics or descriptors have various areas of application. Some of the metrics mentioned below were adapted from (Page et al., 2015) and (Plotkin et al., 2011); however, it is important to state categorically that from a scientific point of view, the best noise metric to employ is the one that performs best in predicting the effect of interest (WHO, 2018). A single global noise metric that would capture all the factors influencing people's perception of aircraft noise and produce a definitive measure of annoyance is highly desirable, but such does not exist.

i. *Equivalent Sound level (L_{eq})*

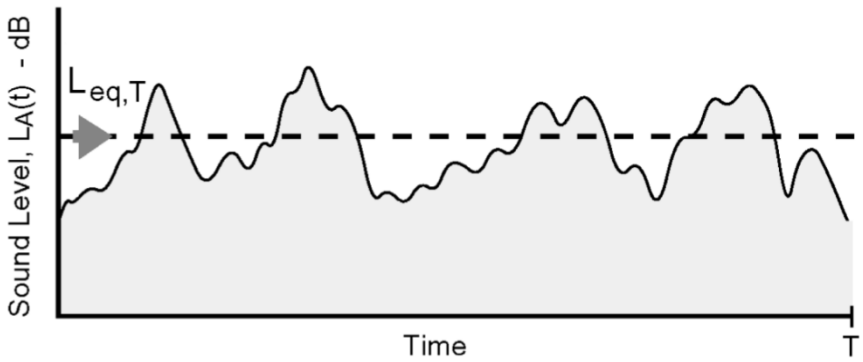
Equivalent Sound Level (L_{eq}) is a measure of the exposure resulting from the accumulation of A-weighted sound levels over a period of interest, which could be an hour, 8-hour, night-time, or 24 hours. It is defined as the hypothetical steady sound, which contains the same energy as the actual variable sound, over a defined measurement period, T (Figure 1). It is important to state the applicable period because the length of the period can be different depending on the time frame of interest. L_{eq} is the most used noise metric for all types of noise sources, and for aircraft noise, its use is widespread across the world. It is the metric used in Germany, the United Kingdom, Nigeria, and the International Organization for Standardization (ISO) for measuring aircraft noise (Airbus, 2003). Conceptually, L_{eq} may be thought of as a constant sound level throughout the period of interest that contains as much sound energy as the actual time-varying sound level with its normal crests and troughs. It is an energy-based indicator as it represents the total amount of acoustic energy over the specified period. The equation for computing L_{eq} is presented as shown in Eq1 as:

$$L_{eq} = 10\log_{10}\left[\frac{1}{T}\sum_{i=1}^{n} 10^{(0.1L_i)}\right] \quad (1)$$

Assuming the reference pressure $= 20\ \mu Pa$
Where:

L_i= A - weighted pressure (dB)

T = time (seconds)



Source: (Jones and Cadoux, 2009)

Figure 1: Graphical illustration of L_{eq}

Note that the average sound level suggested by L_{eq} is not an arithmetic mean but a logarithmic or energy-averaged sound level. L_{eq} can be measured or calculated in a variety of ways. The total noise exposure is determined if the meter runs continuously during the measurement period. If we want to monitor only the contribution of aircraft noise to the total, as aircraft events are discontinuous, the meter can be programmed to read only when aircraft noise is controlling the overall sound level. When individual aircraft noise levels are higher than those due to other sources, this is often readily accomplished with

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automatic noise monitoring systems by choosing a suitable threshold level to trigger the integration (Jones and Cadoux, 2009).

ii. *Maximum Noise Level (L_{max})*

The most basic measure of a noise event, such as the over-flight of an aircraft is the maximum sound level recorded (Jones and Cadoux, 2009). L_{max} represents the highest noise level measured during a single event in which the sound changes with time (Murphy and King, 2014). For instance, during an aircraft over flight, the noise level starts at the ambient or background noise level, rises to the maximum level as the aircraft flies closest to the observer, and returns to the background level as the aircraft recedes into the distance (Wyle, 2008). So, L_{max} depicts the highest noise level reached during a flyover. L_{max} is important in judging if a noise event will affect the conversation, watching television or listening to the radio and other routine activities. L_{max} is frequently used in noise disturbance research as it has been found to correlate well with levels of both sleep disturbance and reading and speech interference for school children. However, L_{max} is not able to reflect the number of or frequency with which very noisy events occur. The disadvantage of L_{max} is that it describes only one dimension of an event and provides no information on the cumulative noise exposure generated by a noise source. Although it gives some measure of the intrusiveness of the event, it does not entirely describe the total event because it does not take into consideration the period that the sound is heard (Wyle, 2008). To further emphasize, two events with identical L_{max} may produce very different total exposures with one having a very short duration and the other may be much longer.

iii. *Peak Noise Level (L_{peak})*

The peak sound pressure level is the highest instantaneous level obtained by a sound level measurement device. The peak sound pressure level usually measured using 20 microseconds or faster sampling rate and is usually based on unweighted or linear response of the meter (Wyle, 2008). It is the highest C-weighted sound level measured during a single event with no time constant applied. It is used for the assessment of impulsive noise (Murphy and King, 2014).

iv. *Single Exposure Level(SEL)*

The most common measure of noise exposure for a single aircraft flyover is the *SEL*. *SEL* is a normalized value of L_{eq}; the period considered being one second. This *SEL* value represents the A-weighted sound level, which, when produced during one second, would result in the same L_{eq}. This allows us to get rid of the influence of the measurement period and compare events of different durations. It is also expressed in dB(A) (Airbus, 2003). (Murphy and King, 2014)further clarified that the *SEL* of a noise event is the constant level, which if maintained for only one second, would contain the same A-weighted noise energy as the actual event itself. In other words, *SEL* is essentially an A-weighted L_{eq} level normalized to one second. Since SEL is normalized to one second, it will almost always be bigger in magnitude than the L_{max} for the same event. For most aircraft events, the SEL is about 7 to 12 dB higher than the L_{max}. *SEL* is used in aircraft noise assessments allowing for an easy comparison of different types of aircraft(Murphy and King, 2014).Since SEL combines an event's overall sound level along with its duration, SEL provides a comprehensive way to describe noise events for use in modelling and comparing noise environments. Although the SEL noise metric attempts to capture the total noise energy, it is difficult to accurately account for differences in background noise. It is also complex and difficult for communities to understand. The main disadvantage of SEL is that, for events lasting more than one second, it provides a measure of the net impact of the entire acoustic event. Still, it does not directly represent the sound level heard at any given time.

v. *Single Event Noise Exposure Level (SENEL)*

SENEL is a very slight variation on *SEL*. Just like *SEL*, it is the one-second-long steady-state level that contains the same amount of energy as the actual time-varying level. However, unlike *SEL*, it is calculated only over the period when the level exceeds a selected threshold. *SENEL* is derived from *SEL* in the way that only transient sounds exceeding a certain level are accounted for [typically 65 dB(A)] (Airbus, 2003).

vi. *Percentile Noise Levels or Statistical Sound Levels (L_{10}, L_{50}, L_{90})*

Sometimes, it may be preferable to represent noise levels with statistical indicators, and these give the noise level exceeded for a certain percentage of the measurement time. This metric is commonly used for traffic noise measurement. The most common are L_{10} (which represents the noise level exceeded for 10% of the time, L_{50}(which stands for the noise level exceeded 50% of the time, and L_{90} (which stands for the noise level exceeded 90% of the time) (Murphy and King, 2014). L_{90} is a good measure of background noise; L_{50} is the median noise, which is not necessarily the same thing as L_{eq}(the mean); L_{10} is a good measure of intermittent or intrusive noises, such as traffic, aircraft flyovers, barking dogs, etc. (Lamancusa, 2000).

vii. *Noise Pollution Level (NPL)*

Noise pollution level can be determined using Eq. 2 found in (Peirce, Weiner, and Vesilind, 1998), and also cited in (Nwaogozie and Owate, 2000)

$$NPL\,[dB(A)] = L_{50} + (L_{10} - L_{90}) + \frac{(L_{10} - L_{90})^2}{60} \quad (2)$$

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Where:
L_{10} = Noise level at 10% time exceeded
L_{50} = Noise level exceeded 50% of the time
L_{90} = Noise level exceeded 90% of the time
The NPL may also be determined using Eq. 3 as:

$$NPL = L_{eq} + K\sigma \quad (3)$$

Where:
K = Constant with a value of 2.56
σ = the standard deviation of the computed L_{eq} values

viii. *Noise Criteria (NC) Curves*

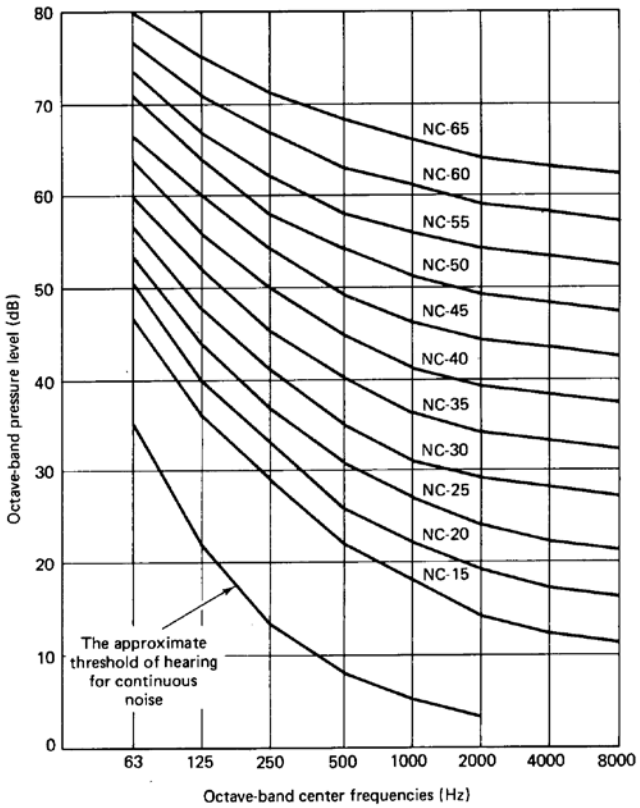
Noise levels below 80 dB are considered safe from a hearing loss perspective. However, they can still be highly annoying and interfere with the smooth performance of occupational tasks or other activities. Noise criterion curves were established in 1957 in the USA and are used to rate the background levels in buildings and rooms, for example, noise from air-conditioning equipment. For a given noise spectrum, the *NC* rating may be obtained by plotting its octave band levels on the set of *NC* curves (shown in Figure 2 below). The noise spectrum is specified as having an *NC*rating the same as the lowest *NC* curve, which is not exceeded by the spectrum(Lamancusa, 2000).

Table 1

Centre Frequency (Hz)	62.5	125	250	500	1000	2000	4000	8000
Band Pressure Level (dB)	41	45	48	50	46	42	40	38

Source: (Eargle, 1994)

For example, a sound having the following octave-band noise (Table 1) is rated as NC-46 since when plotted in Figure 2, it exceeds the NC-45 curve by 1 dB at 500 Hz. The recommended Noise Criteria range for urban residence is 25-35 NC (ASHRAE, 1996).



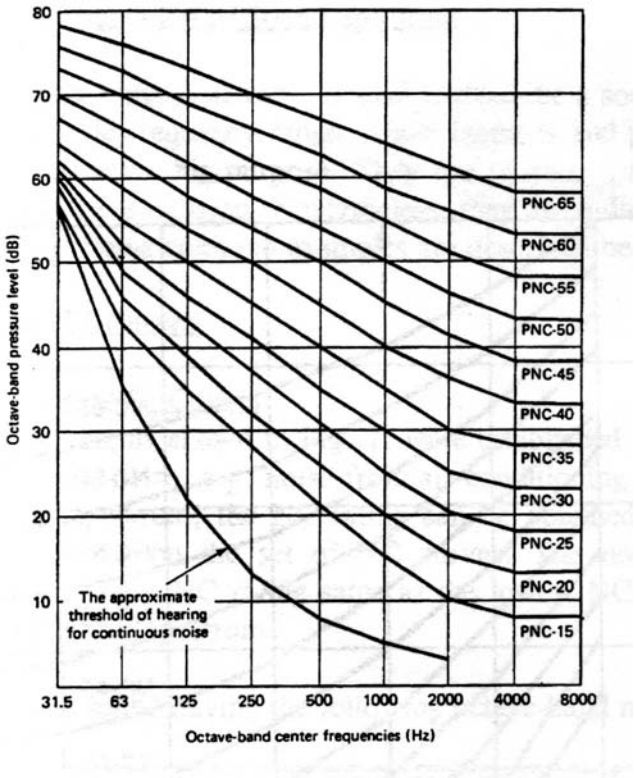
Source: (Robinson and Dadson, 1956)

Figure 2: Noise Criterion (*NC*) curves

ix. *Preferred Noise Criteria (PNC) Curves*

The *PNC* curves were introduced in 1971 as a modification on the *NC* curves in response to criticism that in offices designed to *NC* curves, the air-conditioning noise was too rumbly (low-frequency sound) and hissy (high-frequency sound). The curves are shown in Figure 3 below. In the previous example given earlier, the noise spectrum will have a rating of PNC-47 as it exceeds the PNC-45 curve by about 2 dB at 4 kHz. The recommended Preferred Noise Criteria (PNC) range for living quarters is 20-30 PNC (ASHRAE, 1996).

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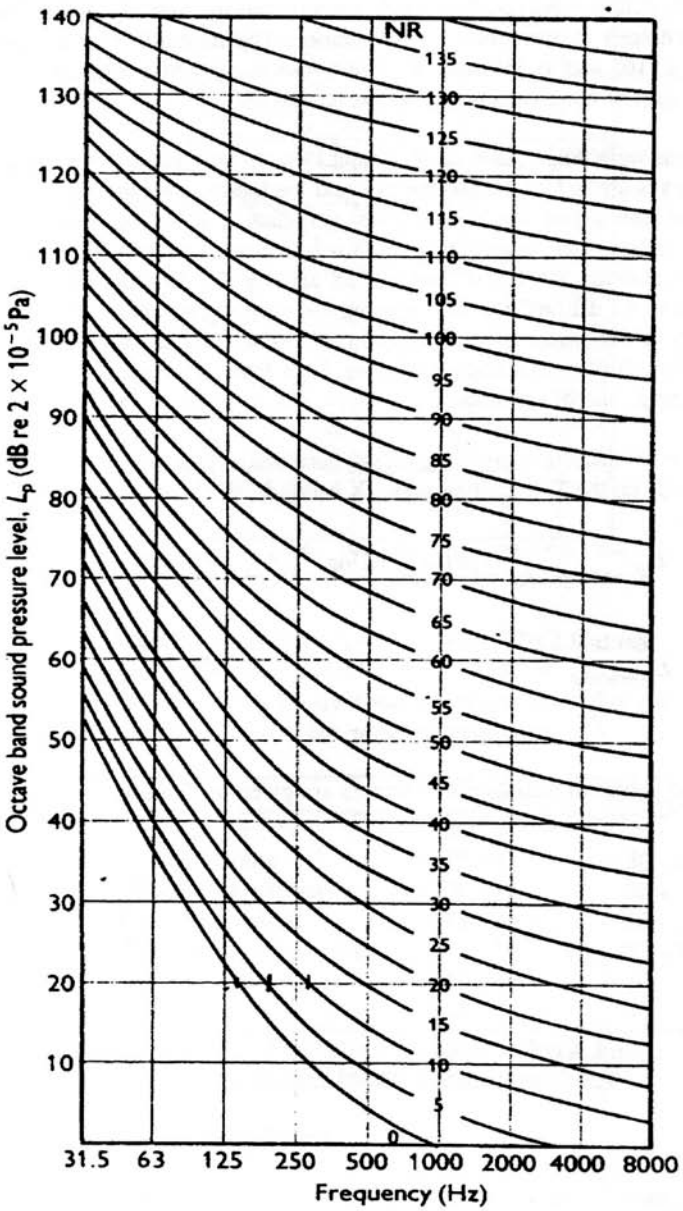
Source: (Beranek, Blazier, and Figwer, 1971)

Figure 3: Preferred Noise Criterion (PNC) curves

x. *Noise Rating (NR) Curves*

These curves were developed in Europe to assess community noise complaints. They are shown in Figure 4. Their use is like that for the *NC* and *PNC* curves.

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Source: (Schultz, 1982)

Figure 4: Noise Rating (NR) Curves

xi. *The Articulation Index (AI)*

(French and Steinberg, 1947) developed the Articulation Index (AI) noise metric. The basic concept of AI is that speed intelligibility is proportional to the average difference in dB between the masking level of noise and the long-term root mean squared dB level (plus 12 dB) of the speech signal. Twenty relatively narrow frequency bands are used, corresponding to the critical bandwidth of the ear. This method determines a masking spectrum of a noise that may be different from the noise spectrum due to the spread of masking. It considers background noise, masking, and non-flat noise spectra. The disadvantage of the AI noise metric is that the calculation of AI is relatively complicated. It is not well suited for highly reverberant environments or when the speech is distorted, such as by mumbling or poor-quality amplification.

xii. *Speech Interference Level (SIL)*

Speech interference level (*SIL*) is a metric that estimate show much a given noise spectrum will disrupt, or interfere with, effective speech communication. *SIL* is evaluated using different formulae depending on the industry. All the various forms of *SIL* are computed by taking the arithmetic mean of un-weighted, full-octave band sound pressure levels, as expressed in decibels (dB). The only difference between the various forms of *SIL* is the octave bands included in the calculation. The various forms are: Preferred Speech Interference Level

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(*PSIL*) used by the Acoustical Society of America, *SIL* used by the aviation industry, and *ANSI SIL* used by the American National Standards Institute (ANSI). According to (Lamancusa, 2000), some industries, especially the aviation industry, prefer to use the 1 000, 2 000, and 4 000 Hz bands to calculate *SIL*.

$$PSIL = \frac{L_{500} + L_{1000} + L_{2000}}{3} \quad (4)$$

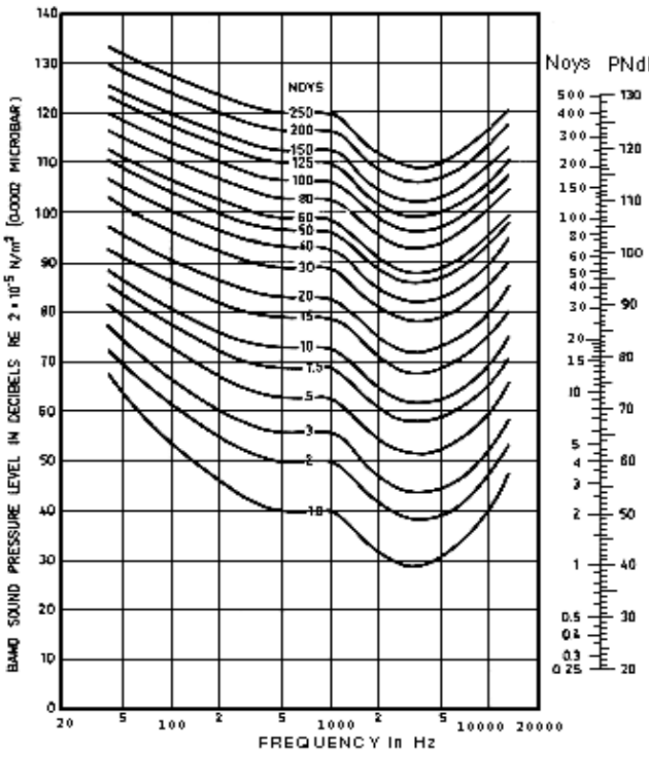
$$SIL = \frac{L_{1000} + L_{2000} + L_{4000}}{3} \quad (5)$$

$$ANSI\ SIL = \frac{L_{500} + L_{1000} + L_{2000} + L_{4000}}{4} \quad (6)$$

xiii. *Perceived Noise level (PNL)*

Different types of aircraft, such as jets, propeller-driven aircraft, and helicopters, all have distinctive noise characteristics due to combinations of sound from various sources having different frequency ranges, intensities, and time histories. The annoyance perceived by an observer as an aircraft type flies over is described by its noisiness. Perceived noisiness may be defined as a measure of how unwanted, objectionable, disturbing, or unpleasant the sound is. The PNL scale allows for different human sensitivity to different frequencies, but it is more complicated (Jones and Cadoux, 2009). *PNL* has been adopted as the best descriptor of aircraft noise nuisance, according to (Airbus, 2003). *PNL* is determined by a combination of measurement and mathematical calculation, involving spectra analysis. To determine *PNL*, it is measured with a sound level meter equipped with electronic one-third octave filters. Each frequency band level in the spectrum is converted to a noisiness value, and these are summed specially to obtain the total noisiness of the sound (Jones and Cadoux, 2009). It is used in rating the noisiness of sounds, and it is evaluated in three steps.

Step 1: The measured one-third octave band sound pressure level in the range 50 - 1 000 Hz that occurs in each instant of time is converted to perceived noisiness (noy) using the noy chart in Figure 5.



Source: (Sincero and Sincero, 1996)

Figure 5: Chart showing the noy scale

Step 2: The perceived noisiness values gotten from step I is then combined using Eq. 7

$$N_t = 0.15 \sum N_i + 0.85 N_{max} \quad (7)$$

Where:

N_i = the noy value corresponding to each frequency band and sound pressure level.

N_{max} = the maximum noy value obtained in the conversion of the octave band data to noy.

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Step 3: The effective noy value (N_t) is finally converted to Perceived Noise Level (*PNL*) using the Eq 8

$$PNL = 40 + \frac{10 \log_{10} N_t}{\log_{10} 2} \quad (8)$$

The unit of *PNL* is PNdB (Perceived Noise Decibel).

xiv. *Noise and Number Index (NNI)*

The noise and number index attempt to measure the subjective noisiness of an aircraft. It uses the PNdB as a basis and considers the number of aircraft per day (or night) as a primary annoyance factor. NNI represents a composite level measure of exposure to aircraft noise, considering the average event noise level and the number of aircraft in a specific period (0700-1900 hours).Mathematically, it is expressed as:

$$\text{NNI} = (\text{Average Peak PNdB}) + 15 \log_{10} \text{N} - 80 \quad (9)$$

Where:

N = Number of flights

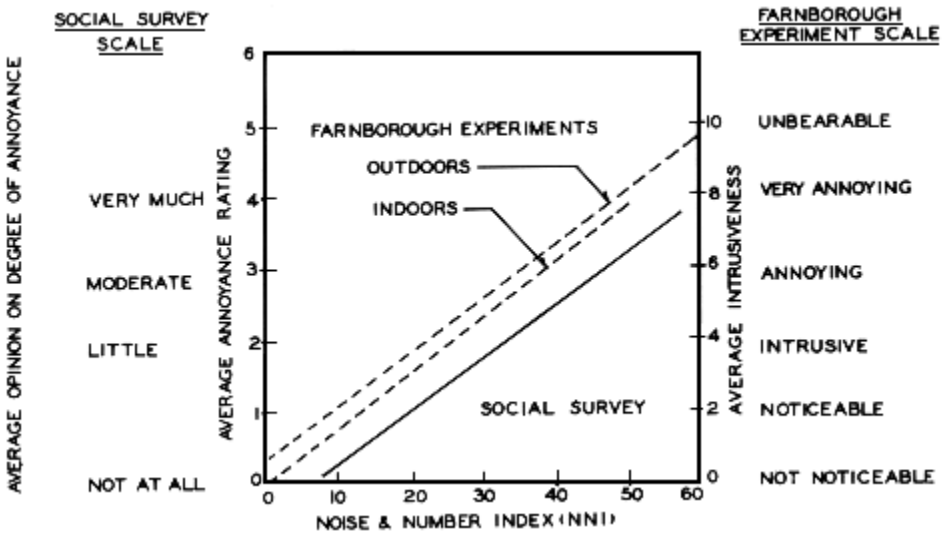
PNdB = Average peak PNdB is the logarithmic average of the highest levels of all over-flights.

80 = Normalized constant.

This considers the results of social surveys that showed that the annoyance factor was zero at 80 PNdB.

NNI was propounded using social surveys and noise measurements. Social surveys measured, amongst other things, the annoyance from aircraft noise expressed by a sample of individuals living at different places around Heathrow airport. Noise data were then matched to this reported disturbance, measured by scales constructed from the social survey data (Jones and Cadoux, 2009). According to (Airbus, 2003), the *NNI* scale (Fig 6) was first proposed by the Wilson Committee on noise in Britain. It spans from 0 – 60, and based on social surveys, the Wilson committee assigned values of annoyance to the index with the committee agreeing that an unreasonably high level of aircraft noise is attained between 50 - 60. An NNI of 55 was used to indicate a high annoyance area, and NNI = 35 was used to indicate the threshold of community annoyance(Jones and Cadoux, 2009).

The main criticisms of NNI were that it was out of date; that people's reactions and the change in attitudes to aircraft traffic and noise invalidated its use. It was also considered to be out of line with the metrics used by other countries and therefore was not standardized. The weighting was not considered to be sufficient for the number of aircraft. The noise level and number are not the arithmetic mean from all aircraft, including all aircraft in this count would constitute a better match with annoyance. A final disadvantage of the *NNI* was that the exclusion of night movements led to an under-estimation of disturbance, which eventually led to a change from *NNI* to L_{eq} as the metric for monitoring aircraft noise exposure for airports in the United Kingdom in 1990 (Jones and Cadoux, 2009).



Source:(Airbus, 2003)

Figure 6: Chart showing the *NNI*

xv. *Tone-Corrected Perceived Noise Level (PNLT)*

When some pure sounds are in the frequency spectra, the annoyance appears to be higher. The sound pressure level obtained by adding a tone correction to the perceived noise level is the *PNLT* and was developed for aircraft noise. It is evaluated from octave or one-third octave spectra. Each individual spectrum is examined using a specified process for the presence of tones, identified by spikes, for which a tone-correction is evaluated. This is a penalty added to the PNL calculated for that individual spectrum to give the so-called tone-corrected perceived noise level or PNLT (Jones and Cadoux, 2009). Mathematically, it may be represented as:

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$$PNLT = PNL + C \quad (10)$$

C is a tone correction factor calculated for each spectrum to account for the subjective response to the maximum tone (Airbus, 2003).

xvi. *Effective Perceived Noise level (EPNL)*

The noise made by an aircraft flying over is complicated by its motion, which causes its intensity and frequency composition to change with time. Much research into human perception of aircraft noise led to the conclusion that *PNL* did not adequately reflect the true noisiness of a complete aircraft event unless the effects of both tones and duration are considered (Jones and Cadoux, 2009). *EPNL* is commonly used when assessing aircraft noise, and it is vital to note that this metric is used for noise certification of all commercial subsonic jet aircraft and also propeller-driven airplanes (Airbus, 2003; Murphy and King, 2014). It is a metric that considers the duration of the noise event based on a tone corrected perceived noise level time history. In order to determine *EPNL*, the complete set of ½-second *PNLT* values is integrated to determine the level of the 10-second long steady sound, which would have the same perceived noisiness. Mathematically, it is defined as:

$$EPNL = PNL_{max} + 10\log\left(\frac{t_{10}}{20}\right) + F\ (dB) \quad (11)$$

where

PNL_{max} is the maximum perceived noise level during a flyover in PNdB,

t_{10} is the duration (in seconds) of the noise level within 10 dB of the peak PNL,

and *F* is a correction (generally found to be more annoying than broadband noise without perceived tones). For many practical applications, *F* is about +3 dB.

The unit of *EPNL* is EPNdB (Effective Perceived Noise Decibel).

The reason for normalizing EPNLs to 10 seconds is to penalize those aircraft that make a lot of noise for a relatively long time. EPNL tends to be more accurate at high noisier events than quieter events. EPNL is usually larger than the certified values, which is particularly noticeable for departure noise levels. This means EPNL is unlikely to represent the noise experienced by communities surrounding an airport or heliport. Coupled with the tone corrections that are thought to be subjective, EPNL, and related noise metrics are less powerful and complex to communicate.

xvii. *Weighted Equivalent Continuous Perceived Noise Level (WECPNL)*

WECPNL may be considered as a hybrid of *EPNL*, since it incorporates *EPNL* which is tone and duration corrected, but also includes a time-of-day energy average and a seasonal correction based on temperature (Jones and Cadoux, 2009). It characterizes flyover and run-up noise events with *EPNL* and *PNLT,* respectively. *WECPNL*, like *CNEL*, averages sound levels at a location over a 24-hour period, with penalties of 5 and 10 dB representing the evening and night-time, because of increased sensitivity to noise during those hours. It is the metric used for aircraft noise measurement in Japan, although there is now a move towards the L_{eq} metric (Airbus, 2003).

xviii. *Day Equivalent Sound Level (L_{day})*

Day Equivalent Sound Level (L_{day}) represents the noise exposure level over the day-time period, typically 0700-1900 hours.

xix. *Night Equivalent Sound Level (L_{night})*

According to (Jones and Cadoux, 2009), L_{night} represents the noise exposure level over the night-time period, typically 2300-0700 hours. Measures of L_{night} have been used to assess night flying restrictions, but this metric is not widely used.

xx. *Day-Night Average Sound Level (DNL or L_{dn})*

For the evaluation of community noise effects, and particularly aircraft noise effects, the Day-Night Average Sound Level (*DNL* or L_{dn}) is used. It is a cumulative metric that accounts for all noise events in 24 hours with a night-time penalty of 10 dB for events during the night. It considers a night time (2200-0700 hrs) event ten times more disturbing than a daytime (0700-2200 hrs). It is widely used in Belgium, New Zealand, and the United States of America, especially the Environmental Protection Agency (EPA) (Murphy and King, 2014). Mathematically, it is expressed as:

$$L_{dn} = 10.\log\left[\frac{1}{86400} * \left[\sum_{i=1}^{n} 10^{\frac{L_{AE\,(i)day\ [0700-2200\,]}}{10}}\right] + 10\sum_{j=1}^{n} 10^{\frac{L_{AE\,(j)day\ [2200-0700\,]}}{10}}\right] \quad (12)$$

Where:

n is the number of events

$L_{AE(i)day[0700\text{-}2200]}$ is the *SEL* produced by a trajectory during the [0700-2200] period.

$L_{AE(j)day[2200\text{-}0700]}$ is the *SEL* produced by a trajectory during the [2200-0700] period.

86400 is the day duration in seconds. That is, $24 \times 60 \times 60 = 86400$

The values of *DNL* or L_{dn} can be measured with standard monitoring equipment or predicted with computer models. Due to the *DNL* or L_{dn} metric's close correlation with the degree of community annoyance

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from aircraft noise, it has been formally adopted by most federal agencies in the United States for measuring and evaluating aircraft noise for land use planning and noise impact assessment. Countries currently using this metric include Denmark and Finland (SI, 2005). EPA recommends a maximum residential level of 55 L_{dn}, which is equivalent to a steady noise of 48.6 dB(A) (Lamancusa, 2000).

Several issues have arisen from the use of *DNL* or L_{dn} and the percentage of persons highly annoyed: no one actually "hears" a DNL; there is a high variability from study to study around a nominal Schultz curve, and in many situations "highly annoyed" is not an appropriate measure of human response. Although the percent highly annoyed and DNL approach has been widely accepted, variability around a nominal Schultz curve is troubling. There are reports that this approach is not enough to predict community response (Fidell, 2002).

xxi. *Community Noise Equivalent Level (CNEL)*

CNEL was developed in the early 1970s by the State of California in the United States of America for community noise exposure, with particular emphasis on airport noise. It is similar to L_{dn} but considers three time periods, namely day (0700-1900 hours) for which there is no weighting or penalty; evening (1900-2200 hours) for which there is a three times weighting corresponding to approximately 4.8 dB penalty; and night (2200-0700 hours) with ten times weighting equal to 10 dB penalty. It is used in comparing the noise impact of communities and for regulating airport noise impact. Mathematically, it is expressed as:

$$CNEL = 10.\log\left[\frac{1}{86400}\left[\sum_{i=1}^{ni} 10^{\frac{L_{AE\,(i)day\ [0700-1900]}}{10}}\right] + 3\sum_{j=1}^{nj} 10^{\frac{L_{AE\,(j)evening\ \ [1900-2200]}}{10}} + 10\sum_{k=1}^{nk} 10^{\frac{L_{AE\,(k)night[2200-0700]}}{10}}\right] \quad (13)$$

Where:

n is the number of events

$L_{AE(i)day[0700\text{-}1900]}$ is the *SEL* produced by a trajectory during the [0700-1900] period.

$L_{AE(j)evening[1900\text{-}2200]}$ is the *SEL* produced by a trajectory during the [1900-2200] period.

$L_{AE(k)evening[2200\text{-}0700]}$ is the *SEL* produced by a trajectory during the [2200-0700] period.

86400 is the day duration in seconds. That is, $24 \times 60 \times 60 = 86\,400$

The use of CNEL has been criticized as not accurately representing community annoyance and land-use compatibility with aircraft noise (Wyle, 2008).

xxii. *Day-Evening-Night Average Sound Level (L_{den})*

For long-term noise exposure, L_{den} has a proven relationship with the degree of community noise annoyance and particularly with the percentage of highly annoyed respondents. It has been a noise metric in use in the Netherlands since 2003.

L_{den}, in combination with special dose-effect relations, is also applicable in the following cases: annoyance due to noise with strong tonal components, annoyance due to noise with an impulsive character, and adverse effects on learning by children.

The definition of the L_{den} is like the *CNEL*. The only difference is that the weighting factor for the evening for L_{den} is 5 and 3 for *CNEL* respectively. This is the metric adopted for use for aircraft noise measurement by the World Health Organization (WHO, 2018). Mathematically, it is expressed as:

$$L_{den} = 10.\log\left[\frac{1}{86400}\left[\sum_{i=1}^{ni} 10^{\frac{L_{AE\,(i)day\ [0700-1900]}}{10}}\right] + 5\sum_{j=1}^{nj} 10^{\frac{L_{AE\,(j)evening\ \ [1900-2200]}}{10}} + 10\sum_{k=1}^{nk} 10^{\frac{L_{AE\,(k)night[2200-0700]}}{10}}\right] \quad (14)$$

Where:

n is the number of events

$L_{AE(i)day[0700\text{-}1900]}$ is the *SEL* produced by a trajectory during the [0700-1900] period.

$L_{AE(j)evening[1900\text{-}2200]}$ is the *SEL* produced by a trajectory during the [1900-2200] period.

$L_{AE(k)evening[2200\text{-}0700]}$ is the *SEL* produced by a trajectory during the [2200-0700] period.

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86400 is the day duration in seconds. That is, $24 \times 60 \times 60 = 86400$

Note that in France, the day-time period is 0600-1800 hrs, the evening is 1800-2200 hrs, and the night-time period is 2200-0600 hrs (Jones and Cadoux, 2009).

xxiii. *Störindex (Q)*

The German Störindex (Q) is like L_{dn} but gives a greater emphasis to the number factor (trade-off factor $\approx$ 13.3) and less to the night-time weighting (5 dB penalty only). Luxembourg has also adopted this noise metric (Jones and Cadoux, 2009).

xxiv. *Airport Noise Level (L_{VA})*

This metric is used in Italy as an equivalent continuous sound level. A 10 dB weighting factor is applied to the night movements (Jones and Cadoux, 2009).

According to (Cotana and Nicolini, 2003), an airport noise level (L_{VA}) is defined as:

$$L_{VA} = 10 \log \frac{1}{N} \sum_{j=1}^{N} 10^{\frac{L_j}{10}} \quad dB(A) \qquad (15)$$

Where:

N is the observation time (days), which must be equal to 21 days.

L_j is the airport noise level referred to as a one-day observation time.

The one-day airport noise level is defined mathematically as:

$$L_j = 10 \log \left[\left(\frac{17}{24} \right) 10^{\frac{L_d}{10}} + \left(\frac{7}{24} \right) 10^{\frac{L_n}{10}} \right] dB(A) \qquad (16)$$

Where:

L_d and $L_n$is the airport noise levels referred respectively to a daytime period (0600-2300 hours) and a night-time period (2300-0600 hours)

xxv. *Flygbuller (FBN)*

The Swedish equivalent of L_{eq}, this metric includes a 9-hour night period (2200-0700 hours), with a weighting of 10 dB, and a 3-hour evening period (1900-2200 hours) with a weighting of 4.78 dB. Using 4.78 dB gives a numerical weighting on the number of flights of exactly 3, whereas the 5 dB weighting in L_{den} effectively makes one evening flight count as 3.162-day flights (Jones and Cadoux, 2009).

xxvi. *Equivalent Aircraft Noise (EFN)*

Equivalent Aircraft Noise (EFN) is Norway's L_{eq} based metric. It is a composite index based on the equivalent continuous A-weighted sound level comparable to L_{den} but including a continuous-time weighting factor. This applies the commonly used night weighting factor of 10 but avoids discontinuities at the beginning and end of the night period. Also, a Sunday day-time penalty is introduced. These functions are based on considerations of both sleep disturbance and annoyance (Jones and Cadoux, 2009).

xxvii. *Hourly L_{eq} around the shoulder hours*

In civil airports in Switzerland, the 16-hour L_{eq} is used (0600-2200 hours) for the daytime, whereas for the night-time, three 1-hour L_{eq} values apply, for 2200-2300, 2300-2400, and 0500-0600 hours. The 1-hour L_{eq} at night has a twofold function: they impose a limitation of the maximum allowable noise from a single event to minimize sleep disturbance, while on the other hand, they are also sensitive to the number of movements (Jones and Cadoux, 2009).

xxviii. *Kosten Index (Ke)*

Kosten Index (Ke) is a noise metric based on L_{max} and has been in use in the Netherlands since 2003. However, in February 2003, the Kosten Index was replaced by L_{den}, after a new Aviation Act came into effect for Schiphol Airport. Metrics based on L_{max} do not consider the duration of the noise, and hence are possibly less representative of the disturbance due to the noise event. However, they are easier to measure and often much simpler for the public to understand (Jones and Cadoux, 2009).

xxix. *Psophic Index (IP)*

The Psophic Index (IP) is based on the PNL scale, with night-time movements weighted by a 10 dB factor, and with a trade-off of 10, and has been in use in France until April 2002. It was also used in French-speaking areas of Belgium. However, the Psophic Index (IP) has been replaced with L_{den} since 2002 (Jones and Cadoux, 2009).

xxx. *Noise Exposure Forecast (NEF)*

The NEF noise metric was first developed by the United States in the 1960s to predict noise levels in commercial airports. It combines the sound level expressed in EPNL with the number of events. A trade-off factor of 16.7 is applied to night-time operations only (10 for day-time movements). It is like NNI in that only events above a certain EPNL are considered. NEF is used in Canada, Hong Kong, Spain, and Greece. A practical disadvantage of NEF is the difficulty of routine noise monitoring in EPNL. Australia uses a modified version of NEF, the Australian Noise Exposure Forecast (ANEF), which incorporates a weighting for1900-0700 hours.

xxxi. *Number of Events Above a Specified Level (NA)*

The Number of events Above (NA) is a noise metric that reflects the average number of times noise equals or exceeds a chosen threshold level during a specified period. NA contours can be depicted at any noise threshold level (x) and any user-defined number of events (z), using the notation 'NAx(z),' meaning 'z' events at or above noise level 'x.' These analysis

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parameters (x and z) may differ in each affected community, based on specific circumstances. No guidelines have yet been established for NA analyses, but individual jurisdictions may apply national guidelines in such a way as to reflect unique conditions at each airport or heliport. So, each jurisdiction has some latitude in establishing local noise standards. The NA metric provides for much flexibility and can be applied to any noise environment, such as daytime, night-time, or any user-defined number of hours.

xxxii. *N_{70}*

To provide an easier way to relate the effects of aircraft noise to the Australian public, a new metric called the N_{70} noise metric was developed (Southgate et al., 2000).The N_{70} is useful because it can easily be understood by a novice. Also, the N_{70} noise metrics are more sensitive to changes in noise levels than the ANEF. The N_{70} also has the advantage of permitting measured noise levels to be very neatly summarized for any given period. This type of information is useful as a supplement to L_{eq}-based noise metrics and as a communication tool. A strong drawback of this noise metric is that it treats a noise event at 70 dB(A) the same as one at 90 dB(A) (Jones and Cadoux, 2009).

xxxiii. *Time-Above a Specified Level (TA)*

The Time-Above a Specified Level (TA) metric describes the total number of minutes that instantaneous sound level (usually from an airplane or helicopter) is above a given threshold. For instance, if 90 dB is the specified threshold, the metric would be referred to as "TA90." Any threshold may be chosen for the TA calculation. The metric can be sensitive to the type of aircraft that creates the noise, as different aircraft models will have different noise signatures.

Time above threshold TA is determined from:

$$TA\ (in\ minutes) = Time\ (L_A \geq L_T) \qquad (17)$$

Where:

L_A = A-weighted sound level

L_T = Threshold of reference in dB(A)

The *TA* metric is typically associated with 24-hour annual average daily conditions but can represent any period.

xxxiv. *Person Events Index (PEI)*

According to (Jones and Cadoux, 2009), the PEI allows the total noise load generated by an airport to be evaluated by summing, over the exposed population, the total number of instances where an individual is exposed to an aircraft noise event above a specified noise level over a given period. For example, if a departure off a specific runway at an airport by an aircraft type leads to 20 000 people being exposed to a single event noise level greater than 70 dB(A) then the PEI(70) for that event would be 20 000. If there were a further similar event, the PEI(70) would double to 40 000 since there would have been that number of instances where a person was exposed to a noise level louder than 70 dB(A). The PEI is expressed mathematically as:

$$PEI(x) = \sum P_N\, N \qquad (18)$$

where,

x = the single event threshold noise level expressed in dB(A)

P_N = the number of persons exposed to N events $> x$ dB(A)

xxxv. *The Average Individual Exposure (AIE)*

(Jones and Cadoux, 2009) argued that the PEI does not indicate the extent to which aircraft noise is distributed throughout a community. For instance, an annual PEI(70) of 2 million for an airport could mean that one person has been exposed to two million events over70 dB(A) (if we imagine it were possible), or that two million people have each received one event or it could be arrived at by any other combination of the two factors. The AIE is mathematically expressed as:

$$\text{AIE} = \frac{\text{PEI}}{\text{Total exposed population}} \qquad (19)$$

xxxvi. *Composite Loudness level (L)*

This measure provides a quantitative measure of the overall loudness, and the relative contribution of each octave band to the overall loudness. It is useful for comparison purposes and gives vital information for the cost-effective application of noise control treatments. It was derived from empirical data with relatively flat spectra (no pure tones) and diffuse sound fields.

Loudness levels in each octave band are determined from Tables. The composite loudness level L for all the octave bands is then:

$$L\ (sones) = 0.7S_{max} + 0.3\sum S_i \qquad (20)$$

where

S_{max} = Loudness index of loudest octave band

S_i= Loudness index of the i^{th} octave band

xxxvii. *Noise Gap Index (NGI)*

The *NGI* is defined as the difference between aircraft noise and background noise. The *NGI* assumes that people living in areas of different background environmental noise levels may have different reactions to the same aircraft noise level. Mathematically, it is given as prescribed by (Issarayangyun, Samuels, and Black, 2004) as:

$$NGI = {L_{eq}}^{A} - {L_{eq}}^{B} \qquad (21)$$

where

${L_{eq}}^{A}$= Aircraft flyover noise determined from 0700 to 1700 hours

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$L_{eq}{}^{B}$ = Background noise determined from 0700 to 1700 hours

xxxviii. *Low-frequency noise level (LFNL)*

It was developed in response to airport low-frequency noise issues. It rates the community annoyance from low-frequency noise. It is derived from the composite maximum of levels in one-third octave bands.

III. Review of Previous Studies

In the quest to determine the best and efficient method to evaluate noise, studies have been conducted on the different methods used in noise evaluation. One study is research by (Lamancusa, 2000), where he shed more light on the basic noise metrics, their application, computation, and drawbacks. Another study by (Miedema and Oudshoorn, 2001) produced a modelled noise annoyance distribution system with the mean varying as a function of noise where day–night level (L_{dn}) and day–evening–night level (L_{den}) were used as noise metrics. (Revoredo and Slama, 2008)went further to present the Integrated Noise Model (INM) generated noise footprints method for establishing relationships between L_{dn} used in airport noise zoning and L_{eq} used in urban areas for evaluating annoyance. Also, (You and Jeon, 2008) investigated just noticeable differences (JND) of sound quality metrics using refrigerator sounds. A substantial amount of improvement for each sound quality metric, which affects subjective responses to refrigerator noise, was noticed.

In a review by (Hooper et al., 2009), the authors concluded that there was no best method to demonstrate aircraft noise exhibition, and any attempt to improve noise management should be engaged with the physiological, psychological, and sociological determinants of disturbance. From another survey on metrics, (Jones and Cadoux, 2009) stated that the L_{eq} indicator constitutes the basis for aircraft noise computation, it can quantify the number of noise occurrence, the noise energy, and the period in which the event occurred. Sound metrics for the description of environmental noise were reviewed by (Fiebig and Genuit, 2010).In apsychoacoustic test (More et al., 2010)showed that loudness has a higher annoyance magnitude than toughness, while roughness varies slightly in annoyance due to aircraft noise. These noise characteristics hurt humans living around airports as calculated and measured by (Osueke and Ofondu, 2011) using NNI, CNR, NEF, and CNEL noise metrics. (Mertre et.al., 2011) developed a method for rating noises of diverse spectra character called perceived noise level (PNL) to rate annoyance effect of aircraft flyover noise. It was computed from sound pressure magnitudes quantified in octave. (Wang, Xia, and Xu, 2012) analyzed the foundational principles, computational method, and control standard of noise metrics of major countries of the world. He observed that existing airport noise metrics are not complete and needs improvement.

In another development by (Helenoand Slama, 2013), a fuzzy logic system was used to evaluate the relationship between annoyance percentage, L_{dav}, and L_{night} metrics for noise effects on aircraft inhabitants. Similarly, (Heleno, Slama, and Bentes, 2014)used L_{eq}-based noise metrics to lessen aircraft noise since L_{day} and L_{night} metrics report the effect generated by aircraft movement better. (McMullen, 2014) concluded in a psychoacoustic test to examine the effect of rotorcraft sound characteristics on annoyance that *EPNL* and *SEL* were better forecasters of annoyance. (Cho et al., 2014) proposed a conversion based on noise annoyance (CBA) method regarding interoperable use between aircraft noise metrics, noise measurements, and socio-acoustic surveys in converting Korean WECPNL into L_{den}.

Furthermore, (Loubeau et al., 2015) recommended eight metrics (PL, ASEL, BSEL, ESEL, LASmax, LAFmax, PNL, and a hybrid metric ISBAP) for their ability to predict human response to sonic boom out of twenty-five evaluated metrics. Also, (Torija, Self, and Flindell, 2016) estimated the 57dB(A) L_{eq} contour area for the UK for several projected aviation growth rates and noise reduction rates due to new technologies. (Johansen, Horney, and Tien, 2017) reviewed the strength, limitations, and classified the existing community resilience metrics that apply across hazard and geographic areas.

Out of the different noise metrics analyzed by (Spilski et al., 2019), L_{eq} predicts annoyance better compared to L_{den}, L_{max}, Emergence, and NAT. Sound quality metrics, loudness, roughness, tonality, sharpness, and fluctuation strength analyzed in (Vieira et al., 2019) showed that sound quality metrics for aircraft landing and taking off were different, and the two metrics *EPNL* and PA_{mod} were not in agreement for all aircraft types. (Taufner et al., 2020) compared metrics for environmental noise identification in schools in the airport area. The L_{dn} and *TA* were investigated using acoustic simulation and noise mapping. Results showed that the criteria adopted by municipal and airport officials were unsatisfactory and do not reflect the intermittent behavior of this type of noise.

Recently, (Asensio, Pavón, and de Arcas, 2020)proposed a minimum set of basic energetic indicators that allows communication and reporting, as the COVID-19 pandemic lockdown has affected environmental noise and modified urban soundscapes. In a review by (Rob, 2020) he emphasized the need to keep up with the use of the L_{eq}-based metrics presently used for noise tracking and statutory description and also suggested that additional single event metrics be regularly issued by airports to better illustrate how noise is encountered on the ground.(Ma, Mak, and Wong,

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2020) studied the impact of spatial factors on physical sound metrics and psychoacoustic metrics; the role and statistical parameters of the metric in characterizing acoustical properties. The study showed that that the sound intensity metrics L_Z or L_A, as well as the subjective loudness metric *N* are distance-dependent.

Research by (Issarayangyun, Samuels, and Black, 2004) dealt with the development of a new noise metric for reporting and evaluating aircraft noise. The noise metric, which was termed the Noise Gap Index (NGI) was formed on the presumption that people living in places of dissimilar surrounding noise react dissimilarly to the same aircraft noise magnitude.

Despite the detailed analysis done in all the reviewed literature, none of these studies captured all the important aircraft noise metrics in a single volume. This review paper has been able to itemize all the important aircraft noise metrics used internationally in a single volume. This will be a very useful reference for future researchers in environmental noise.

IV. Conclusion

A descriptive account of all the global aircraft noise metrics was given, emphasizing that L_{eq} is the best for aircraft noise measurement because it is easy to measure and easy to understand by laypersons. The equivalent sound level (L_{eq}) gives the steady-state noise level over a specified period. It is the most widely used global aircraft noise metric since it considers the number of noise events, the noise energy, and duration of events. The L_{eq} metric provides a more accurate evaluation of aircraft noise exposure for a specific period, particularly for day-time periods when the night-time penalty under the *DNL* or L_{dn} metric is not suitable. Just as *SEL* has proven to be a good measure of the noise impact of a single event, L_{eq} has been established to be a good measure of the impact of a series of events during a given period. L_{eq} can be adapted to account for different time sensitivities and have different weightings applied. This means that it has the potential to be adjusted to suit the preferences or characteristics of a community or noise source. L_{eq} provides the basis for which other secondary aircraft noise metrics such as *DNL* or L_{dn} and *CNEL* are developed. The multiple advantages of L_{eq} as an aircraft noise metric makes it the preferred choice for airport and heliport noise impact assessments, especially in Nigeria. This has resulted in a substantial volume of consistent aircraft noise data over the years, which can be easily compared to make a more informed judgment on the effects of aircraft noise on host communities.

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Conflicts of Interest
The authors declare that there is no conflict of interest.

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Pulmonary Lymphangioleiomyomatosis and Extra-Pulmonary Lymphangioleiomyomas in Postmenopausal Women

By Orozco Maira, Garay M. Florencia & Mattar Daniel

Abstract- Lymphangioleiomyomatosis (LAM) is a rare disorder of unknown cause characterized by progressive cystic destruction of the lung, lymphatic abnormalities and abdominal tumors. It occurs almost exclusively in women of fertile age due to a hormonal influence, for this reason it is extremely rare in post-menopausal patients. While LAM is a systemic disease, the main manifestations are pulmonary. Lymphangioleiomyomas are larger cystic masses; these most commonly occur in the abdomen, retroperitoneum and pelvis but occasionally in the mediastinum and neck. In the cases of older women the disease presents a similar clinical manifestation than younger's female, with the exception that the clinical course is benign and longer.

Keywords: Lymphangioleimyomatosis, mediastinal lymphangioleiomyomas, postmenopausal women, cystics lungs.

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Pulmonary Lymphangioleiomyomatosis and Extra-Pulmonary Lymphangioleiomyomas in Postmenopausal Women

Orozco Maira [α], Garay M. Florencia [σ] & Mattar Daniel [ρ]

Abstract- Lymphangioleiomyomatosis (LAM) is a rare disorder of unknown cause characterized by progressive cystic destruction of the lung, lymphatic abnormalities and abdominal tumors. It occurs almost exclusively in women of fertile age due to a hormonal influence, for this reason it is extremely rare in post-menopausal patients. While LAM is a systemic disease, the main manifestations are pulmonary. Lymphangioleiomyomas are larger cystic masses; these most commonly occur in the abdomen, retroperitoneum and pelvis but occasionally in the mediastinum and neck. In the cases of older women the disease presents a similar clinical manifestation than younger's female, with the exception that the clinical course is benign and longer.

Resumen- La linfangioleiomiomatosis es una enfermedad poco común de causa desconocida que se caracteriza por la destrucción quística progresiva del pulmón, anomalías linfáticas y tumores abdominales. Ocurre casi exclusivamente en mujeres en edad fértil debido a influencia hormonal, por esta razón es extremadamente raro en pacientes posmenopáusicas. Si bien la LAM es una enfermedad sistémica, las principales manifestaciones son pulmonares. Los linfangioleiomiomas son masas quísticas grandes; se encuentran con mayor frecuencia en el abdomen, retroperitoneo y pelvis, pero ocasionalmente en el mediastino y el cuello. En los casos de mujeres mayores la enfermedad presenta una manifestación clínica similar a la de las mujeres más jóvenes, con la excepción de que el curso clínico es más benigno y prolongado.

Resumo- Linfangioleiomiomatose é uma doença rara de causa desconhecida, caracterizada por destruição cística progressiva do pulmão, anormalidades linfáticas e tumores abdominais. Ocorre quase exclusivamente em mulheres em idade fértil devido a uma influência hormonal, por isso é extremamente raro em pacientes pós-menopáusicas. Embora a LAM seja uma doença sistêmica, as principais manifestações são pulmonares. Linfangioleiomiomas são massas císticas maiores; estes ocorrem mais comumente no abdômen, retroperitônio e pelve, mas ocasionalmente no mediastino e pescoço. Nos casos de mulheres mais velhas, a doença apresenta manifestação clínica semelhante à das mulheres mais jovens, exceto que o curso clínico é benigno e mais longo.

Keywords: Lymphangioleimyomatosis, mediastinal lymphangioleiomyomas, postmenopausal women, cystics lungs.

I. Introduction

We report a case of 72 years-old women, former smoker, denies hormone therapy replacement. She presents a history of dyspnea grade 2, rhonchi and wheezing symptoms diagnosed 4 year prior as Chronic Obstructive Pulmonary Diseases (COPD) and treated with inhaled corticoids and bronchodilators. The physical exam shows diffuse hypoventilation. The spirometry presents a reversible obstructive pattern. The Echocardiography reveals normal pulmonary arterial pressure.



Fig.1: High-resolution CT scan demonstrates multiples bullae of emphysema and some cysts (yellow arrows) characterized by the absence of intralesional vessels with thin walls.

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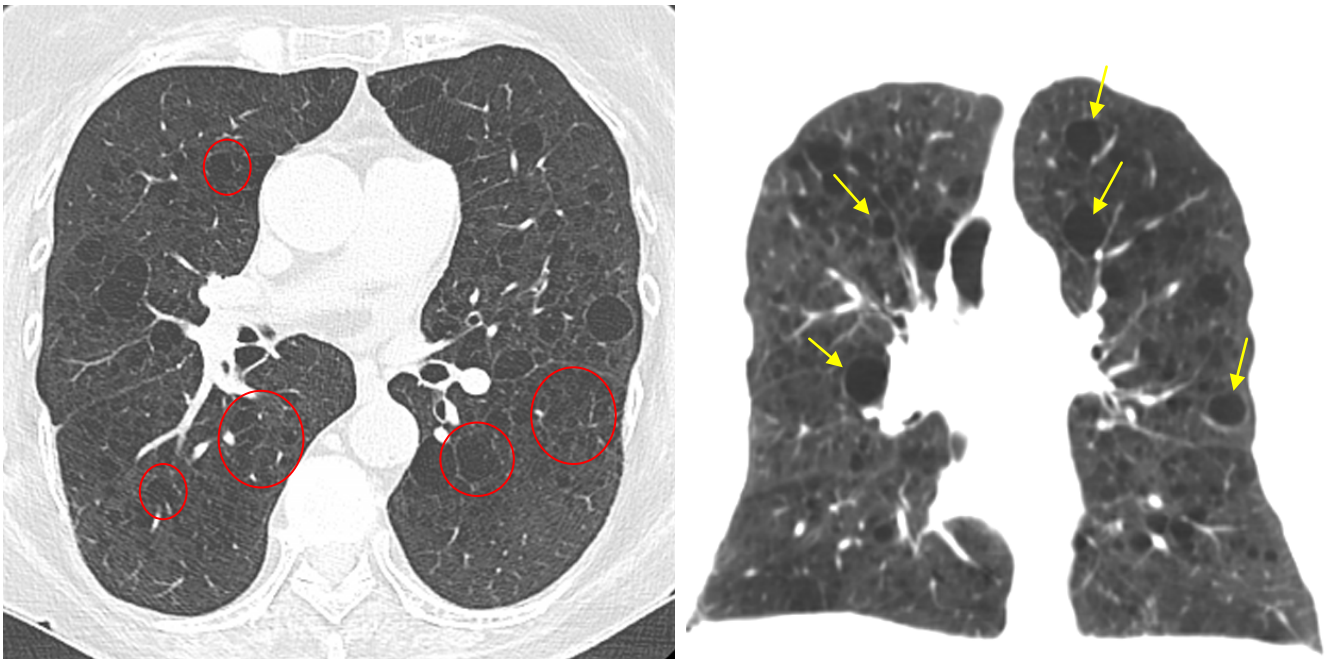


Fig. 2: High-resolution CT scan. A axial. B. coronal. Multiples bulles of emphysema and cysts (yellow arrows) with random distribution.

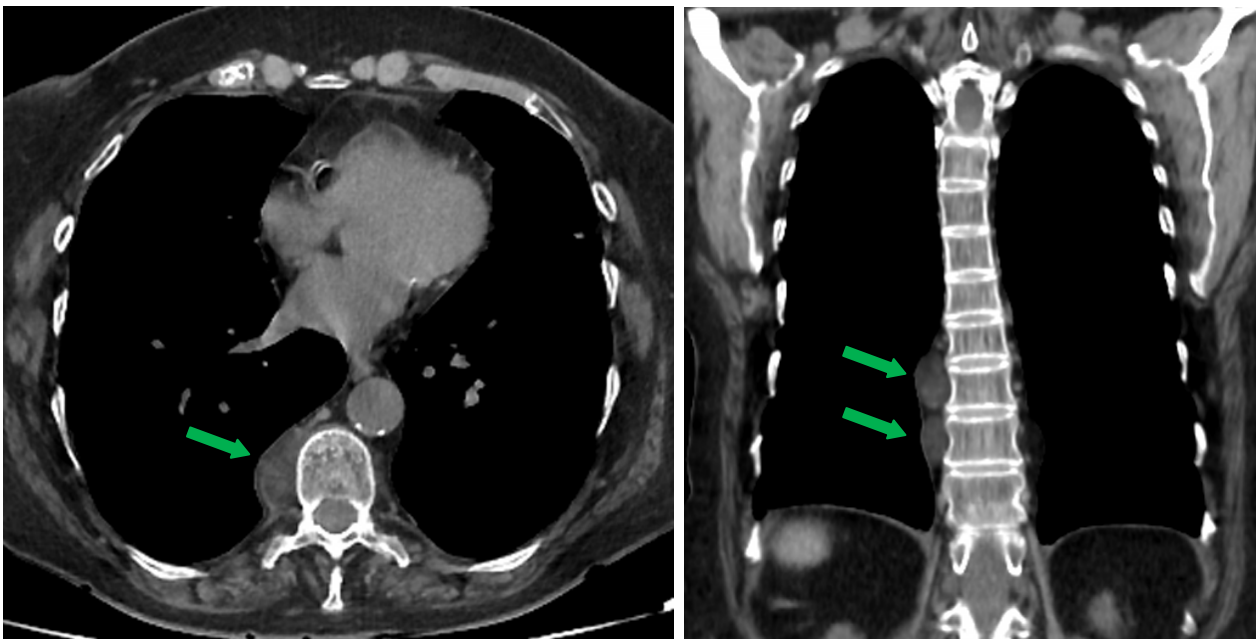


Fig. 3: High-resolution CT scan. A axial. B. coronal. Paravertebral masses, well circunscripte, with fat density, compatible with lymphangioleiomyomas (green arrows).

II. Discussion

Lymphangioleiomyomatosis (LAM) is a rare disorder of unknown cause characterized by peribronchial, perivascular, and perilymphatic proliferation of abnormal smooth muscle cells (1) leading to progressive cystic destruction of the lung, lymphatic abnormalities and abdominal tumors (2).

It occurs almost exclusively in women of fertile age due to a hormonal influence, for this reason it is extremely rare in post-menopausal patients. In these cases it is usually associated with hormone replacement therapies. It is known that this disease is strongly associated with other conditions, such as tuberous sclerosis and renal angiomyolipomas (3).

In the cases of older women the disease presents a similar clinical manifestation than younger's female, with the exception that the clinical course is benign and longer after menopause (3).

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a) Physiopathology

Pathologically, LAM cells contain proteins related to melanoma, including glycoprotein 100, the HMB-45 and receptors for estrogens and progesterone. These cells have a high proliferation capacity, damaging the airway through the production of metalloproteinases with the obstructing capillaries, lymphatics and the airway. Lymphatic obstruction usually causes chylothorax and airway obstruction conditions an obstructive functional pattern. A 30% -40% of cases present pneumothorax, which can be bilateral and recurrent (4).

b) Pulmonary Manifestations

While LAM is a systemic disease, the main manifestations are pulmonary. In lungs, the atypical progressive proliferation is seen around small airways giving rise to cystic pulmonary changes and progressive respiratory failure (5).

The pulmonary symptoms tend to dominate the clinical course, with the most common features being pneumothorax, progressive dyspnoea and chylous pleural effusions .Other respiratory symptoms include cough, haemoptysis and chyloptysis. Dyspnea is suffered by the vast majority of patients with LAM and is the result of airflow obstruction and replacement of the lung parenchyma by cysts. Approximately two thirds of patients will have a pneumothorax at some point in their clinical course, which are recurrent in most and a cause of significant morbidity. Chylous pleural effusions are less common, but again can be difficult to treat conservatively and tend to recur after simple aspiration. Haemoptysis and chyloptysis are due to LAM cell obstruction of pulmonary capillaries and lymphatics, respectively, and both occur in a small number of patients (2).

The chest radiograph often appears normal in early disease, although it may show pleural effusions or pneumothorax (2) in a 40% de los pacientes (7).

The main pulmonary finding includes cysts these are a thin-walled (usually <3 mm), well-defined and circumscribed, air- or fluid-containing lesion 1 cm or more in diameter, nevertheless, some do not have walls and others have an irregular configuration (7). Cysts are scattered in a bilateral roughly symmetric pattern, without any lobar predominance. These cysts range in size from barely perceptible to several centimeters and in number from a few scattered cysts to near complete replacement of the lung parenchyma (2) with increased lung volume (7).

c) Extrapulmonary manifestations

Extrapulmonary manifestations of LAM are angiomyolipoma, which occur mostly in the kidneys, chylous ascites, abdominal lymphadenopathy and large cystic lymphatic masses termed lymphangioleiomyomas (2). Lymphangioleiomyomas are larger cystic masses; these most commonly occur in the abdomen, retroperitoneum and pelvis but occasionally in the mediastinum and neck. Symptoms associated with lymphangioleiomyomas are nausea, bloating, abdominal distension, peripheral oedema and urinary symptoms (6).

Abdominal findings may be present in more than 70% of patients with LAM, and the most common abdominal finding is renal angiomyolipoma. These are often small (<1 cm), multiple, bilateral, and asymptomatic (7) and can usually be identified by CT because of the presence of fat, which gives lesions a characteristic CT appearance. MRI may be adequate for the diagnosis when iodinated contrast is contraindicated. Diagnostic difficulty may arise in the small number of angiomyolipomas showing little evidence of fat (2).

Lymphangioleiomyomas are produced by a proliferation of smooth muscle cells in the lymph vessels with the production of cystic masses consistent with dilatations of the abdominal lymph vessels due to lymphatic obstruction (7). Lymphangioleiomyomas are usually localized in the mediastinum, retroperitoneum, and pelvis along the axial lymphatics and can appear larger in the evening due to accumulation of chyle in the cystic structures (2).

Enlarged lymph nodes are described in up to 40% of cases and Chylous Ascites is an unusual abdominal complication of LAM that can occur in the absence of pleural effusion (7).

d) Imaging Diagnosis

High-resolution CT (HRCT) is the recommended imaging technique for LAM. The diagnosis of LAM is probable when a characteristic lung CT is found in a patient with compatible clinical history or when compatible CT features are present in a patient with angiomyolipoma or chylous effusion (2).

e) Differential diagnoses

Within the main differential diagnoses we mention tuberous sclerosis, pulmonary Langerhans cell histiocytosis, emphysema, and pulmonary fibrosis (8).

f) Treatment

The treatment of this pathology is based on treating complications. Hormone treatment should be discouraged except in individual cases with rapid progression of the disease in which progesterone may be trialled (2). The first successful lung transplantation for LAM was performed in 1983. However, is unclear whether lung transplantation actually improves long-term survival in patients with LAM compared with continued medical management (8).

III. Conclusion

LAM is a systemic disease, the main manifestations are pulmonary. The extrapulmonary

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manifestations are unusual. The clinical course is benign and longer in post-menopausal women.

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Extrapulmonary Tuberculosis Scoring System Development. A Design for Android Studio Application

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Abstract- Tuberculosis is an infectious disease with high incidence and mortality rates in the world. TB not only attacks lung, but other organs called Extrapulmonary Tuberculosis (EPTB) as well. At present, the diagnostic for EPTB is challenging since there are many examinations needed. This study developed a scoring system for EPTB diagnosis based on some parameters. The parameters derived from our studies evaluating AFB stain examination of biopsy tissue associated with the clinical feature of EPTB patients. Parameter included a detailed medical history and clinical examination, radiological, microbiological, molecular, and histopathological investigations. The proposed scoring system used a minimum android version of jellybean 4.1. The application is simple to accommodate users' low ability to operate. The scoring system is proposed for accommodating many parameters important for diagnostic. It differentiates which conditions are highly suspicious and should be included in the differential diagnosis. EPTB Scoring system can be an alternative for EPTB diagnostic tools.

Keywords: *application, extrapulmonary tuberculosis, scoring system, diagnostic tools.*

GJMR-F Classification: *NLMC Code: WF 200*



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Extrapulmonary Tuberculosis Scoring System Development. A Design for Android Studio Application

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Abstract- Tuberculosis is an infectious disease with high incidence and mortality rates in the world. TB not only attacks lung, but other organs called Extrapulmonary Tuberculosis (EPTB) as well. At present, the diagnostic for EPTB is challenging since there are many examinations needed. This study developed a scoring system for EPTB diagnosis based on some parameters. The parameters derived from our studies evaluating AFB stain examination of biopsy tissue associated with the clinical feature of EPTB patients. Parameter included a detailed medical history and clinical examination, radiological, microbiological, molecular, and histopathological investigations. The proposed scoring system used a minimum android version of jellybean 4.1. The application is simple to accommodate users' low ability to operate. The scoring system is proposed for accommodating many parameters important for diagnostic. It differentiates which conditions are highly suspicious and should be included in the differential diagnosis. EPTB Scoring system can be an alternative for EPTB diagnostic tools.

Keywords: application, extrapulmonary tuberculosis, scoring system, diagnostic tools.

I. Introduction

Tuberculosis is an infectious disease with high incidence and mortality rates in the world. Based on the World Health Organization (WHO) report in 2019, there is no single country free from Tuberculosis (TB).(1) Around 7 million Tuberculosis (TB) received treatment globally; however, the number of deaths was still hovering at 1.5 million patients. (2) Several factors that contribute to the high incidence of TB are sociocultural, including herbal medicines and stigma, adherence to drugs, TB program, and environment.(2)(3)(4)(5)(6)(7)

The estimated incidence of TB cases in Indonesia is 845,000 cases per year, with 570,289 notified cases. Approximately 32% of cases have not been counted, either because they are not detected or not reported. (8)(9) Other than infected the lung, TB can also attack other organs such as bones, lymph nodes, and abdominal areas known as extrapulmonary tuberculosis (EPTB).(10)(11)

The incidence of EPTB varies across regions ranging from 8%−34% of all TB cases. Extrapulmonary tuberculosis (EPTB) levels vary widely - depending on their risk factors - including host immunological response, socio-demographics, comorbidities, lifestyle behaviors, genetic factors, and lymph node pathogenesis.(12)(13) It also depends on the previous history of pulmonary TB, non-adherence to taking anti TB drugs, and failure to therapy due to drug resistance.(3)(14) Drugs of choice and inaccurate diagnoses depend on a country's socio-economic level and the resources devoted to the TB program.(2)(15) Direct sputum smear microscopy is the most widely used method for diagnosing pulmonary TB and is available in most primary health-care laboratories at the health-center level. Because TB can present with many different symptoms, the first obstacle in diagnosing smear-negative TB is discerning the varied clinical presentations. (13) (16) It is essential to determine which conditions are highly suspicious and included in the differential diagnosis.(17)(18) Previous studies have found that using a scoring system can support pulmonary TB diagnosis.(19)(20) This paper discussed the proposed scoring system for EPTB diagnostic tools based on several parameter discussed above. The data used for the parameters in the application were based on our study of 1,034 TB cases registered from 2015-2018 in Bandung.

II. Approach

A diagnostic approach to an AFB smear-negative patient with possible TB includes, where available, a detailed medical history and clinical examination, as well as radiological, microbiological, molecular, and histological investigations.(21) Diagnosis of pulmonary tuberculosis in adults with clinical manifestations of chronic cough and sputum can be

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quickly made using the production of sputum smears with the Ziehl Neelsen AFB staining method. However, this method is challenging for the diagnose in patients with a non-productive cough that cannot expel phlegm and TB patients with HIV/AIDS or other immune-compromised conditions. (8)(22)(23) For such a person, other tests are needed to diagnose pulmonary TB, such as rapid molecular tests. (24)

Below is the diagram showing the overall phase used in this study. Figure 1 taken initially from (21) described the approach used for the base of this study.

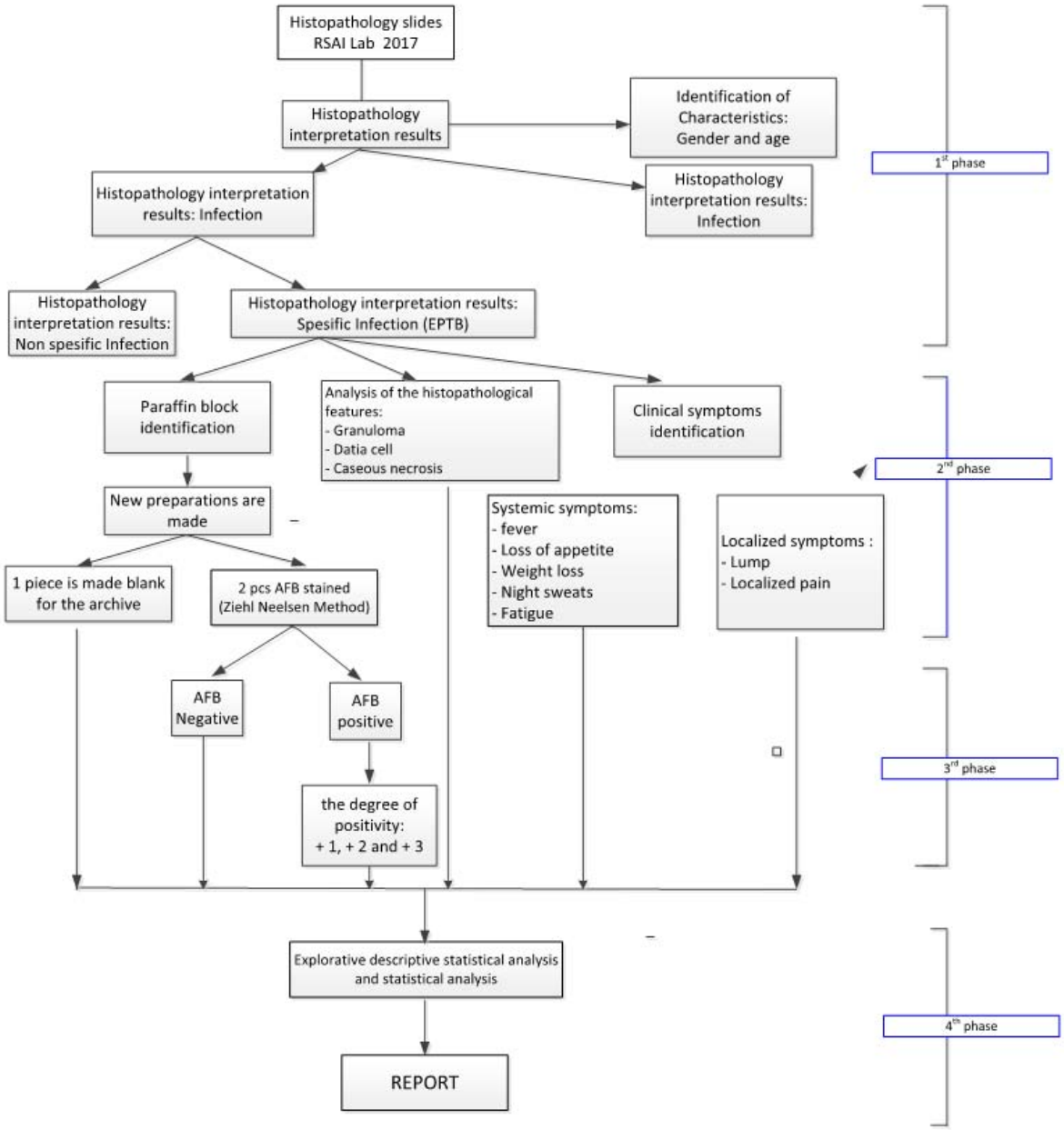


Figure 1: Research Procedures

The study used medical records from patients diagnosed with EPTB. The study used characteristics associated with the degree of tissue biopsy preparations stained with the Ziehl Neelsen Acid Fast Bacillus (AFB) method positivity, clinical symptoms of patients, both localized and systemic. It also recorded patients with histopathological diagnosis of infection (using Hematoxylin-eosin staining) and with process-specific infection of EPTB. The analysis results used in collaboration with the TB scoring method that previously existed used to develop our scoring system. The study received approval from the Ethics Committee of Medical Faculty UNISBA No. 362 / Ethics Committee.FK/XII/2017

The first step in this study was reviewing a contingency table provided by the previous study to see AFB's clinical manifestations and the histopathological

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results. The results were presented according to the number of systemic manifestations and combined local manifestations and AFB and histopathological results. From 1,034 biopsied TB sputum smear using the AFB staining method and other supporting examination, we found 44 patients with EPTB, 3.4% of the total, which less than the average figure from the literature.

Positivity degree of EPTB recorded by AFB staining from paraffin block test preparations, using International Union Against Tuberculosis and Lung Disease (UATLD) scale modification on sputum smears. AFB staining from the test material's sputum smear can be homogeneous, while the preparations from paraffin blocks cannot be homogenized because the test preparations come from different tissues. To accommodate those, the analysis of the data developed using two types of interpretation, some using the degree of positivity, and others used positive and negative findings only. EPTB based on the BTA count results and its relationship with systemic manifestations and local manifestations in EPTB patients is in the table below.

Table 1: Acid Fast Bacillus Status to Systemic and Local Manifestation

Clinical Manifestation	AFB stained							
	NA		−		+		Total	
	n	%	n	%	n	%	n	%
Systemic Manifestation								
Fever								
Yes	3	10	21	70	6	20	30	100
No	2	28,6	5	71,4	0	0	7	100
Total	5	13,5	26	70,3	6	8,1	37	100
Weight Loss								
Yes	4	11,4	25	71,4	6	17,2	35	100
No	1	50	1	50	0	0	2	100
Total	5	13,5	26	70,3	6	8,1	37	100
Night Sweat								
Yes	4	11,4	25	71,4	6	17,2	35	100
No	1	50	1	50	0	0	2	100
Total	5	13,5	26	70,3	6	8,1	37	100
Fatique								
Yes	4	11,4	25	71,4	6	17,2	35	100
No	1	50	1	50	0	0	2	100
Total	5	13,5	26	70,3	6	8,1	37	100
Local Manifestation								
Yes	0	0	0	0	0	0	0	100
No	5	13,5	26	70,3	6	16,2	37	0
Total	5	13,5	26	70,3	6	16,2	37	100

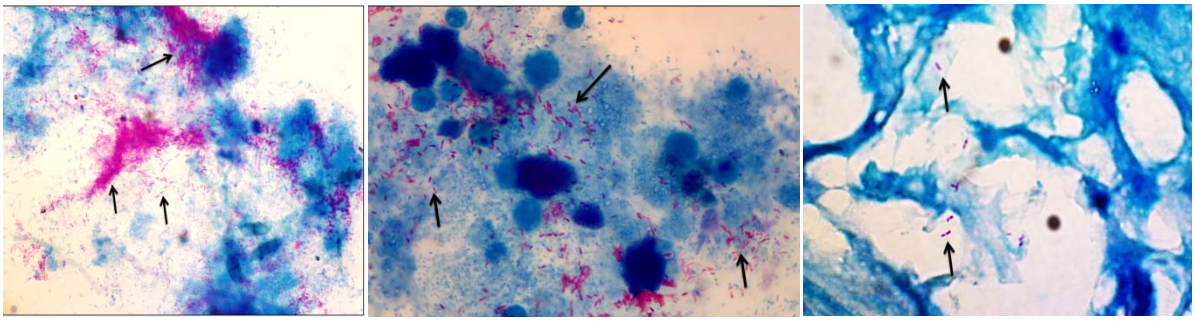
Detected clinical manifestations in EPTB patients are divided into systemic manifestations and local manifestations. Systemic manifestations consist of fever, night sweats, fatigue, and weight loss. It appears that the number of patients who complain of fever is the same as those who complain of fatigue. Interestingly, the number of patients who complained of night sweats was the same as patients complained of weight loss. In addition to systemic clinical manifestations, there are also local clinical manifestations.

On these local manifestations, the symptoms depend on the origin of the organ where EPTB is located. Patients diagnosed with lymph node EPTB complain of enlarged lymph nodes accompanied by pain, while patients diagnosed with EPTB have lumps and pain. Overall, all EPTB patients complained of symptoms related to the origin of the organ where EPTB locate, although the number of complaints differed from patient to patient.

Most of EPTB occurred in the lymph nodes (48.6%), while the rest were evenly distributed among other organs, including bones, breasts, perianal, ileum. The findings were consistent with studies in other developing countries that have previously reported that the most frequent EPTB incidence location is in the lymph nodes (12–16).

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Below is the histopathological features of AFB stained tissue biopsy



Notes
Left: AFB stain's tissue biopsy (Lymph node), AFB abundant (Black arrow)
Middle: AFB stain's tissue biopsy (Cystitis).
Right: AFB (+) at < 10 (Black arrow)

Figure 2: Histopathological features of AFB stained tissue biopsy

Histopathological readings from EPTB infection paraffin blocks found 97% of cases with granuloma (+); however, the AFB (+) was only 8.5%. It can be explained since granuloma collects several inflammatory cells, especially mature macrophages that form aggregates in response to an antigen. An antigen can come from a bacterium, a fungus, a foreign object, or an immune complex. The purpose of granuloma formation is to isolate the host body's antigen and facilitate the eradication of the antigen. Early in granuloma formation, antigen-presenting cells express a wide variety of pro-inflammatory and chemoattractant cytokines. The AFB staining results on the extrapulmonary TB patients' biopsy tissue based on the degree of positivity were mostly with a value of +1 (8.1%). There was no correlation between the degree of AFB's degree of positivity from biopsy tissue with clinical symptoms in this study.

Most EPTB sufferers do not experience systemic symptoms such as intermittent fever, night sweats, weight loss as experienced by TB patients in general. It is different from previous studies, which explained that systemic symptoms in EPTB patients were around 52.2% .(16) In this study, it was found that systemic fever complaints only occurred in about 16% of cases, night sweats in 5%, 5% experienced weight loss, 16% fatigue. In contrast, in the previous study, fever complaints were found in 37-80% of cases. (12)

Table 2: Histopathology findings of EPTB on Systemic and Local Manifestation

Clinical Manifestation	Histopathology				Total	
	No Granuloma		Granuloma			
	n	%	n	%	n	%
Systemic Manifestation						
Fever						
Yes	1	3,3	29	96,7	30	100
No	0	0	7	100	7	100
Total	1	2,7	36	97,3	37	100
Weight Loss						
Yes	1	2,9	34	97,1	35	100
No	0	0	2	100	2	100
Total	1	2,7	36	97,3	37	100
Night Sweat						
Yes	1	2,9	34	97,1	35	100
No	0	0	2	100	2	100
Total	1	2,7	36	97,3	37	100
Fatique						
Yes	1	3,2	30	96,8	31	100
No	0	0	6	100	6	100
Total	1	2,7	36	97,3	37	100
Local Manifestation						
Yes	0	0	00	0	0	0
No	1	2,7	36	97,3	37	100
Total	1	2,7	36	97,3	37	100

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This study found that 100% of local clinical symptoms were statistically significant in patients with extrapulmonary TB based on the histopathological features and AFT staining with various positivity degrees. In contrast with previous studies, which explained that local symptoms in EPTB patients were only around 72%. (17) The histopathological examination results on the biopsy tissue were almost entirely with (+) granulomas since granuloma image is a characteristic feature of TB infected tissue. (15,18,19) There were no systemic clinical symptoms (97%) such as fever, night sweats, weight loss, and fatigue in patients with granuloma (+) features found on the histopathological result. In contrast with the other studies, which stated that the characteristic of TB infection histopathological is associated with the clinical manifestations of EPTB patients (15,18–21). Based on the above results and considering the scoring system that was previously used to enforce TB in children, a new scoring system is planned as an innovation to assist in diagnosing EPTB. This design expected to capture EPTB cases, taking into account several long-used laboratory parameters found in this study. Other laboratory parameters will also support it as predictors of TB, such as erythrocyte sedimentation rates, monocyte/lymphocyte ratio, and neutrophil/lymphocyte ratio. (22–24)

This scoring system's design uses a simple application that can be used using Android Studio since the aims are to use a broader community for EPTB case finding networking. (25) The simple design is chosen considering user ability on operating apps, which is relatively low.

Table 3: Parameter used for EPTB Scoring Application

PARAMETER	VALUE			
	0	1	2	3
TB contact	Not clear	-	There are reports of families with AFB (-) / AFB unclear / don't know	AFB(+)
BCG vaccination	Not clear	Scar (+)		
Tuberculin test (Mantoux test)	Negative			Positive (≥10 mm or ≥5 mm Immunocompromised patient)
Body weight/ Nutritional status	Normal	WB/BH<90% or WB/Age<80%; or BMI < 18,5 or BMI > 18,5	Malnourish or BW/BH<70% or BW/Age<60%	
Weight loss	No	Yes		
Fever with unknown origin		≥2 weeks		
Chronic cough		≥3 weeks		
HIV/AIDS	No	Yes		
Comorbid (DM/ Cancer/ degenerative)	No	Yes		
Night sweat	No	Yes		
Enlarged Lymph node		≥1 cm, >1 Lymph node, No tender		
No response to antibiotic therapy		Yes		
Swelling knee/ joints/ other's body site		Yes		
Thorax X-ray	No	TB (+)		
Nonpulmonary X-ray	No	TB (+)		
Histopathological Biopsy with Giant cell	No	(+)		
Histopathological Biopsy with Cheese necrosis	No	(+)		

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Histopathological Biopsy with Granuloma	No	(+)		
AFB stain's tissue biopsy	No	AFB (+) at < 10 EOF	AFB (+) at > 10 EOF	AFB abundance
Monocyte/Lymphocyte ratio		> 0.476		
Neutrophyl/Lymphocyte ratio		>7		
Erythrocyte sedimentation rate		> 100 mm/hour		

The "Extra-pulmonary TB Score Calculation System (EPTBScore)" application is an android based mobile application run on an android smartphone with a minimum android version of jelly bean 4.1. This system works by calculating the total score based on 22 parameters, as described in Table 3. In the application there are seven application pages, as follows:

Opening Page; The opening page in the application only displays information of the the application name and originator. Figure 3 illustrates the opening page.

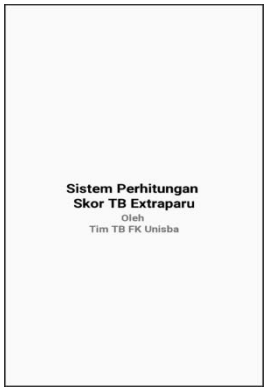
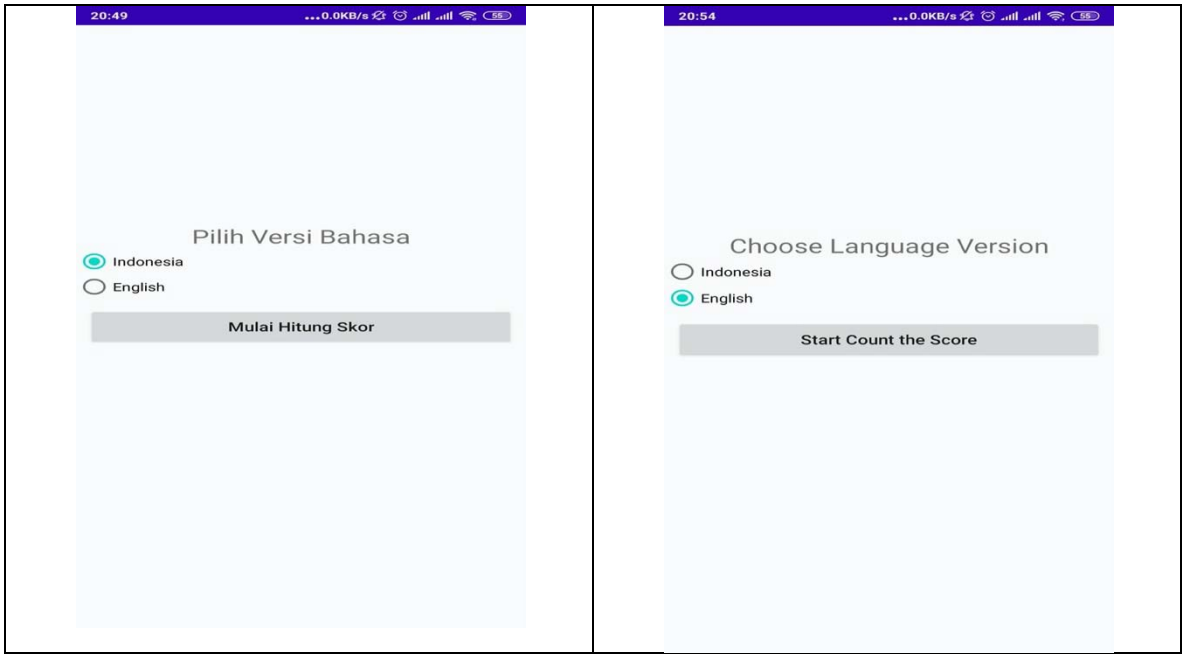


Figure 3: EPTB Scoring Opening Page

The following pages will be for language preferences followed by pages for personal information such as name, age, and gender of the patient. The pages are illustrated in Figure 4



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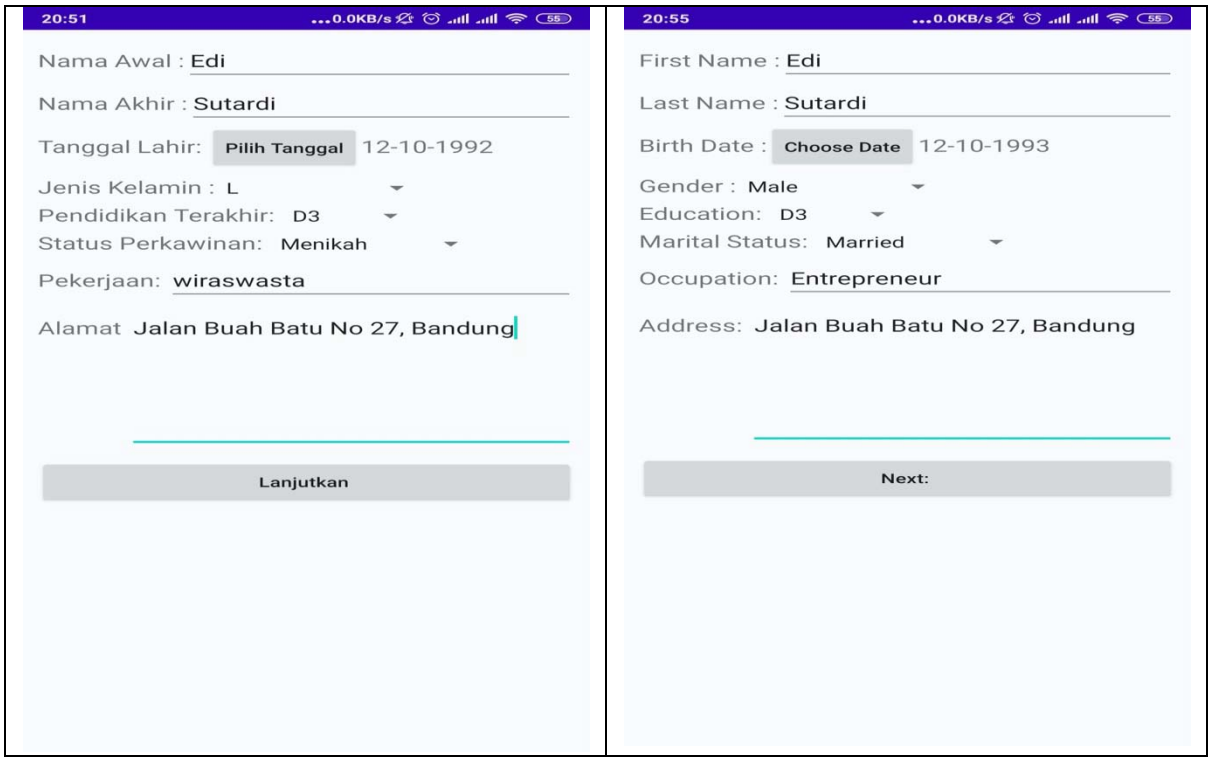
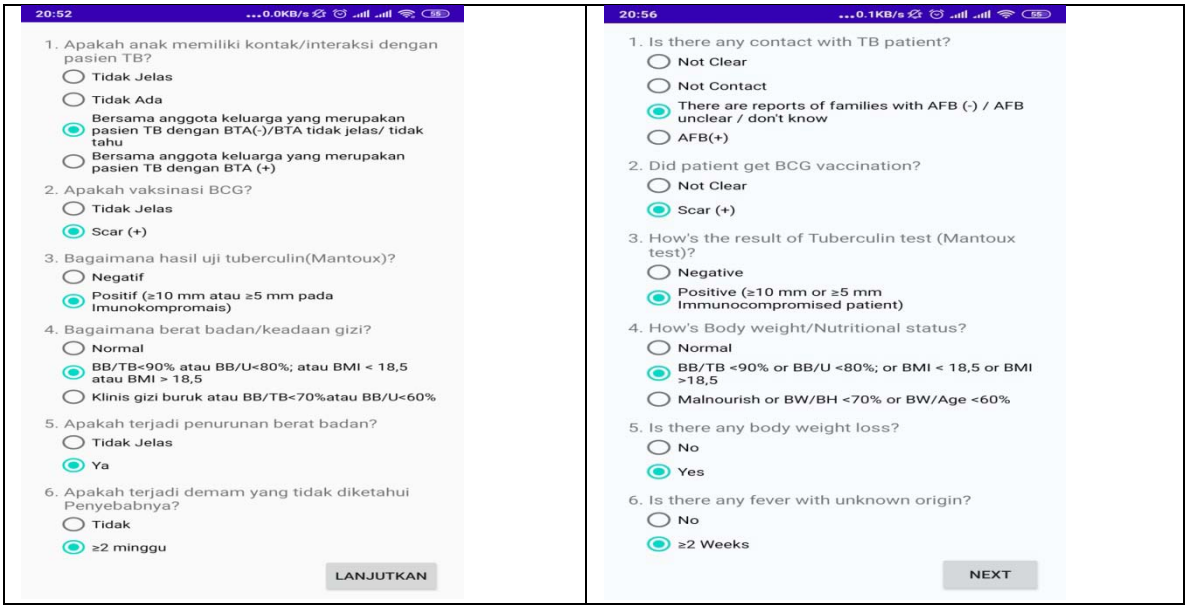


Figure 4: Language preferences and personal information pages

There will be 3 pages comprised of questions regarding some parameters for EPTB. For each question, a button provided for answer choices. This process is illustrated in Figure 5.



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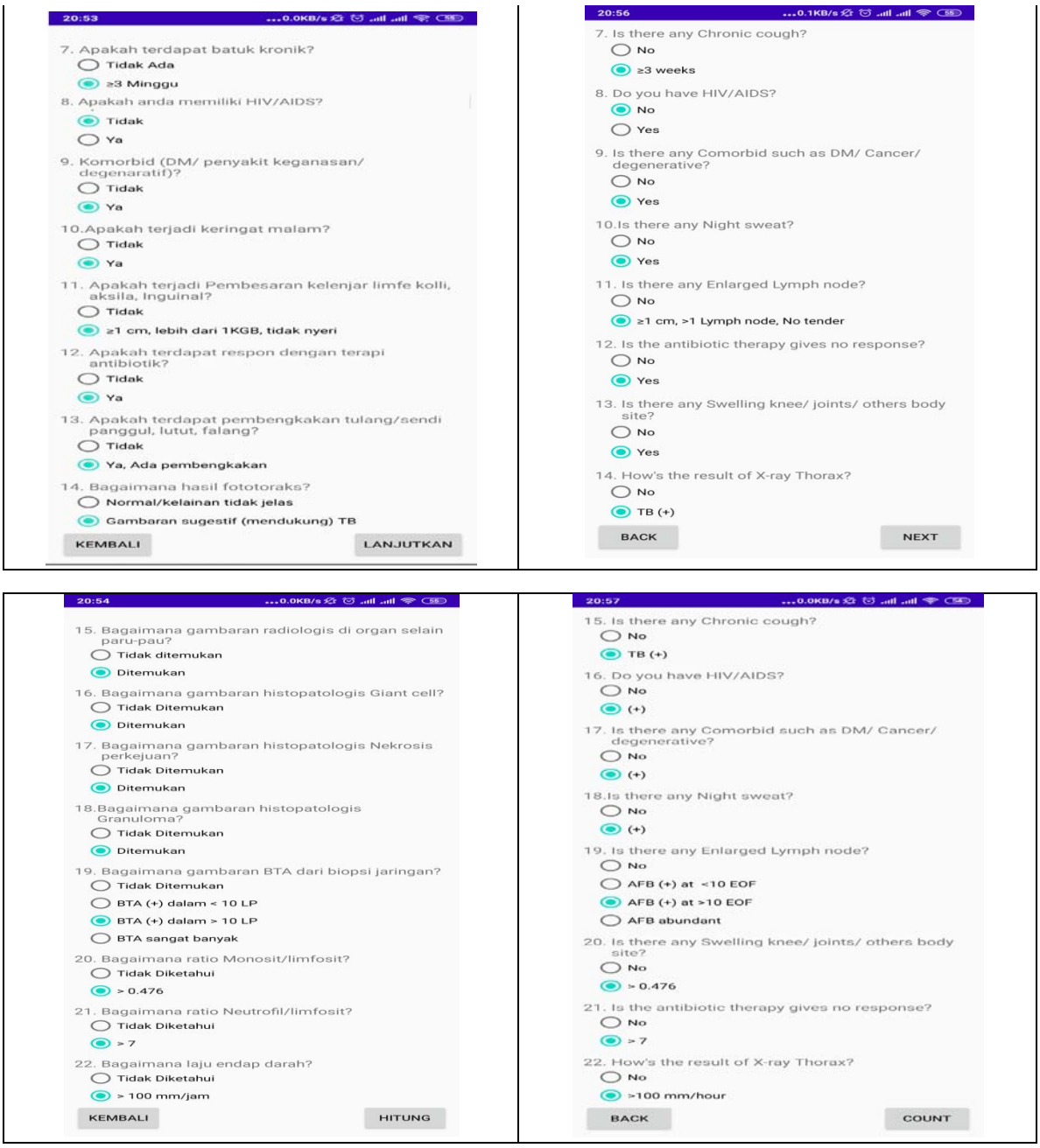


Figure 5: Symptom Pages

User need to fill all questions before continuing to the next page. There will be notes if they fail to fill question. The last pages will be for final score of the symptom.

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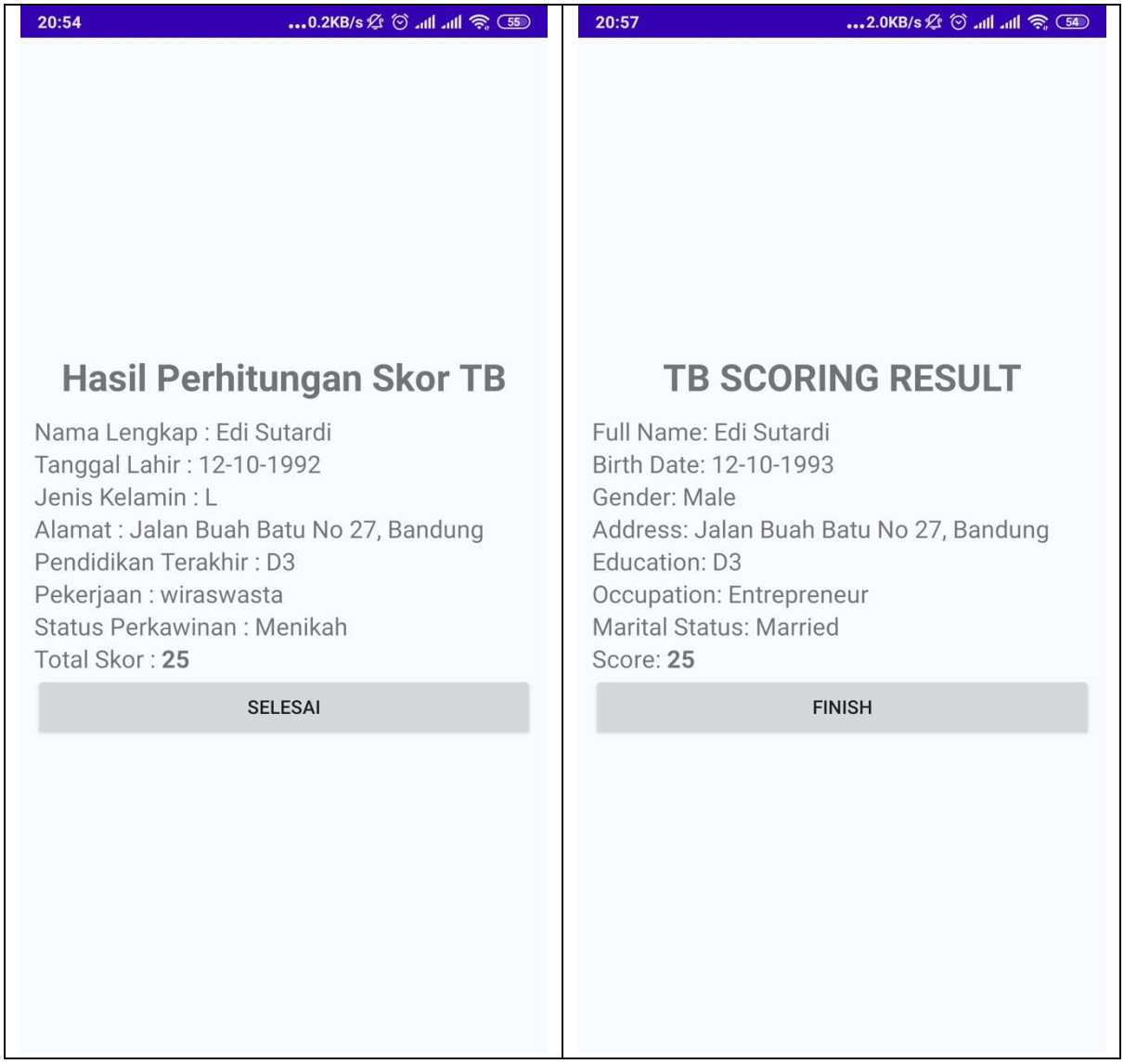


Figure 6: EPTB Scoring Result

The above proposed application designed to accommodate the need for several parameter inclusion. We developed a very simple application with regard to the user ability in operating application. This application is still in the development process with future plan of accomodataing user experience and needs.

III. Conclusion

This paper presented the proposed EPTB Scoring Application used to diagnose Extrapulmonary Tuberculosis. The scoring system is ideal for accommodating many parameters from either systemic and local manifestation. Parameters chose using detailed medical history and clinical examination and radiological, microbiological, molecular, and histological investigations. It can also differentiate which conditions are highly suspicious and should be included in the differential diagnosis. EPTB Scoring system can be an alternative for EPTB diagnostic tools.

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A Step towards Strategy for Prevention of Diabetes

By Vijayam Balaji, Veeraswamy Seshiah, Madhuri S. Balaji, N. Bhavatharani, C. Anjalakshi & A. Paneerselvam

Abstract- Pre-Life exposure relates to development during the time preceding the first appearance of life, a time course from "conception to confinement". From single cell zygote to finally formed fetus at confinement, a remarkable change occurs due to maternal fuels and hormonal influence on the fetal development. The crucial period in the fetal development is the first trimester. Early exposure to aberrant maternal metabolism in the embryonic developmental stage would result in congenital malformation and fetal wastage. Maintaining maternal glucose at the recommended level of fasting80 – 90 mg (4.4 – 5.0 mmol/dl) and 2hr postprandial plasma glucose 110 – 120 mg/dl (6.1 -6.7 mm0l/dl) during pre-conceptional period and throughout pregnancy is the assurance for the healthy offspring with ideal birth weight of 2.5 to 3.5 kg and breastfeeding is "a step towards strategy forprevention of diabetes".

Keywords: *gestational diabetes mellitus; fetal maturation; maternal hyperglycaemia.*

GJMR-F Classification: *NLMC Code: WD 200*



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A Step towards Strategy for Prevention of Diabetes

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Abstract- **Pre-Life exposure relates to development during the time preceding the first appearance of life, a time course from "conception to confinement". From single cell zygote to finally formed fetus at confinement, a remarkable change occurs due to maternal fuels and hormonal influence on the fetal development. The crucial period in the fetal development is the first trimester. Early exposure to aberrant maternal metabolism in the embryonic developmental stage would result in congenital malformation and fetal wastage. Maintaining maternal glucose at the recommended level of fasting80 – 90 mg (4.4 – 5.0 mmol/dl) and 2hr postprandial plasma glucose 110 – 120 mg/dl (6.1 -6.7 mm0l/dl) during pre-conceptional period and throughout pregnancy is the assurance for the healthy offspring with ideal birth weight of 2.5 to 3.5 kg and breastfeeding is "a step towards strategy forprevention of diabetes".**

Keywords: gestational diabetes mellitus; fetal maturation; maternal hyperglycaemia.

I. Introduction

The prevalence of diabetes is increasing globally from 463 million in 2019 to 700 million in 2045a 51% increase[1]. While several reasons are ascribed for this rising trend including aging population, urbanization, genetic predisposition, nutrition and lifestyle transition, etc., one factor that has not received adequate attention is Gestational Diabetes Mellitus (GDM) currently coined as Hyperglycemia in Pregnancy (HIP) which is defined as any degree of glucose intolerance with onset or first recognition during pregnancy[2]. GDM may play a crucial role in the increasing prevalence of diabetes and obesity[3]. In 2019 the global prevalence of Hyperglycemia in Pregnancy (HIP) in the age group 20-49 years was estimated to be 20.4 million or 15.8% of live births[1]. They had some form of hyperglycemia in pregnancy, of which 83.6% were due to GDM[1]. Hence, it has become necessary that all pregnant women should be screened for GDM, even if they have no symptoms[4].

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II. Intra Uterine Programming

David Barker hypothesized that all adult diseases are of fetal origin. The human body's susceptibility to "lifestyle" disease(s) was "programmed intrauterine". The Intrauterine programming, that is Gestational programming is a process whereby stimuli (hyperglycemia) or stresses that occur at critical or sensitive periods of fetal development, permanently change structure, physiology, and metabolism, which predispose individuals to disease in adult life, "Fetal Origin of Adult Diseases[5]".

III. Maternal Hyperglycemia & Progeny

Exposure to a diabetic environment in utero is associated with increased occurrence of impaired glucose tolerance and a defective insulin secretary response in adult offsprings, independent of genetic predisposition to type 2 diabetes[6]. The ovum is well supplied with mitochondria but the sperm contains a few and even those few do not persist in the offspring. At fertilization it is only the nucleus of the spermatozoon that enters the ovum and thus all the cytoplasm, mitochondria and mitochondrial DNA are exclusively maternally inherited[7]. Maternal inheritance is attributed to mutation in the gene(s) present on mitochondrial (mt) DNA and is transmitted invariably by an affected mother to her progeny. The unique feature of mitochondrial (mt) DNA is its maternal inheritance[7].

There is a great variability in fetal growth in the human, based on both genetics and environmental factors. Although one cannot control one's genes, fetal growth may be affected through alteration in the maternal environment by medical nutrition therapy (MNT). MNT plays a vital role in every stage of fetal development[8].

a) Diagnosis of GDM

Universal screening for GDM has to be made mandatory as intrauterine exposure of the fetus to hyperglycemia is at a higher risk of developing glucose intolerance in the future.Unfortunately, for this there is no uniformity in the guidelines for diagnosing GDM. All the diagnostic criteria require women to be in fasting, including that of International Association of Diabetes in Pregnancy Study Group guideline (IADPSG)[9]. The concern of this guideline is that, it over diagnoses GDM

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without clear clinical benefit[10]. Presently, this guideline's importance is declining because even at centers that accepted IADPSG recommendation, the approach varies and needs revision for standardization of the strategy for diagnosing GDM[11].

In this context, a study established that the two-hour Plasma Glucose≥ 140 mg/dl (7.8 mmol/dl) with 75g oral glucose administered to a pregnant woman in the fasting or non-fasting state, without regard to the time of the last meal was able to identify woman with GDM[12,13,14]. This "Single Test procedure" which isfeasible to perform in all resource settings has been adopted by Diabetes in Pregnancy Study Group India (DIPSI) for diagnosing GDM. National Institute of Clinical Excellence(NICE) guidelines also recommend 2hr PG ≥7.8 mmol/dlas one of the diagnostic criteria for GDM based on the study performed in multi ethnic population of UK[15]. The DIPSI procedure is approved by the Ministry of Health & Family Welfare Government of India[16] and recognized by, World Health Organization (WHO)[17], International Federation of Obstetrics and Gynecologists (FIGO)[18] & International Diabetes Federation (IDF)[19].

b) Appropriate trimester for Screening

In planning for pregnancy, the metabolic state has to be maintained at normal level. During Pre-conception period, the recommend target glycemic level is fasting plasma glucose ≤ 5.0 mmol/dl, 2hr postprandial ≤ 6.7 mmol/dlmg/dl and A1c ≤ 6%. The current observation is that GDM manifests in all trimesters of pregnancy [20].In a study, out of N=11785 screened, 31.5% were in the first trimester, 42.2% in the second trimester and 25.3% in the third trimester[21] (Table – 1). The first trimester begins on the first day of the last period and lasts until the end of week 12. This means that by the time one knows for sure of her pregnancy, she might already be five or six weeks of pregnancy. By seventh week all the essential organs began to form and by ninth week almost completed (Fig-1). A lot happens during the first three months (Fig - 2). Hence, the present recommendation is that there is a "Need for testing glucose tolerance in the early weeks of pregnancy"[22].

In fetal pancreas each islet cell functions as an endocrine organ appears at 11th week of gestation recognizes and responds to maternal glycemia at 15-16 weeks of gestation[23]. Fetuses are exposed to increased amniotic fluid glucose before 16th weeks of gestation, suggesting that metabolic perturbations are underway before normally recommended 24th to 28th weeks of gestation for diagnosis and that earlier screening and intervention may be warranted.It is wiser to test the maternal glucose level on the next day woman misses her period. Very early diagnosis of pregnancy can be made by estimating serum beta Hydroxy Chorionic Gonadotropin (HCG) at the end of 3rdwk of menstrual cycle and by urine beta HCG by the end of 4thwk of menstrual cycle[24]. As alluded earlier it is advisable to screen for GDM in all the trimesters and most importantly the first trimester.

IV. Maternal Nutrition & Target for Glycemic Control

The goal of nutrition in pregnancy is to support maternal, placental, and fetal metabolic needs, and it may be the first introduction to a lifetime of healthy eating[25]. Postprandial hyperglycemia plays a more important role in causing fetal overgrowth. Data suggests that postprandial glucose levels more closely relates to macrosomia risk compared to fasting glucose levels [26,27]. Based on studies in preterm births renal threshold for glucose in the fetus is probably <6.7 mmol/dl. When maternal glucose level is > 6.1 mmol/dl, the fetal blood glucose load causes fetal glycosuria and consequently a glucose-enriched amniotic fluid. After 20 weeks of gestation, the fetus begins to swallow the amniotic fluid. In addition to the placental transfer of glucose, ingested high glucose amniotic fluid also stimulates insulin secretion. Thus, even transient elevations of blood glucose on the maternal side not only result in elevation of blood glucose on the fetal side but also provide for glucose ingestion by the fetus for many hours. Thus, post prandial hyperglycemia for less than1 h once a day in the mother may produce fetal insulin stimulus, through the oral route for hours. Elevations of maternal glucose levels more frequently (after every meal, for example) may produce a more prolonged oral glucose load for the fetus resulting in an overfed fat fetus[28].Monitoring maternal glycemia and maintaining 2 hr postprandial plasma glucose between 6.1 – 6.7 mmol/dl by using plasma calibrated glucometer level every week, may be a wise decision.

V. Conclusion

Fetal Development invariably involves exquisite interplay between maternal physiology, metabolism and hormones. Nature Nurtures the embryogenesis from conception to confinement. The environment that the oocyte is exposed to, during the peri-conception period can have a significant impact on oocyte developmental competence. The ability of the oocyte to support fertilisation and subsequent embryo development and the long-term health of the resulting offspringdepends upon the optimum metabolic control early in pregnancy. This will necessitate pre-pregnancy planning for women with pre-existing diabetes, as well as for those at increased risk of GDM, and better means to safely normalize glycemia. The aim in the management is, the "Growing fetus should not know that its mother has Glucose Intolerance". For that glycemic target should be that of normal pregnancy, the FPG 4.4 – 5.0 mmol/dl, Post prandial glucose 6.1 -6.7 mmol/dl and Mean PG

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glucose 95 – 105 mg/dl(5.3 – 5.9 mmol/dl)[29]. The goal is to obtain newborn babies birth weight appropriate for gestational age between 2.5 and 3.5 kg, a step to prevent offspring developing diabetes[30]. Breastfeeding for the first 6 months protects offspring developing Type 2 DM[31]. Preventive measures against diabetes should start during intra uterine period and continue throughout life from early childhood[32]. GDM offers an important opportunity for the development, testing and implementation of clinical strategies for diabetes prevention[33]. Though the fetal development is discussed in days and weeks, it is wiser to maintain recommended target glycemic level during pre-conception period and from conception to confinement. This continued care is a "A step towards strategy for prevention of diabetes".

Compliance with Ethical Standards

Conflicts of Interest: All the authors are governing council members of Diabetes in Pregnancy Study group of India (DIPSI)

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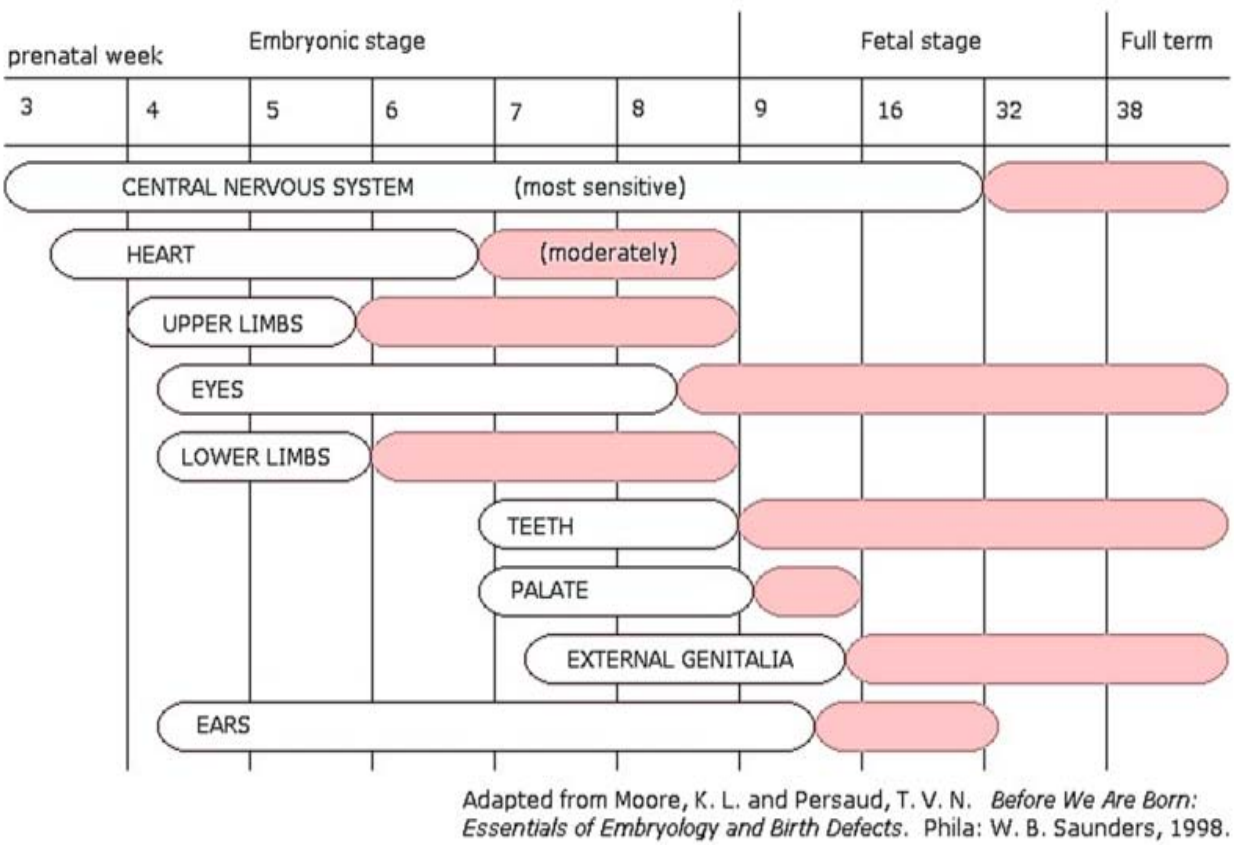


Fig. – 1: Timeline of development of major organs in utero:

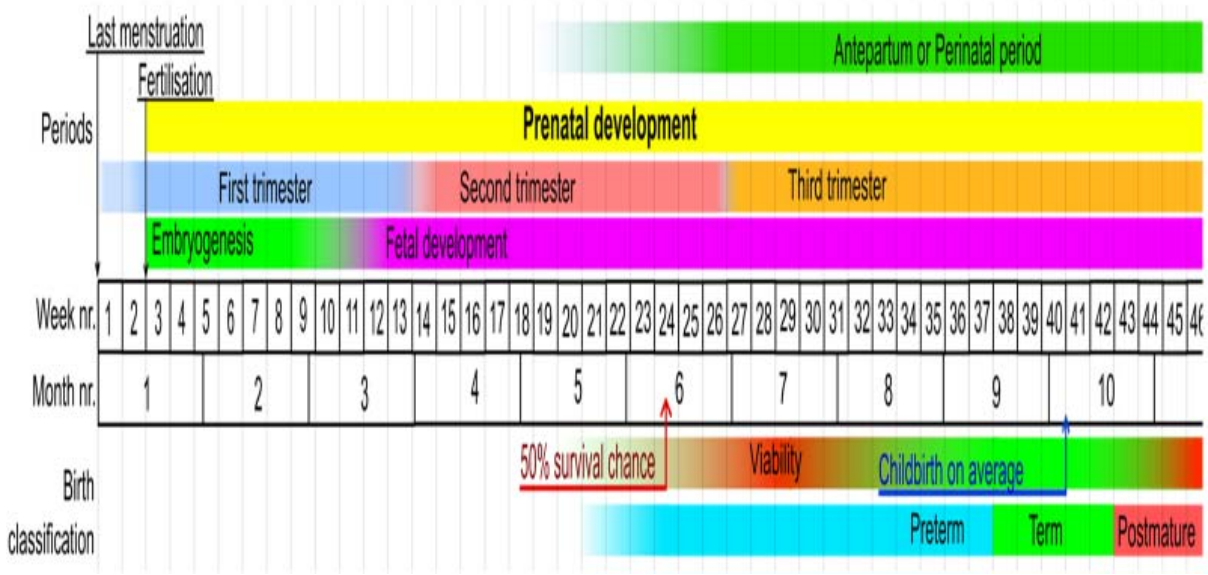


Fig. – 2: Progress of embryogenesis and fetal development

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Table -1: Manifestation of GDM detected in each trimester

Trimester	Number of mothers screened	GDM N(%)
1	4300	233 (31.5)
2	4632	320 (42.2)
3	2853	187 (25.3)
Total	11785	745 (100)

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6. Proper permissions must be acquired for the use of any copyrighted material.
7. Manuscript submitted *must not have been submitted or published elsewhere* and all authors must be aware of the submission.

Declaration of Conflicts of Interest

It is required for authors to declare all financial, institutional, and personal relationships with other individuals and organizations that could influence (bias) their research.

Policy on Plagiarism

Plagiarism is not acceptable in Global Journals submissions at all.

Plagiarized content will not be considered for publication. We reserve the right to inform authors' institutions about plagiarism detected either before or after publication. If plagiarism is identified, we will follow COPE guidelines:

Authors are solely responsible for all the plagiarism that is found. The author must not fabricate, falsify or plagiarize existing research data. The following, if copied, will be considered plagiarism:

- Words (language)
- Ideas
- Findings
- Writings
- Diagrams
- Graphs
- Illustrations
- Lectures

- Printed material
- Graphic representations
- Computer programs
- Electronic material
- Any other original work

Authorship Policies

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1. Substantial contributions to the conception and acquisition of data, analysis, and interpretation of findings.
2. Drafting the paper and revising it critically regarding important academic content.
3. Final approval of the version of the paper to be published.

Changes in Authorship

The corresponding author should mention the name and complete details of all co-authors during submission and in manuscript. We support addition, rearrangement, manipulation, and deletions in authors list till the early view publication of the journal. We expect that corresponding author will notify all co-authors of submission. We follow COPE guidelines for changes in authorship.

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Appealing Decisions

Unless specified in the notification, the Editorial Board's decision on publication of the paper is final and cannot be appealed before making the major change in the manuscript.

Acknowledgments

Contributors to the research other than authors credited should be mentioned in Acknowledgments. The source of funding for the research can be included. Suppliers of resources may be mentioned along with their addresses.

Declaration of funding sources

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Preparing your Manuscript

Authors can submit papers and articles in an acceptable file format: MS Word (doc, docx), LaTeX (.tex, .zip or .rar including all of your files), Adobe PDF (.pdf), rich text format (.rtf), simple text document (.txt), Open Document Text (.odt), and Apple Pages (.pages). Our professional layout editors will format the entire paper according to our official guidelines. This is one of the highlights of publishing with Global Journals—authors should not be concerned about the formatting of their paper. Global Journals accepts articles and manuscripts in every major language, be it Spanish, Chinese, Japanese, Portuguese, Russian, French, German, Dutch, Italian, Greek, or any other national language, but the title, subtitle, and abstract should be in English. This will facilitate indexing and the pre-peer review process.

The following is the official style and template developed for publication of a research paper. Authors are not required to follow this style during the submission of the paper. It is just for reference purposes.

Manuscript Style Instruction (Optional)

- Microsoft Word Document Setting Instructions.
- Font type of all text should be Swis721 Lt BT.
- Page size: 8.27" x 11'", left margin: 0.65, right margin: 0.65, bottom margin: 0.75.
- Paper title should be in one column of font size 24.
- Author name in font size of 11 in one column.
- Abstract: font size 9 with the word "Abstract" in bold italics.
- Main text: font size 10 with two justified columns.
- Two columns with equal column width of 3.38 and spacing of 0.2.
- First character must be three lines drop-capped.
- The paragraph before spacing of 1 pt and after of 0 pt.
- Line spacing of 1 pt.
- Large images must be in one column.
- The names of first main headings (Heading 1) must be in Roman font, capital letters, and font size of 10.
- The names of second main headings (Heading 2) must not include numbers and must be in italics with a font size of 10.

Structure and Format of Manuscript

The recommended size of an original research paper is under 15,000 words and review papers under 7,000 words. Research articles should be less than 10,000 words. Research papers are usually longer than review papers. Review papers are reports of significant research (typically less than 7,000 words, including tables, figures, and references)

A research paper must include:

a) A title which should be relevant to the theme of the paper.
b) A summary, known as an abstract (less than 150 words), containing the major results and conclusions.
c) Up to 10 keywords that precisely identify the paper's subject, purpose, and focus.
d) An introduction, giving fundamental background objectives.
e) Resources and techniques with sufficient complete experimental details (wherever possible by reference) to permit repetition, sources of information must be given, and numerical methods must be specified by reference.
f) Results which should be presented concisely by well-designed tables and figures.
g) Suitable statistical data should also be given.
h) All data must have been gathered with attention to numerical detail in the planning stage.

Design has been recognized to be essential to experiments for a considerable time, and the editor has decided that any paper that appears not to have adequate numerical treatments of the data will be returned unrefereed.

i) Discussion should cover implications and consequences and not just recapitulate the results; conclusions should also be summarized.
j) There should be brief acknowledgments.
k) There ought to be references in the conventional format. Global Journals recommends APA format.

Authors should carefully consider the preparation of papers to ensure that they communicate effectively. Papers are much more likely to be accepted if they are carefully designed and laid out, contain few or no errors, are summarizing, and follow instructions. They will also be published with much fewer delays than those that require much technical and editorial correction.

The Editorial Board reserves the right to make literary corrections and suggestions to improve brevity.



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Format Structure

It is necessary that authors take care in submitting a manuscript that is written in simple language and adheres to published guidelines.

All manuscripts submitted to Global Journals should include:

Title

The title page must carry an informative title that reflects the content, a running title (less than 45 characters together with spaces), names of the authors and co-authors, and the place(s) where the work was carried out.

Author details

The full postal address of any related author(s) must be specified.

Abstract

The abstract is the foundation of the research paper. It should be clear and concise and must contain the objective of the paper and inferences drawn. It is advised to not include big mathematical equations or complicated jargon.

Many researchers searching for information online will use search engines such as Google, Yahoo or others. By optimizing your paper for search engines, you will amplify the chance of someone finding it. In turn, this will make it more likely to be viewed and cited in further works. Global Journals has compiled these guidelines to facilitate you to maximize the web-friendliness of the most public part of your paper.

Keywords

A major lynchpin of research work for the writing of research papers is the keyword search, which one will employ to find both library and internet resources. Up to eleven keywords or very brief phrases have to be given to help data retrieval, mining, and indexing.

One must be persistent and creative in using keywords. An effective keyword search requires a strategy: planning of a list of possible keywords and phrases to try.

Choice of the main keywords is the first tool of writing a research paper. Research paper writing is an art. Keyword search should be as strategic as possible.

One should start brainstorming lists of potential keywords before even beginning searching. Think about the most important concepts related to research work. Ask, “What words would a source have to include to be truly valuable in a research paper?” Then consider synonyms for the important words.

It may take the discovery of only one important paper to steer in the right keyword direction because, in most databases, the keywords under which a research paper is abstracted are listed with the paper.

Numerical Methods

Numerical methods used should be transparent and, where appropriate, supported by references.

Abbreviations

Authors must list all the abbreviations used in the paper at the end of the paper or in a separate table before using them.

Formulas and equations

Authors are advised to submit any mathematical equation using either MathJax, KaTeX, or LaTeX, or in a very high-quality image.

Tables, Figures, and Figure Legends

Tables: Tables should be cautiously designed, uncrowned, and include only essential data. Each must have an Arabic number, e.g., Table 4, a self-explanatory caption, and be on a separate sheet. Authors must submit tables in an editable format and not as images. References to these tables (if any) must be mentioned accurately.

Figures

Figures are supposed to be submitted as separate files. Always include a citation in the text for each figure using Arabic numbers, e.g., Fig. 4. Artwork must be submitted online in vector electronic form or by emailing it.

Preparation of Eletronic Figures for Publication

Although low-quality images are sufficient for review purposes, print publication requires high-quality images to prevent the final product being blurred or fuzzy. Submit (possibly by e-mail) EPS (line art) or TIFF (halftone/ photographs) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Avoid using pixel-oriented software. Scans (TIFF only) should have a resolution of at least 350 dpi (halftone) or 700 to 1100 dpi (line drawings). Please give the data for figures in black and white or submit a Color Work Agreement form. EPS files must be saved with fonts embedded (and with a TIFF preview, if possible).

For scanned images, the scanning resolution at final image size ought to be as follows to ensure good reproduction: line art: >650 dpi; halftones (including gel photographs): >350 dpi; figures containing both halftone and line images: >650 dpi.

Color charges: Authors are advised to pay the full cost for the reproduction of their color artwork. Hence, please note that if there is color artwork in your manuscript when it is accepted for publication, we would require you to complete and return a Color Work Agreement form before your paper can be published. Also, you can email your editor to remove the color fee after acceptance of the paper.

Tips for writing a good quality Medical Research Paper

1. Choosing the topic: In most cases, the topic is selected by the interests of the author, but it can also be suggested by the guides. You can have several topics, and then judge which you are most comfortable with. This may be done by asking several questions of yourself, like "Will I be able to carry out a search in this area? Will I find all necessary resources to accomplish the search? Will I be able to find all information in this field area?" If the answer to this type of question is "yes," then you ought to choose that topic. In most cases, you may have to conduct surveys and visit several places. Also, you might have to do a lot of work to find all the rises and falls of the various data on that subject. Sometimes, detailed information plays a vital role, instead of short information. Evaluators are human: The first thing to remember is that evaluators are also human beings. They are not only meant for rejecting a paper. They are here to evaluate your paper. So present your best aspect.

2. Think like evaluators: If you are in confusion or getting demotivated because your paper may not be accepted by the evaluators, then think, and try to evaluate your paper like an evaluator. Try to understand what an evaluator wants in your research paper, and you will automatically have your answer. Make blueprints of paper: The outline is the plan or framework that will help you to arrange your thoughts. It will make your paper logical. But remember that all points of your outline must be related to the topic you have chosen.

3. Ask your guides: If you are having any difficulty with your research, then do not hesitate to share your difficulty with your guide (if you have one). They will surely help you out and resolve your doubts. If you can't clarify what exactly you require for your work, then ask your supervisor to help you with an alternative. He or she might also provide you with a list of essential readings.

4. Use of computer is recommended: As you are doing research in the field of medical research then this point is quite obvious. Use right software: Always use good quality software packages. If you are not capable of judging good software, then you can lose the quality of your paper unknowingly. There are various programs available to help you which you can get through the internet.

5. Use the internet for help: An excellent start for your paper is using Google. It is a wondrous search engine, where you can have your doubts resolved. You may also read some answers for the frequent question of how to write your research paper or find a model research paper. You can download books from the internet. If you have all the required books, place importance on reading, selecting, and analyzing the specified information. Then sketch out your research paper. Use big pictures: You may use encyclopedias like Wikipedia to get pictures with the best resolution. At Global Journals, you should strictly follow here.



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6. Bookmarks are useful: When you read any book or magazine, you generally use bookmarks, right? It is a good habit which helps to not lose your continuity. You should always use bookmarks while searching on the internet also, which will make your search easier.

7. Revise what you wrote: When you write anything, always read it, summarize it, and then finalize it.

8. Make every effort: Make every effort to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in the introduction—what is the need for a particular research paper. Polish your work with good writing skills and always give an evaluator what he wants. Make backups: When you are going to do any important thing like making a research paper, you should always have backup copies of it either on your computer or on paper. This protects you from losing any portion of your important data.

9. Produce good diagrams of your own: Always try to include good charts or diagrams in your paper to improve quality. Using several unnecessary diagrams will degrade the quality of your paper by creating a hodgepodge. So always try to include diagrams which were made by you to improve the readability of your paper. Use of direct quotes: When you do research relevant to literature, history, or current affairs, then use of quotes becomes essential, but if the study is relevant to science, use of quotes is not preferable.

10. Use proper verb tense: Use proper verb tenses in your paper. Use past tense to present those events that have happened. Use present tense to indicate events that are going on. Use future tense to indicate events that will happen in the future. Use of wrong tenses will confuse the evaluator. Avoid sentences that are incomplete.

11. Pick a good study spot: Always try to pick a spot for your research which is quiet. Not every spot is good for studying.

12. Know what you know: Always try to know what you know by making objectives, otherwise you will be confused and unable to achieve your target.

13. Use good grammar: Always use good grammar and words that will have a positive impact on the evaluator; use of good vocabulary does not mean using tough words which the evaluator has to find in a dictionary. Do not fragment sentences. Eliminate one-word sentences. Do not ever use a big word when a smaller one would suffice.

Verbs have to be in agreement with their subjects. In a research paper, do not start sentences with conjunctions or finish them with prepositions. When writing formally, it is advisable to never split an infinitive because someone will (wrongly) complain. Avoid clichés like a disease. Always shun irritating alliteration. Use language which is simple and straightforward. Put together a neat summary.

14. Arrangement of information: Each section of the main body should start with an opening sentence, and there should be a changeover at the end of the section. Give only valid and powerful arguments for your topic. You may also maintain your arguments with records.

15. Never start at the last minute: Always allow enough time for research work. Leaving everything to the last minute will degrade your paper and spoil your work.

16. Multitasking in research is not good: Doing several things at the same time is a bad habit in the case of research activity. Research is an area where everything has a particular time slot. Divide your research work into parts, and do a particular part in a particular time slot.

17. Never copy others' work: Never copy others' work and give it your name because if the evaluator has seen it anywhere, you will be in trouble. Take proper rest and food: No matter how many hours you spend on your research activity, if you are not taking care of your health, then all your efforts will have been in vain. For quality research, take proper rest and food.

18. Go to seminars: Attend seminars if the topic is relevant to your research area. Utilize all your resources.

19. Refresh your mind after intervals: Try to give your mind a rest by listening to soft music or sleeping in intervals. This will also improve your memory. Acquire colleagues: Always try to acquire colleagues. No matter how sharp you are, if you acquire colleagues, they can give you ideas which will be helpful to your research.

20. Think technically: Always think technically. If anything happens, search for its reasons, benefits, and demerits. Think and then print: When you go to print your paper, check that tables are not split, headings are not detached from their descriptions, and page sequence is maintained.

21. Adding unnecessary information: Do not add unnecessary information like "I have used MS Excel to draw graphs." Irrelevant and inappropriate material is superfluous. Foreign terminology and phrases are not apropos. One should never take a broad view. Analogy is like feathers on a snake. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Never oversimplify: When adding material to your research paper, never go for oversimplification; this will definitely irritate the evaluator. Be specific. Never use rhythmic redundancies. Contractions shouldn't be used in a research paper. Comparisons are as terrible as clichés. Give up ampersands, abbreviations, and so on. Remove commas that are not necessary. Parenthetical words should be between brackets or commas. Understatement is always the best way to put forward earth-shaking thoughts. Give a detailed literary review.

22. Report concluded results: Use concluded results. From raw data, filter the results, and then conclude your studies based on measurements and observations taken. An appropriate number of decimal places should be used. Parenthetical remarks are prohibited here. Proofread carefully at the final stage. At the end, give an outline to your arguments. Spot perspectives of further study of the subject. Justify your conclusion at the bottom sufficiently, which will probably include examples.

23. Upon conclusion: Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium though which your research is going to be in print for the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects of your research.

Informal Guidelines of Research Paper Writing

Key points to remember:

- Submit all work in its final form.
- Write your paper in the form which is presented in the guidelines using the template.
- Please note the criteria peer reviewers will use for grading the final paper.

Final points:

One purpose of organizing a research paper is to let people interpret your efforts selectively. The journal requires the following sections, submitted in the order listed, with each section starting on a new page:

The introduction: This will be compiled from reference matter and reflect the design processes or outline of basis that directed you to make a study. As you carry out the process of study, the method and process section will be constructed like that. The results segment will show related statistics in nearly sequential order and direct reviewers to similar intellectual paths throughout the data that you gathered to carry out your study.

The discussion section:

This will provide understanding of the data and projections as to the implications of the results. The use of good quality references throughout the paper will give the effort trustworthiness by representing an alertness to prior workings.

Writing a research paper is not an easy job, no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record-keeping are the only means to make straightforward progression.

General style:

Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

To make a paper clear: Adhere to recommended page limits.



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Mistakes to avoid:

- Insertion of a title at the foot of a page with subsequent text on the next page.
- Separating a table, chart, or figure—confine each to a single page.
- Submitting a manuscript with pages out of sequence.
- In every section of your document, use standard writing style, including articles ("a" and "the").
- Keep paying attention to the topic of the paper.
- Use paragraphs to split each significant point (excluding the abstract).
- Align the primary line of each section.
- Present your points in sound order.
- Use present tense to report well-accepted matters.
- Use past tense to describe specific results.
- Do not use familiar wording; don't address the reviewer directly. Don't use slang or superlatives.
- Avoid use of extra pictures—include only those figures essential to presenting results.

Title page:

Choose a revealing title. It should be short and include the name(s) and address(es) of all authors. It should not have acronyms or abbreviations or exceed two printed lines.

Abstract: This summary should be two hundred words or less. It should clearly and briefly explain the key findings reported in the manuscript and must have precise statistics. It should not have acronyms or abbreviations. It should be logical in itself. Do not cite references at this point.

An abstract is a brief, distinct paragraph summary of finished work or work in development. In a minute or less, a reviewer can be taught the foundation behind the study, common approaches to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Use comprehensive sentences, and do not sacrifice readability for brevity; you can maintain it succinctly by phrasing sentences so that they provide more than a lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study with the subsequent elements in any summary. Try to limit the initial two items to no more than one line each.

Reason for writing the article—theory, overall issue, purpose.

- Fundamental goal.
- To-the-point depiction of the research.
- Consequences, including definite statistics—if the consequences are quantitative in nature, account for this; results of any numerical analysis should be reported. Significant conclusions or questions that emerge from the research.

Approach:

- Single section and succinct.
- An outline of the job done is always written in past tense.
- Concentrate on shortening results—limit background information to a verdict or two.
- Exact spelling, clarity of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else.

Introduction:

The introduction should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable of comprehending and calculating the purpose of your study without having to refer to other works. The basis for the study should be offered. Give the most important references, but avoid making a comprehensive appraisal of the topic. Describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will give no attention to your results. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here.

The following approach can create a valuable beginning:

- Explain the value (significance) of the study.
- Defend the model—why did you employ this particular system or method? What is its compensation? Remark upon its appropriateness from an abstract point of view as well as pointing out sensible reasons for using it.
- Present a justification. State your particular theory(-ies) or aim(s), and describe the logic that led you to choose them.
- Briefly explain the study's tentative purpose and how it meets the declared objectives.

Approach:

Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done. Sort out your thoughts; manufacture one key point for every section. If you make the four points listed above, you will need at least four paragraphs. Present surrounding information only when it is necessary to support a situation. The reviewer does not desire to read everything you know about a topic. Shape the theory specifically—do not take a broad view.

As always, give awareness to spelling, simplicity, and correctness of sentences and phrases.

Procedures (methods and materials):

This part is supposed to be the easiest to carve if you have good skills. A soundly written procedures segment allows a capable scientist to replicate your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order, but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt to give the least amount of information that would permit another capable scientist to replicate your outcome, but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section.

When a technique is used that has been well-described in another section, mention the specific item describing the way, but draw the basic principle while stating the situation. The purpose is to show all particular resources and broad procedures so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step-by-step report of the whole thing you did, nor is a methods section a set of orders.

Materials:

Materials may be reported in part of a section or else they may be recognized along with your measures.

Methods:

- Report the method and not the particulars of each process that engaged the same methodology.
- Describe the method entirely.
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures.
- Simplify—detail how procedures were completed, not how they were performed on a particular day.
- If well-known procedures were used, account for the procedure by name, possibly with a reference, and that's all.

Approach:

It is embarrassing to use vigorous voice when documenting methods without using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result, when writing up the methods, most authors use third person passive voice.

Use standard style in this and every other part of the paper—avoid familiar lists, and use full sentences.

What to keep away from:

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings—save it for the argument.
- Leave out information that is immaterial to a third party.



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Results:

The principle of a results segment is to present and demonstrate your conclusion. Create this part as entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Use statistics and tables, if suitable, to present consequences most efficiently.

You must clearly differentiate material which would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matters should not be submitted at all except if requested by the instructor.

Content:

- Sum up your conclusions in text and demonstrate them, if suitable, with figures and tables.
- In the manuscript, explain each of your consequences, and point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation of an exacting study.
- Explain results of control experiments and give remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or manuscript.

What to stay away from:

- Do not discuss or infer your outcome, report surrounding information, or try to explain anything.
- Do not include raw data or intermediate calculations in a research manuscript.
- Do not present similar data more than once.
- A manuscript should complement any figures or tables, not duplicate information.
- Never confuse figures with tables—there is a difference.

Approach:

As always, use past tense when you submit your results, and put the whole thing in a reasonable order.

Put figures and tables, appropriately numbered, in order at the end of the report.

If you desire, you may place your figures and tables properly within the text of your results section.

Figures and tables:

If you put figures and tables at the end of some details, make certain that they are visibly distinguished from any attached appendix materials, such as raw facts. Whatever the position, each table must be titled, numbered one after the other, and include a heading. All figures and tables must be divided from the text.

Discussion:

The discussion is expected to be the trickiest segment to write. A lot of papers submitted to the journal are discarded based on problems with the discussion. There is no rule for how long an argument should be.

Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implications of the study. The purpose here is to offer an understanding of your results and support all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of results should be fully described.

Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact, you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved the prospect, and let it drop at that. Make a decision as to whether each premise is supported or discarded or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."

Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work.

- You may propose future guidelines, such as how an experiment might be personalized to accomplish a new idea.
- Give details of all of your remarks as much as possible, focusing on mechanisms.
- Make a decision as to whether the tentative design sufficiently addressed the theory and whether or not it was correctly restricted. Try to present substitute explanations if they are sensible alternatives.
- One piece of research will not counter an overall question, so maintain the large picture in mind. Where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

When you refer to information, differentiate data generated by your own studies from other available information. Present work done by specific persons (including you) in past tense.

Describe generally acknowledged facts and main beliefs in present tense.

The Administration Rules

Administration Rules to Be Strictly Followed before Submitting Your Research Paper to Global Journals Inc.

Please read the following rules and regulations carefully before submitting your research paper to Global Journals Inc. to avoid rejection.

Segment draft and final research paper: You have to strictly follow the template of a research paper, failing which your paper may get rejected. You are expected to write each part of the paper wholly on your own. The peer reviewers need to identify your own perspective of the concepts in your own terms. Please do not extract straight from any other source, and do not rephrase someone else's analysis. Do not allow anyone else to proofread your manuscript.

Written material: You may discuss this with your guides and key sources. Do not copy anyone else's paper, even if this is only imitation, otherwise it will be rejected on the grounds of plagiarism, which is illegal. Various methods to avoid plagiarism are strictly applied by us to every paper, and, if found guilty, you may be blacklisted, which could affect your career adversely. To guard yourself and others from possible illegal use, please do not permit anyone to use or even read your paper and file.

Criterion for Grading a Research Paper (Compilation) by Global Journals

Please note that following table is only a Grading of "Paper Compilation" and not on "Performed/Stated Research" whose grading solely depends on Individual Assigned Peer Reviewer and Editorial Board Member. These can be available only on request and after decision of Paper. This report will be the property of Global Journals.

Topics	Grades		
	A-B	**C-D**	**E-F**
Abstract	Clear and concise with appropriate content, Correct format. 200 words or below	Unclear summary and no specific data, Incorrect form Above 200 words	No specific data with ambiguous information Above 250 words
Introduction	Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited	Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter	Out of place depth and content, hazy format
Methods and Procedures	Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads	Difficult to comprehend with embarrassed text, too much explanation but completed	Incorrect and unorganized structure with hazy meaning
Result	Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake	Complete and embarrassed text, difficult to comprehend	Irregular format with wrong facts and figures
Discussion	Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited	Wordy, unclear conclusion, spurious	Conclusion is not cited, unorganized, difficult to comprehend
References	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring

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