Association of Pleural Effusion with Hematocrit and Platelet Counts among Patients Diagnosed with Dengue Fever in De La Salle University Medical Center from January 2010 – January 2015 (5 years retrospective study)

Principal Investigator: Tandy Chintya Tanaji, MD

Department of Radiology

De La Salle University Medical Center

Emmie B. Consolacion, MD, FPCR
Adviser

Author Information:
Address: Department of Radiology, DLSU-Medical Center, Dasmariñas City 4114 Cavite
Contact #: (0915)7888718/ 09479114338
Email address:tandytanaji@yahoo.com

DE LA SALLE UNIVERSITY MEDICAL CENTER
De La Salle Health Sciences Institute
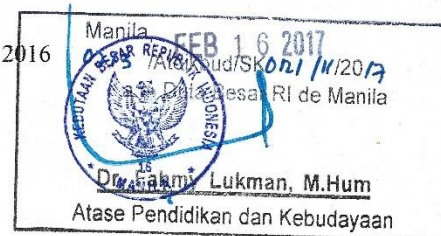Dasmariñas City, Cavite 4114
Tel. No.: (+6346) 4818000/ (+632) 98831000

DEPARTMENT OF RADIOLOGY

TANDY CHINTYA TANAJI, MD

Residency Training Period:

JANUARY 1, 2013 – DECEMBER 31, 2016

Research Presentation:

Association of Pleural Effusion with Hematocrit and Platelet Counts among Patients Diagnosed with Dengue Fever in De La Salle University Medical Center from January 2010 – January 2015

(5 years retrospective study)

THIS PAPER HAS BEEN ACCOMPLISHED IN CONSONANCE WITH THE GUIDELINES
MANDATED FOR ACCREDITED RADIOLOGY RESIDENCY TRAINING PROGRAM BY
PHILIPPINE COLLEGE OF RADIOLOGY (PCR)
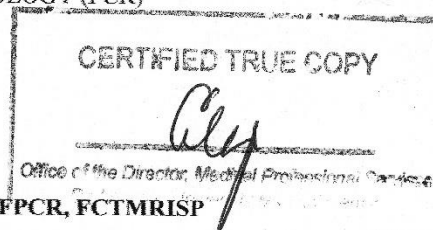
ASELA P. BUSTOS-BARROSO, MD, FPCR, FCTMRISP
Training Officer

PETRONILO B. PARUNGAO, JR., MD, FPCR, FUSP, FCTMRISP, CCD
Chairman

2

TABLE OF CONTENTS

Association of Pleural Effusion with Hematocrit and Platelet Counts among Patients Diagnosed with Dengue Fever in De La Salle University Medical Center from January 2010 – January 2015 (5 years retrospective study)

ABSTRACT

Objectives: To determine the association of presence of pleural effusion with elevated hematocrit level and decreased platelet count

Design: Retrospective analytic cross-sectional study

Patients: All dengue patients which admitted at DLSUMC

Methods: Demographic, platelet count, hematocrit and chest x-ray findings were retrieved. Patients demographic data, platelet count and hematocrit levels then will be looked for the presence of pleural effusion on their chest x-ray examination.

Results: Only 252 patients from the total of 548 Dengue patients (46%) admitted at De LaSalle University Medical center from January 1, 2010- January 1, 2015 were included in this study. Pediatric age group (52.4%) and male (57.5%) patients are found to be more prone to develop pleural effusion, with a right-sided pleural effusion as most common finding. Logistic regression linear analysis study shows significant relationship between the elevated hematocrit value and decreased platelet count with the presence of pleural effusion, both with p value < 0.05. This study found that most of Dengue patients with elevated hematocrit of ≥ 40% and platelet counts below 56.744/mL have pleural effusion. Furthermore, this study revealed that the incidence of pleural effusion significantly increased (> 50%) on the 7th and 8th days after onset of fever.

Conclusion: Dengue patients with elevated hematocrit ≥ 40% and platelet counts < 56.744/ mL are more likely to develop pleural effusion than those who has hemoconcentration of ≥ 20% and platelet counts of > 56.744/ mL.

INTRODUCTION

Background of the Study

Dengue fever is a febrile illness caused by any one of the 4 flavivirus serotypes (DEN-1, DEN-2, DEN-3, and DEN-4). It is characterized by sustained high grade fever for 2–7 days; bleeding diathesis evidenced by positive tourniquet test, petechiae, epistaxis and hematemesis; thrombocytopenia with platelet counts ≤150.000 cells/mm3 and plasma leakage due to increased vascular permeability which is evidenced by hemoconcentration, pleural effusion and ascites. Given these complications, dengue fever continues to be a significant cause of morbidity and mortality in the Philippines[1].

Dengue is considered to be endemic in the Philippines with clustering of cases and outbreaks occurring in unpredictable intervals due to inability to control and prevent this arthropod-borne disease. According to the Philippine Integrated Disease Surveillance and Response (PIDSR) of the Department of Health (DOH), 204,906 dengue cases were reported in 2013 nationwide[2].

Dengue was formerly classified into two nosological entities: Dengue Fever (DF) and Dengue Hemorrhagic Fever (DHF). In 2011, a revised classification has been adapted by DOH and the Philippine Pediatric Society (PPS), changing it to three categories: (1) dengue without warning signs, (2) dengue with warning signs, and (3) severe dengue.

Dengue is the most common mosquito-borne disease of human that in the recent years, it has become a major international public health concern that led to significant mortality due to its complications. There are many complications caused by this disease, most common of which is pulmonary manifestation (i.e. pleural effusion). Pleural effusion develops when there is excessive

pleural fluid formation (from the interstitial spaces of the lung or parietal pleura) or when there is decreased fluid removal by the lymphatic system.

Pleural effusion can be easily detected by simply doing a chest radiograph examination. Although many studies have been conducted on the epidemiology of dengue, there are only few studies correlating radiographic findings of dengue cases with different blood parameters. Since the hematocrit and platelet counts are the most important blood parameters in estimating the severity of Dengue and pleural effusion as the most common clinical manifestation of this disease. Thus, prompting the author to conduct this investigation.

General Objective

This study aims to determine the association between the presence of pleural effusion on chest radiograph with blood parameters (hematocrit and platelet counts) among in-patients diagnosed with dengue at the De La Salle University Medical Center from January 1, 2010 to January 1, 2015.

Specific Objectives

1. To described the demographic profile of Dengue patients admitted in DLSUMC.
2. To determine the prevalence of pleural effusion in chest radiographs of admitted dengue patients
3. To determine the prevalence of elevated hematocrit and decrease platelet count of dengue patients
4. To determine association of presence of pleural effusion as seen on chest radiograph with elevated hematocrit level.

5. To determine association of presence of pleural effusion as seen on chest radiograph with decreased level of platelet count.

6. To described the distribution of the presence of pleural effusion (PE) on chest radiograph according to the duration of illness.

Significance of the Study

This study will provide evidence-based information on the use of laboratory examination, such as hematocrit and platelet count on predicting the presence of pleural effusion on dengue patients since the pleural effusion is the most common manifestation in this disease. This will also provide additional information for future studies on timing of chest radiograph examination in Dengue patients and hopefully will be able to minimize the unnecessary radiation exposure for dengue patients, especially in pediatric group.

Scope and limitations

The study aims to find out the association between pleural effusion and laboratory findings, such as hematocrit and platelets among patients diagnosed with dengue fever at De La Salle University Medical Center during a 5 year period (January 1, 2010 to January 1, 2015). Other hematologic parameters like white blood cell count, prothrombin time (PT), activated partial thromboplastin time (APTT), aspartate aminotransferase (AST), and alanine aminotransferase, will not be included in this study.

REVIEW OF RELATED LITERATURE

Dengue Fever

Dengue infection is characterized by sustained high grade fever for 2–7 days; bleeding diathesis such as positive tourniquet test, petechiae, epistaxis and hematemesis; thrombocytopenia with platelet counts ≤ 150.000 cells/mm3 and plasma leakage due to increased vascular permeability which is evidenced by hemoconcentration, pleural effusion and ascites. With those kinds of complications Dengue continues to be a significant cause of morbidity and mortality in the Philippines[1].

Epidemics of dengue occur every 3-4 years in the Philippines[2], its peak incidence occur during the wet season in the Philippines.[3] Symptoms such as fever and rash in young children and fever, severe headache, pain behind the eyes, rash, and muscle and joint pain are the common findings in dengue fever[4].

Dengue infection was formerly classified into two nosological entities: Dengue Fever (DF) and Dengue Hemorrhagic Fever (DHF). In 2011, a revised classification has been adapted by DOH and the Philippine Pediatric Society (PPS), changing it to three categories: (1) dengue without warning signs, (2) dengue with warning signs, and (3) severe dengue.[5]

Epidemiology

The incidence of dengue has grown dramatically around the world in recent decades. Over 2.5 billion people – over 40% of the world's population – are now at risk from dengue. WHO currently estimates there may be 50–100 million dengue infections worldwide every year. Before 1970, only nine countries had experienced severe dengue epidemics. The disease

is now endemic in more than 100 countries in Africa, the Americas, the Eastern Mediterranean, South-east Asia and the Western Pacific.[6]

There are four distinct dengue virus serotypes, all of which originate from the family Flaviviridae and genus *Flavivirus*.[7,8,9] The serotypes are termed DENV-1, DENV-2, DENV-3, and DENV-4, and infection with any of the four viruses results in lifelong immunity to that specific serotype.[10,11,12] Each of the four serotypes has been individually found to be responsible for dengue epidemics and associated with more severe dengue.[9,13]

In the Philippines, the first dengue hemorrhagic fever known as the Philippine dengue hemorrhagic fever was reported in 1953. After 5 years, due to an increasing number of reported cases, the disease was included as one of the most commonly reported disease by the Department of Health. In 1996, the biggest recorded epidemic occurred in Metro Manila with a morbidity rate of 28/100,000 population. Since then, dengue fever/dengue hemorrhagic fever is a closely monitored disease in the region.[14]

Pathophysiology of Dengue

Macrophage/monocyte infection is central to the pathogenesis of dengue fever and to the origin of hemorrhage and shock. Previous infection with heterologous dengue-virus serotype may result in the production of non-protective condition on people who were infected with dengue virus for the 2nd time. Antiviral antibodies that nevertheless bind to the virion's surface and through interaction with the Fc receptor focus secondary antibody response when viral antigens are released and immune complexes lead to activation of the classic complement pathway, with consequent phlogistic effects. Cross reactivity at the T-cell level results in the release of

physiologically active cytokines, including interferon and tumor necrosis factor. The induction of vascular permeability and shock depends on multiple factors such as age, sex, race, etc.

Pleural Effusion

Pleural effusion is an abnormal fluid accumulation in pleural space. It's the most common among all Dengue complications and may develop when there is excess pleural fluid formation (from the interstitial spaces of the lung or parietal pleura) or when there is decreased fluid removal by the lymphatic.

Pleural effusion can be radiographically detected by a chest radiograph but its appearance depends upon the amount of fluid present, the position of the patient during the radiographic examination and the presence or absence of adhesion between the parietal and visceral pleura. Small amount of pleural fluid initially collect between the lower lobe and diaphragm in a subpulmonic location. On chest x-ray a moderate amount of pleural fluid (> 175 mL) in the erect position will have a characteristic appearance on frontal radiograph as a homogenous lower zone opacity seen in the lateral costophrenic sulcus with a concave interface toward the lung.

Presence of pleural effusion in dengue

During the phase of plasma leakage in dengue, fluid accumulation may be noted in various parts of the body. A study by Venkata, et al. in 2005 showed common sonographic findings among dengue patients include gallbladder thickening, pleural effusion and ascites.[17]

A retrospective study done by Wang, et al. in 2007 observed the chest radiographic findings of patient with serologically confirmed dengue infection. In this research, a total of 468 chest radiograph has been reviewed and 50% of them showed abnormalities after the 3rd day onset of illness, with infiltration (109, 23.3%) and small pleural effusion (117, 25%) as the major findings.

It is also noted in the same study that the presence of pleural effusion upon chest radiograph is significantly correlated with decrease of the platelet count (<150.000/ mL). [18]

Another retrospective study by Ejaz, et al. done in 2011 shows that chest radiography readily shows the presence of pleural effusion among patients with dengue syndrome. It is also stated in their study that timing of the imaging procedure is essential. If the imaging modality was done early in the course of the disease, normal findings are most probably noted.

Operational Definitions

Age   The chronological age of subject as of his/her last birthday in years

Gender   The biological sex of the subject categorized as either male or female

Pleural Effusion   Described as an abnormal fluid accumulation present between the visceral and parietal pleura as seen on chest radiograph done within ≥72 hours from the onset of fever.

Hematocrit   The proportion of the blood that consists of packed red blood cells. It is expressed as a percentage by volume (%).

- Normal range for hematocrit is different between the sexes and age. According to the study done by Henny H. Billet, normal hematocrit in adult population for men is of about 40-54% and for women it is 36-48%. In pediatric population, another study done by S. Balasubramanian, et.al in Chennai was defined the area of specific hematocrit cut off values for hemoconcentration to occur as >34.8% in less than 5 years of age group and >37.5% in the age group more than 5 years.

- **Hemoconcentration** can be marked by elevated of the hematocrite values above the upper limit of the aforementioned normal values for age and groups; ≥ 20% rise of the hematocrit for the age and group relative to baseline and/or a >20% drop in the hematocrit following volume replacement compared to the baseline. However, extent of hemoconcentration in this study was quantitated by taking a difference between the maximum hematocrit at admission or anytime during the

hospital stay and the minimum hematocrit recording at convalescence stage or discharge.

- Another study done by Surangratpongpang, et. al. done in 2013 was uniquely divided the level of hemoconcentration into three categories based on Dengue severity grading:

  - Group 1   = Not present (0%)

  - Group 2 = ≥ 20%

  - Group 3 = ≥ 40%

Platelet count   The calculated number of platelets in a volume of blood (Normal value: 150.000-450.000 /mL).

- **Decreased platelet count:** If the level of platelets falls below normal value (Less than <150.000 /mL). However, study done by Surangrat pongpang, et. al. done in 2013 was divided the decreased platelet counts into three categories based on Dengue severity:

  - Group 1 (Dengue fever)   = 122693.6 ± 9763.9

  - Group 2 (Dengue Hemorrhagic Fever)   = 81869.0 ± 7975.7

  - Group 3 (Dengue Shock Syndrome)   = ≤ 56.744

Dengue Fever   is a disease caused by a virus categorized in the family of Flaviviridae which is transmitted by the Aedes aegypti or Aedes albopictus mosquito. This disease has several categories as explained in the following table:

Table I. Comparison of the WHO 1997/2011 Case Definition and case Classifications for Dengue With the Revised DOH Dengue case classification

WHO 1997/2011 Case Definition of Dengue and Levels of Severity	Revised DOH/PPS Classifications and Levels of Severity 2011
Case Definition for <u>Dengue Fever</u> **Probable:** An acute febrile illness with two or more of the following: - Headache - Retro-orbital pain - Arthralgia - Rash - Hemorrhagic manifestations - Leukopenia, AND - Supportive serology (A reciprocal HI antibody titer ≥1280, a comparable IgG assay ELISA titer or (+) IgM antibody test on a late or acute convalescent phase serum specimen) **Confirmed:** A case confirmed by laboratory criteria	**Case Definition for <u>Dengue without Warning signs</u>** **Probable Dengue:** Lives or travels to dengue-endemic area, with fever, plus any two of the following: - Headache - Body malaise - Myalgia - Arthralgia - Retro-orbital pain - Anorexia - Nausea - Vomiting - Diarrhea - Flushed skin - Rash (petechial, Hermann's sign) - Tourniquet test positive AND - Laboratory test, at least CBC (leukopenia with or without thrombocytopenia) and/or dengue NS1 antigen test or dengue IgM antibody test (optional) **Confirm Dengue:** - Viral culture isolation - PCR

Case Definition for <u>Dengue Hemorrhagic Fever (DHF)</u>

The following all must be present:
1. Fever, or history of fever, lasting for 2-7 days, occasionally biphasic
2. Hemorrhagic tendencies evidenced at least one of the following:
   a. (+) tourniquet test
   b. Petechiae, ecchymosis, purpura
   c. Bleeding from the mucosa, GIT injection sites or other locations
   d. Hematemesis or melena
3. Thrombocytopenia (100.000 cells/mm3 or less)
4. Evidence of plasma leakage due to increased vascular permeability, manifested by at least one of the following:
   a. A rise in the haematocrit equal to or greater than 20% above average for age, sex and population
   b. A drop in the hematocrit following volume replacement treatment equal to greater than 20% of baseline
   c. Signs of plasma leakage such as pleural effusion, ascites and hypoproteinemia

Case Definition for <u>Dengue Shock Syndrome (DSS)</u>

All of the four criteria for DHF must be present plus evidence of circulatory failure manifested by:
Rapid and weak pulse, AND
Narrow pulse pressure (< 20 mmHg [2.7 kPa) OR manifested by:
Hypotension for age AND
Cold clammy skin and restlessness

<u>Grading of Severity of DHF/DSS</u>

DHF Grade I
Fever accompanied by non specific constitutional signs and symptoms such as anorexia, vomiting, abdominal pain; the only hemorrhagic manifestation is a (+) tourniquet test and/or easy bruising

DHF Grade 2

Spontaneous bleeding in addition to manifestations of grade I patients usually in the form of skin or other haemorrhage (mucocutaneous), GIT

DHF Grade 3 (DSS)

Case Definition for <u>Dengue with Warning Signs:</u>

Lives in or travels to dengue endemic area, with fever lasting for 2-7 days, plus any of the following:
- Abdominal pain or tenderness
- Persistent vomiting
- Clinical signs of fluid accumulation
- Mucosal bleeding
- Lethargy, restlessness
- Liver enlargement
- Decreased or no urine output within 6 hours
- Laboratory: Increase in Haematocrit and/or decreasing platelet count

Confirmed dengue:
- Viral culture isolation
- PCR

Case definition of <u>Severe Dengue</u>

Lives in or travels to a dengue-endemic area with fever of a 2-7 days and any of the above clinical manifestations for dengue with or without warning signs, plus any of the following:
- Severe plasma leakage, leading to
- Severe bleeding
- Severe organ impairment
  - Liver: AST or ALT ≥ 1000
  - CNS: e.g., seizures, impaired consciousness
  - Heart: e.g. myocarditis
  - Kidneys: e.g., renal failure

Note:
Above manifestations and/or laboratory parameters require strict observation, monitoring, and appropriate medical intervention

Circulatory failure manifested by rapid, weak pulse and narrowing of pulse pressure or hypotension, with the presence of colds clammy skin and restlessness.	

There is actually no significant difference between the abovementioned classifications (WHO and PPS) in which Dengue with warning signs is more or less the same as dengue hemorrhagic fever, while severe dengue has similar description as Dengue Shock Syndrome.

Duration of the disease upon x-ray: described as number of days after onset fever at the time when chest radiograph was obtained (D-day)

METHODOLOGY

Study Design

An analytic study using cross-sectional design will be done. A 5-year retrospective review of platelet count and hematocrit levels and their chest radiograph finding (presence of pleural effusion) among all patients diagnosed with dengue and admitted at De La Salle University Medical Center from January 1, 2010 to January 1, 2015 will be conducted.

Research Setting

The study will be conducted at De La Salle University Medical Center, a tertiary hospital in the city of Dasmariñas, Province of Cavite.

Study Population

The study will includes minimum of 206 patients who diagnosed with dengue and admitted at De La Salle University Medical Center from the period of January 1, 2010 to January 1, 2015 who fulfills the eligibility criteria. The study population will also describe according to their disease status according to WHO criteria, such as Dengue Fever (Dengue without warning sign), Dengue Hemorrhagic Fever (Dengue with warning signs) and Dengue Shock Syndrome (Severe Dengue).

Eligibility Criteria

- **Inclusion criteria**
  - Any individual who was diagnosed with dengue by clinicians in De La Salle University Medical Center based on WHO criteria and was admitted within the period of January 1, 2010 to January 1, 2015 who had chest radiograph done in the X-ray section of the Department of Radiology within the period of admission and with blood

examination (platelet count and hematocrit) done within 24 hour from the time the chest radiograph was taken.

- **Exclusion criteria**

  - Any admitted patient across all ages diagnosed with dengue but have blood examinations (hematocrit/platelet count) not done within 24 hour from the time the chest radiograph was taken

  - Any admitted patient across all ages diagnosed with dengue but had history of any lung diseases, which may produce pleural effusion. (e.g. tuberculosis, pneumonia, neoplasm, etc.)

  - Patients who not admitted in the hospital or either treated and discharged from the Emergency department (ED) or seen as outpatient clinic will be excluded.

  - Patients with chest radiograph done less than 72 hours from the onset of fever will be excluded.

Sampling Technique

Medical records of all dengue patients admitted at De La Salle University Medical Center from the period of January 1, 2010 to January 1, 2015 will be reviewed. Only those who fulfill the eligibility criteria will be included in this study.

Sample size

Based on the prevalence of pleural effusion of 16% in the previous study (Ejaz, Khursheed and Raza 2011), 95% confidence level and 5% margin of error, a minimum sample size of 207 charts of Dengue patients will be extracted in this study. The formula shown below:

$$n = \frac{PQz^2}{m^2} = \frac{(0.16)(0.84)(1.96)^2}{(0.05)^2}$$

$$n = 207$$

Where, n= sample size; P=prevalence, Q=1-P; z= z-score=1.96 corresponds to 95% Confidence Level; m= margin of error

Data Gathering

      After securing the approval of the Ethics Committee of DLSUMC to conduct the study, medical records of all admitted dengue patients at De La Salle University Medical Center from January 1, 2010 to January 1, 2015 will be reviewed. Pertinent demographic information, final diagnosis and laboratory information on hematocrit (Ht) and platelet count will be noted. Radiographic reports of eligible subjects accessed through the hospital's Radiology Information System (RIS) will also be noted for presence of pleural effusion. Information gathered will be encoded in the data abstraction form. Data gathering will be conducted for a period of 6 months.

Instrumentation

      A data abstraction form (Appendix A) is developed based on study objectives. This will contain demographic, clinical, radiographic and laboratory information of the subjects. Demographic information will include age and sex. Clinical information will be classified into two categories, good and poor prognosis. Symptoms relating to good prognosis such as fever, headache, arthralgia and abdominal pain and poor prognosis such as of fever, headache, arthralgia and abdominal pain which followed by hemorrhagic manifestation (e.g. epistaxis, hematemesis,

melena, etc) and/or signs of hypotension will be included. Laboratory information will include hematocrit (HCT) and platelet count values as well as the date of the aforementioned examination was done. Radiologic information will include the presence of pleural effusion and its laterality.

Statistical Treatment

Before the data analysis, checks for consistency and completeness of data will be ensure. Summary statistics such as means, standard deviations, ranges, frequencies and percentages will computed to describe the data.

Prevalence of pleural effusion will be computed by counting the number of patients with pleural effusion (as defined in operational defiinition, based on the Fundamental's of diagnostic Radiology by William E. Brant and Clyde A. Helms) and divide by the total number of patients records assessed, then multiplied by 100%.

Logistic regression analysis used to assess the association between the hemoconcentration level and pleural effusion, and platelet count and pleural effusion.

Magnitude of association will be quantified using Odds ratio and corresponding 95% confidence interval.

Data will be encoded using Microsoft Excel 2010 and analyzed using SPSS version 17. A p-value of <0.05 will be considered statistically significant.

Data Collection Form

Correlation of the Presence of Pleural Effusion with Hematocrit and Platelet Levels Among Patients Diagnosed with

Dengue Fever in De La Salle University Medical Center

Demographic and Clinical Information	
Record Number	
Onset of fever (if less than 72 hours, do not include)	
Date of admission and date of discharges (mm/dd/yyyy)	
Age (years)	
Sex	☐ Male ☐ Female

Clinical information:
 	
    - Onset of Fever (on D day)
    - Headache (present/ not present)
    - Abdominal pain (present/ not present)
    - Arthralgia (present/ not present)
    - Hemorrhagic manifestation (present/ not present)
    - Hypotension (present/ not present)
 	
Dengue Immunology: IgG, IgM and NS1
 	
Grading of dengue:
1. Dengue fever / Dengue without warning sign
2. Dengue Hemorrhagic Fever/ Dengue with warning signs
3. Dengue shock syndrome/ Severe Dengue	

Radiologic Information	
Date the chest radiograph was done	(D day)
Presence of pleural effusion	☐ Yes ☐ No
Laboratory Information	
Hematocrit Date hematocrit was done	
Baseline hematocrit Date baseline hematocrit was done	
Platelet count	
Date platelet count was done	

RESULTS

In this study, a total of five hundred forty eight (548) patients were admitted in De La Salle University Medical Center for dengue from January 1, 2010 to January 1, 2015. Of which, a total of three hundred forty three (343) patients have available chest radiograph. However, not all passed the eligibility criteria. Only two hundred fifty two (252) patients, 46% of the total admitted dengue patients, were subjected in this study.

1. **Demographic characteristics of Dengue patients admitted in De La Salle University Medical Center**

   Overall, of the total patients, 52.4% were pediatric and 47.6% were adult patients. The youngest patient that was admitted is 6 months old, while the oldest is seventy (70) years old with the mean age was 8 years old for pediatric and 29 years old on adult population with male (57.5%) a little more than woman (42.5%).

Table 1. Demographic profile of patients

Demographic profile	Category	Count	Percentage (%)	Mean	Min	Max
Age	Pediatric (0-18 years old)	132	52.4	8.18	0.50	18
	Adult (> 18 years old)	120	47.6	29.58	19	70
	Total	252	100	18.37	0.50	70
Gender	Male	145	57.5	NA	NA	NA
	Female	107	42.5			

2. **Prevalence of Pleural Effusion in chest radiographs of admitted Dengue patient and its laterality.**

The table 2 below shows the prevalence of pleural effusion according to their demographic profiles. In this study, from a total of 252 chest radiographs, only 96 radiographs (38%) were found positive of pleural effusion. Most of the chest radiograph that showed pleural effusion is belong to **pediatric (84.4%)** and **male groups (59%)**.

Table 2. Prevalence of Pleural Effusion in chest radiographs of admitted Dengue patient

Demographic profile	Category	Positive		Negative	
		Count	Percentage (%)	Count	Percentage (%)
Age	Pediatric (< 18 years old)	81	84.4	51	32.7
	Adult (> 18 years old)	15	15.6	105	67.3
Gender	Male	57	59.4	88	56.4
	Female	39	40.6	68	43.6
	Total	96	38	156	62

Table 3 below shows that a right-sided pleural effusion found to be more common to develop among dengue patients at fifty three percent (53%), while forty two percent (42%) had pleural effusion on both side (bilateral). Only five percent (5%) showed pleural effusion at the left side of the lungs.

Table.3 Laterality

Laterality	Count	Percentage (%)
Left	5	5
Right	51	53
Bilateral	40	42
Total	96	100

3. The Prevalence of elevated hematocrit and decreased platelet count of Dengue patient.

HEMATOCRIT

In this study, the hematocrit value for dengue patients ranges from 27 to 61%, with a mean value of 43.9%. It shows that most of the pediatric patients have elevated hematocrit value. However, for adult patients, more than half of population has normal hematocrit value. In terms of gender, we found that male tends to have slightly higher incidence of elevated hematocrit value than women.

Table 4. Summary of Hematocrit Classification

Demographic profile	Category	Low		Normal		High		Total
		Count	%	Count	%	Count	%	
Overall		6	2	143	57	103	41	252
Age	Pediatric (< 18 years old)	NA	0	34	26	98	74	132
	Adult (> 18 years old)	6	5	109	91	5	4	120
Gender	Male	3	2	82	57	60	41	145
	Female	3	3	61	57	43	40	107

Some of the patients in this study shows hemoconcentration (marked elevation of the hematocrit value ≥20% relative to baseline), while others didn't. Table 5 shows us that there are 99 patients (39% from the total population) had hemoconcentration with most of the patients are belonging to the pediatric group (63%). It also revealed that female have slightly higher incidence of hemoconcentration than male.

Table 5. Prevalence of hemoconcentration according to their demographic profiles.

| Demographic profile | Category | Hemoconcentration | | | | Total |
| | | Not present | | Present | | |
		Count	%	Count	%	
Overall		153	61	99	39	252
Age	Pediatric (< 18 years old)	49	37	83	63	132
	Adult (> 18 years old)	104	87	16	13	120
Gender	Male	89	62	56	39	145
	Female	64	60	43	40	107

Upon further investigation, as mentioned in Table 7 below, the incidence of hemoconcentration most commonly occur in group 2 (hemoconcentration of ≥20%). The rest of the patients (61% from the total population) didn't have hemoconcentration at all.

Table 7. Level of hemoconcentration

| Demographic profile | Category | ≥20% | | ≥40% | | Total |
		Count	%	Count	%	
Overall		83	84	16	16	99
Age	Pediatric (< 18 years old)	68	82	15	18	83
	Adult (> 18 years old)	15	94	1	6	16
Gender	Male	50	89	6	11	56
	Female	33	77	10	23	43

PLATELET COUNT

Platelet is a component of the blood that helps in clotting. Decreased platelet level in the blood is one of the indicators of dengue. Table 7 below shows the overall platelet count, which ranging from 18.000/mL to 362.000/mL with the average platelet count of about 105.000/mL. There are 205 patients or about 81% from total study population in all age group and gender shows low (decreased) platelet count.

Table 7. Summary of Platelet classification

Demographic profile	Category	Decreased		Normal		Total
		Count	%	Count	%	
Overall		205	81	47	19	252
Age	Pediatric (< 18 years old)	120	91	12	9	132
	Adult (> 18 years old)	85	71	35	29	120
Gender	Male	116	80	29	20	145
	Female	89	83	18	17	107

4. **Association of presence of Pleural Effusion with elevated hematocrit**

Table 9 shows that 62 (60%) of patient who had high hematocrit value also had pleural effusion. The author carefully count and analyzed the association of pleural effusion with hematocrit level based on the logistic regression analysis test. According to this study, there is a statistically significant relationship between elevated hematocrit value and the presence of pleural effusion as seen on chest radiograph at 95% confidence level since the calculated value is less than 0.05. The table below also stated that the Odds od elevated hematocrit is 4.95 higher of having pleural effusion compared with non-elevated group.

Table 8. Association of presence of pleural effusion with elevated hematocrit

Hematocrit Classification	Pleural Effusion				OR	95% CI	p-value
	Negative		Positive				
	Count	%	Count	%			
Non-elevated	114	77	34	23	Reference		
Elevated	42	40	62	60	4.95	2.86-8.56	0.0001
Total	156	62	96	38	252		

According to the Table 8 above, from the total 104 patients with the elevated hematocrit value, 62 patiens show pleural effusion. However, since not all the patients with elevated hematocrit value had hemoconcentration, the author then try to divided the level of hemoconcentration into three groups (in accordance to study done by Surangrat Pongpang, et.all) as seen on Table 10.

Table 9 shows that there is significant association between the presences of pleural effusion with hemoconcentration, wherein the Odds of those patients with hemoconcentration level ≥40% more likely to have pleural effusion compared to those with ≥20%. Highest incidence of pleural effusion commonly found in group 2, wherein their hemoconcentration level fall under ≥20% classification.

Table.9. Association of presence of pleural effusion in relation with hemoconcentration levels.

| Hemoconcentration | Pleural Effusion | | | | OR | 95% CI | p value |
| | Negative | | Positive | | | | |
	Count	%	Count	%			
Not present	3	75	1	25	reference		
≥ 20%	16	19	67	81	12.56	0.90-668.83	0.0084
≥ 40%	3	19	13	82	13.00	0.64-732.89	0.0281
Total	22	21	81	78	103		

5. Association of Presence of Pleural Effusion with decreased platelet count level

Table 10 below shows 95 (46% from the total 252 chest radiograph) patients with decreased platelet count had pleural effusion.

Table 10. Association of Presence of pleural effusion with decreased platelet count

| Platelet Count Classification | Pleural Effusion | | | | OR | 95% CI | p-value |
| | Negative | | Positive | | | | |
	Count	%	Count	%			
Normal	46	98	1	2	Reference		
Decreased	110	54	95	46	39.73	5.38-293.57	0.000
Total	156	62	96	62			

From the overall patients from all age and gender, the author then divided the platelet count levels into three groups (in accordance to study done by Surangrat Pongpang et. all), as we can see in the table 12 below. According to table 11, the highest incidence of pleural effusion was

found in group III 47 (19%), wherein the platelet count level is less than 56.744/ mL. There is significant association between the presences of pleural effusion with decreased platelet count with the calculated P value less than 0.05. The Odds of decreased platelet count is likewise 39.7 times higher for having pleural effusion compared with normal group.

Table 11. Association of presence of pleural effusion with decreased platelet count level

Platelet count levels	Pleural Effusion				OR	95%CI	P value
	Negative		Positive				
	Count	%	Count	%			
NORMAL	1	2	46	98	reference		
Group I	74	74	26	26	16.16	2.41-823.6	0.000
Group II	16	42	22	58	63.25	5.48-1509.4	0.000
Group III	20	30	47	70	108.1	9.88-2642.9	0.000
Total	110	54	95	46	205(100%)		

6. **The distribution of the presence of pleural effusion on chest radiograph according to the duration of the illness**

From the total 252 chest x-ray, the average chest radiograph on dengue patients were taken on the **seventh** day from the onset of fever, with range of **fourth** to **ten** days. Among 252 dengue patient with chest radiograph, 96 (38%) of patients had pleural effusion.

The distribution of those with positive pleural effusion on their chest radiograph was 15% and 31% on day 4 and 5 after onset of fever, respectively and began to increase as of 35% on day 6th. Furthermore, the incidence of positive pleural effusion is significantly increased

about more than 50% on day 7th and 8th and decreased as it reached 9th and 10th days from the onset of fever.

Table 12. Distribution of pleural effusion in D-day

D-Day	Pleural Effusion				Total
	Negative		Positive		
	Count	%	Count	%	
Day-4	46	80	11	20	57 (100%)
Day-5	37	69	16	31	53 (100%)
Day-6	47	65	25	35	72 (100%)
Day-7	**17**	**42.5**	**23**	**57.5**	**40 (100%)**
Day-8	**6**	**27**	**16**	**73**	**22 (100%)**
Day-9	2	40	3	60	5 (100%)
Day-10	1	33	2	67	3 (100%)
Total	156	62	96	38	252 (100%)

DISCUSSION

Dengue is a flu-like illness, and occasionally develops into a potentially lethal complication called severe dengue. It became a leading cause of serious illness and death among people in several countries, especially in the Philippines. There is no specific treatment for dengue/ severe dengue, but early detection and access to proper medical care lowers fatality rates below 1%.

This study aims to determine the association between the presence of pleural effusion on chest radiograph with blood parameters (hematocrit and platelet counts) among in-patients diagnosed with dengue at the De La Salle University Medical Center from January 1, 2010 to January 1, 2015. This study also provides evidence-based information on the use of hematocrit and platelet count on predicting the presence of pleural effusion on dengue patients. This will also hopefully provide additional information for future studies on dengue timing of chest x-ray examination, therefore to minimize the radiation exposure for dengue patients, especially in the pediatric group.

In this study, the author only included 252 or ± 46% of the total admitted Dengue patient to be subjected. From 252 patients, there are 252 chest radiograph available. The mean population of age was 8 years old on pediatric group and 29 years old on adult with all population ranges from 6 month to 70 years old. In terms of gender, male (57.5%) is a little more than a woman (42%).

In 252 patients, there are 103 patients noted to have high hematocrit value, however not all patients with high hematocrit value had hemoconcentration. There are only 99 patients or about 39% from the total population that shows the presence of hemoconcentration, with most of the

patients belonging to pediatric group (63%) with female predominance. And for those people who had hemoconcentration, only 67% had pleural effusion and it belongs to group 1 (hemoconcentration level ≥20%). In this study, based on the Chi-square test, the author found a statistically significant relationship between elevated hematocrit value and decreased platelet count with the presence of pleural effusion at 95% confidence level, since the calculated p value is less than 0.05. Furthermore, the author found that the highest incidence of pleural effusion in relation with platelet count levels fall under group III, wherein the platelet counts are less than 56.744/ mL.

In terms of the radiograph distribution, among 252 chest radiograph, 96 (38%) were positive for pleural effusion, while the rest (156 (62%)) had unremarkable findings. Pleural effusion were found predominantly on the right side (53%), followed by bilateral pleural effusion (43%). It is still unclear why pleural effusion most commonly seen on the right side, however, several studies have been conducted towards the issues and revealed the same findings. Some said pleural effusion most commonly appear on the right-side in correspond with the fact that right lung has 3 lobes, while the other side has only two lobes, so thus amount of blood vessels are greater on the right side than the left. Pleural effusion is also found to be more common to develop on pediatric (84.4%) and male groups (56%).

The distribution of chest radiograph in relation with the duration of illness was described on table 11. On table 11, the distribution of those with positive pleural effusion on chest radiograph is gradually increased since day 4th to day 8th from the onset of fever then it gradually decreases after day 8th. The distribution of pleural effusion was noted for about 13%, 31%, 54% and 55% on 4th, 5th, 6th and 7th days after onset of fever, respectively with the peak incidence of about 73% seen on day 8th. Furthermore, the presence of pleural effusion is starting to decreased on 9th to 10th days

after onset of fever. The presence of pleural effusion is one of the common sign of plasma leakage which occur when endothelial cells are activated or damaged and are followed by the loss of their barrier function. There are many causes of endothelial cells activation that have been investigated in Dengue virus infection, but the exact pathogenesis has not been completely understood until now. However, a study done by Sirichan Chunhakan, et all revealed that there are many causes of plasma leakage such as decreased level of IL-1β and TNF-α interactions.

CONCLUSION AND RECOMMENDATION

In this study, Dengue patients with elevated hematocrit $\geq 40\%$ and platelet counts $< 56.744/$ mL are more likely to develop pleural effusion than those who had hemoconcentration of $\geq 20\%$ and platelet counts of $> 56.744/$ mL. This study likewise revealed that the incidence of pleural effusion gradually increased from day 4 to day 8, with the peak of incidence noted after 8th day from the onset of fever with the incidence of more than 70%. Since the chest radiograph examination is relatively cheap but useful tool to predict pleural effusion, the author hope that this data will provide new methods for DLSUMC clinicians specially pediatricians, about timing of chest x-ray examination on their dengue patients as a tool to predict the presence of pleural effusion. Also, it can hopefully minimize the unnecessary repeated radiation exposure for dengue patients, especially in the pediatric age group. However, the usefulness of physical examination in predicting the presence of pleural effusion cannot be totally ignored.

There are several limitations in this study. First, it was conducted at a single medical center and the patient population may be biased by patient selection and referral pattern. Second, this was a retrospective study, which may result to the incomplete data, causing the author to excluded a lot of number of patient in this study. Follow-up investigation or prospective study should be done.

REFERENCES

1. http://onlinelibrary.wiley.com/enhanced/doi/10.1111/j.1778-428X.2006.00025.x/

2. Oishi K, Mapua C, Carlos C, et al. Dengue and other febrile illnesses among children in the Philippines. Dengue Bulletin 2008;30

3. Su GL.Correlation of climatic factors and dengue incidence in Metro Manila, Philippines. Ambio 2008;37:292–4

4. WHO. Dengue and dengue haemorrhagic fever. Fact sheet no. 117

5. Revised Guidelines Dengue Management 2012 by Philippines Pediatric Society

6. http://www.who.int/mediacentre/factsheets/fs117/en/

7. Gubler DJ. The global emergence/resurgence of arboviral diseases as public health problems. Arch Med Res.2002;33(4):330–342. [PubMed]

8. International Travel and Health DENGUE .Geneva: World Health Organization (WHO); 2013.

9. WHO Regional Office for South-East Asia . Comprehensive Guidelines for Prevention and Control of Dengue and Dengue Haemorrhagic Fever, Revised and Expanded Edition. New Delhi: World Health Organisation South East Asia Regional Office; 2011.

10. WHO TDR Global Alert and Repsonse Dengue/Dengue Haemorrhagic Fever [webpage on the Internet] Geneva: World Health Organization (WHO); 2013..

11. Halstead SB. Etiologies of the experimental dengues of Siler and Simmons. Am J Trop Med Hyg.1974;23(5):974–982. [PubMed]

12. Wilder-Smith A, Ooi EE, Vasudevan SG, Gubler DJ. Update on dengue: epidemiology, virus evolution, antiviral drugs, and vaccine development. Curr Infect Dis Rep. 2010;12(3):157–164. [PubMed]

13. Gibbons RV, Vaughn DW. Dengue: an escalating problem. BMJ. 2002;324(7353):1563–1566.[PMC free article] [PubMed]

14. Center for Health Development-Metro Manila. Dengue Prevention and Control Program Manual of Procedures, 2009

15. Longo, Fauci, et.all. Harrisons Principles of Internal Medicine. 18th edition. McGraws-Hill's. pp.3305-3306

16. Fundamental's of diagnostic Radiology. 3rd edition. William E. Brant and Clyde A. Helms. Lippincotts William & Wilkins. pp 361-362

17. Venkata Sai, R.S. Krishnan. Role of ultrasound in dengue fever. British Journal of Radiology, 78 (929) (2005), pp. 416–418

18. Chin-Chou Wang, Chao-ChienWu, Jien-WeiLiu, An-ShenLin, Shih-FengLiu, Yu-HsiuChung, Mao-ChangSu, Ing-KitLee, and Meng-ChihLin. Chest Radiographic Presentation in Patients with Dengue Hemorrhagic Fever. Am. J. Trop. Med. Hyg., 77(2), 2007, pp. 291–296

19. Ejaz, K. Khurseed, M. and Raza, A. Pleural effusion in dengue. Saudi Med. J. (2011) 32(1), pp 46-49

20. Pongpan, S. Wisitwong, A. Tawichasri, C. and Patumanond. J. Prognosis indicators for Dengue infection severity. International Journal of Clinical Pediatric. Thailand Med. J. (2013)