



## Gastric Emptying Study With Milk: Analysis in Children of Pakistan

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### ABSTRACT

Gastro esophageal reflux (GER) is a widespread physiological phenomenon in children. In some children GER may be described as pathological and contribute to respiratory problems such as bronchial asthma and upper respiratory tract. The main objective of this study was to evaluate the presence of Gastro esophageal reflux disease (GERD) in children. Thirty children (up to 6 months of age) suspected with GERD were included in this study. The gastric emptying (SPECT) study was conducted according to predetermine protocol. All patients underwent Tc-99m DTPA gastric imaging for 30 minutes for children. The study was analyzed qualitatively i.e. visual analysis and quantitatively i.e. time activity curve (TAC) and Reflux index percentage (RI %) analysis for the presence of GER. The detection rate of GER in our study was 33% in children. This shows poor diagnoses of physicians because most of the children suffering from vomiting problems were diagnosed GERD but actually they were suffering from asthma and tonsillitis. The diagnosis and treatment of GER is mandatory in children asthma and tonsillitis. Gastric SPECT represents a significant advance in the diagnosis and quantitation of GER. It is one of the simplest radionuclide investigations which can be conducted with least patient inconvenience at a considerable low radiation burden. It can detect GERD with great accuracy even after physiologic neutral pH meal.

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## 1. Introduction

Gastro-esophageal reflux is one of the basic physiological phenomenon that is frequently observed both in children and adults on daily basis (Ayerbe, Hauser, Salvatore, & Vandenplas, 2019). The normal physiologic GER in newborns can be differentiate from diseased GER, that comprises troublesome symptoms or sever complications. GER is intensified by intake of a pure liquid diet and age related body position and the basic principal of GER is transient lower esophageal sphincter relaxation (TLESR) (Eichenwald, 2018). GER episodes are mostly occur in early infant age around 4 months and dissipate gradually as baby reach one year and it becomes pathological if continuous about 18 months of age and is known as Gastric Esophageal Reflux Disease (GERD) (Vandenplas, 2013). GERD is equally common in infants, children and adults including gastrointestinal, neurologic and respiratory systems (Ayerbe et al., 2019). Most common symptoms of GERD in infants may include feeding difficulties, vomiting, spitting, arching and cough. Typical respiratory systems associated with GERD include pneumonia, cough and asthma. Unfortunately, all these sign/symptoms are also linked with other disorders or might be found in healthy infants (Helin, 2021; Naga, 2020; Rosen, 2014; Sergi, 2020).

Chronic form of GERD is mostly associated with mucosal damage caused by stomach content coming up from stomach into esophagus (Boulton & Dettmar, 2021). Normally, lower esophageal sphincter (LES) serve as an anti-reflux obstacle and provides the protection to esophagus from the acidity of gastric content. The onset of acid reflux is involuntary relaxation of the LES, normally initiated by gastric distention after mealtimes. Acid reflux is mostly appeared when the LES pressure ranges from 1–4 mmHg of the intra-gastric pressure (Chen & Brady, 2019). The main mechanism of non-acidic or acidic reflux in healthy individuals and GERD patients is transient lower esophageal sphincter relaxation and these TLESRs are considered to play a vital role in the development of GERD and primarily initiated by gastric distention and contribute to release gas from the stomach (Singhal & Khaitan, 2014). In GERD patients, acid reflux is most commonly associated with TLESRs. GERD is equally common in infants, children and adults including gastrointestinal, neurologic and respiratory systems (Ayerbe et al., 2019). Typical respiratory systems associated with GERD include pneumonia, cough and asthma. GERD also cause arching, irritability, failure to thrive related to vomiting, anorexia, esophagitis and gastritis (Helin, 2021; Naga, 2020; Sergi, 2020).

Most babies who are taken to the general pediatrician with mild symptoms of GERD or GER do not go through any diagnostic test to prove the condition. Symptoms of GERD also confused with other gastric diseases or might be found in healthy child. It is difficult to determine the GERD from these symptoms (Rosen, 2014). Diagnostic tests are beneficial to report the existence of GERD or its associated complications, to confirm a causal link between symptoms and reflux, to determine the response of therapy and to eliminate other conditions (Li et al., 2008). Most of the time symptomatic descriptions are often subjective and unreliable in infants and the specificity of signs and symptoms linked with GERD are very low (Vandenplas, 2013).

Gastric emptying study, Single Photon Emission Computed Tomography (SPECT) is very important functional tool of the gastrointestinal tract (Kim & Kuo, 2019). The radionuclide gastro esophageal reflux study has been reported to be a sensitive, noninvasive test. According to literature the sensitivity of GER Scintigraphy ranges from 75-100% (Syvolap & Nazarenko, 2017). A nuclear (SPECT) is performed by oral ingestion or installation of technetium-labeled formula with fatty food. Hence technetium-labeled bolus are delivered into the stomach. The stomach and esophagus are then scanned for the evidence of GER and aspiration by the scintillation detector i.e. gamma camera (Mohamed, 2020). Initially esophageal study was done for half an hour in lying posture (Shibli, Skeans, Yamasaki, & Fass, 2020). SPECT was first time reported in 1966 in adults but in 1970 pediatric nuclear medicine has been recognized in North America (Mohamed, 2020). Many radionuclides have been included for SPECT study for different organs but Tc-99m used for both solid and liquid study (Vallabhajoshula, 2017). SPECT is non-invasive, convenient, physiological test and no hospital admission is required. The advantage of nuclear scan is that it can demonstrate reflux of non-gastric contents (McCullough, 2020). Hence, the main objective of this study is to evaluate the presence of GERD in children by SPECT.

## **2. Material and Methodology**

To study SPECT in different patients with different symptoms, a total of 30 children (ages up to 6 months) were included in this experiment. All the children underwent SPECT study for half an hour. After the consent of their parents, protocol which had been approved by committee of Bahawalpur Institute of Nuclear Medicine and Oncology (BINO) cancer hospital, BAHAWALPUR which is state of the art research Centre of Pakistan Atomic Energy Commission (PAEC). These patients were referred by various pediatricians and gastroenterologists.

Tc-99m as sodium pertechnetate, freshly eluted from the Tc/Mo generator was used in this study. Tc-99m DTPA which is not absorbable through gastrointestinal tract was used in a recommended dose of 2 mCi (74 MBq). Dose calibrator provided the exact value of activity in the syringe. Bottle milk mix with fat was used to feed the children

### **2.1. Imaging Device**

Single head whole body gamma camera with a rectangular large field of view, equipped with low energy general purpose, parallel whole collimator was used in SPECT gastric study. Gamma camera was attached with computer, capable of selecting area of interest and quantification.

## **2.2. Preparation of Radiopharmaceutical**

Sodium pertechnetate [Tc-99m] eluted from Mo-Tc generator was added onto lyophilized kit. The vial containing lyophilized freeze-dried form, was placed in a shielded container and reconstituted under strict aseptic conditions with elute. Reconstituted vial was shaken for 10-15 seconds for complete dissolution of the powder. Dose of radiopharmaceutical, given to the patient after mixing with meal (solid, liquid or milk) in 2 ml of normal saline in hot lab.

## **2.3. Quality Control of Radiopharmaceutical and Gamma Camera**

For quality control of phytatekit, the sealing condition of the kit as well as the color and the physical state of phytate kit ingredients were noted. The Tc-99m generator was eluted and the activity (mCi/ml) of Tc-99m was measured using radioisotope dose calibrator in hot lab.

For uniformity quality control (QC) was done. Daily QC was done with 10 million counts, differential as well as integral were calculated. The values of differential as well as integral were always within normal limits I.e. less than 3%.weekly QC was done with 30 million counts. These shows the values are in normal limits i. e less than 10%.Each image was corrected for uniformity with image obtained daily from Tc-99m flood source.

## **2.4. Acquisition Protocol**

Dynamic acquisition was performed by large field of view gamma camera (E-CAM) equipped with low energy general purpose collimator, connected to computer system. A symmetric 20% energy window centered over the 140 Key photo peak of Tc-99m is used for GER study.

## **2.5. Patient Preparation**

All the Procedure was explained to the parents of the children. Children were kept hungry for 2 hours prior to the procedure and all gastrointestinal medications were withdrawn for 48 hours before starting study.

## **2.6. Patient Positioning**

The gastric SPECT study was acquired in an upright comfortable position in the lateral projection. After burping, the child was positioned supine near top of the detector for half an hour and adults for 2 hours' dynamic study.

## **2.7. GER Scintigraphy (SPECT) and Image Acquisition Parameters**

In gastric emptying SPECT study radiopharmaceutical was administered orally according to the prescribed dose in small volume 2ml of normal saline and immediately scan was acquired in upright posture. The dynamic sequential imaging is done in frame mode in a total of 100 frames, time per frame being 5 seconds.

## **2.8. Qualitative Analysis of Gastro Esophageal Reflux**

Computer generated images were reviewed with image intensity was maximized. To detect subtle findings. Films were studied and reflux is divided into 3 grades, mild reflux (less than 10 frames), moderate flux (more than 10 frames) and gross reflux (frames of entire length).

## 2.9. Time Activity Curve (TAC) Analysis

TAC is generated from region of interest (ROI) drawn over the upper portion of esophagus. This region was easily defined when abnormal activity was seen in the esophagus below 35%.

## 2.10. Reflux Index Percentage Analysis

Reflux index percentage (RI %) was calculated using the following formula

$$\text{Reflux index (\%)} = \left[ \frac{\text{Maximum esophageal counts} - \text{background counts}}{\text{Gastric counts at beginning of study}} \right] \times 100 \quad (1)$$

Reflux index more than 4% was taken as positive while the value below 4% was considered as negative for GER. Region of interest (ROI) were also drawn over esophagus areas of various frames showing GER and their counts were also calculated. The frames showing maximum counts in esophageal region were selected and its value was used in the above formula.

## 2.11. Statistical Analysis

Different statistical test were used to compare and correlate the data. Chi-square test was applied to find correlations between visual, TAC and RI% analysis and GER scintigraphy and p values were determined to find the significance of results. The calculated value of this test is compared to 0.05 values to find the credibility of results.

## 3. Results

Total 30 children (male and female babies) up to six month of age, suffering from upper respiratory tract include immediate vomiting after feed. GERD was diagnosed in all patients' referred by physicians for the confirmation of disease. All data of 30 children along with duration of symptoms is shown table 1.

### 3.1. Gastric Emptying (SPECT) Study

Gastric emptying (SPECT) was analyzed qualitatively (visual analysis) as well as quantitatively (TAC and RI%). In our study the maximum age of children was up to six months. During the study, we found 10 (33%) children out of 30 were suffering from GERD. These results are shown in table. All data is summarized in table 3.

### 3.2. Correlation between Visual and TAC Analysis

In this study we found that in 10 (33%) patients both visual analysis and TAC analysis were positive while in 20 (67%) patients both the tests were negative. So, in 67% patients GERD was not confirmed.

### 3.3. Statistical Analysis of Correlation between Visual and TAC Analysis

The calculated value of Chi-Square for the correlation between visual analysis and TAC analysis was 1.77. For one degree of freedom and at p value equals to 0.05. The tabulated Chi-statistic is 3.84. Hence our calculated Chi-square value was smaller than the tabulated value so we accepted our null hypothesis i.e. there is no correlation between visual and TAC analysis, at the level of 0.05 significance. We can even accept our null hypothesis at 0.01 level of significance as 1.77 (calculated chi square value) is smaller than 6.635 (tabulated chi square value for one degree of freedom at p value equals to 0.01). So no correlation is present between visual and TAC analysis.

### 3.4. Correlation between Visual and RI% Analysis

It was found that in 10% patients, reflux was found to be present visually and this finding was supported by RI% values as in these patients the values of RI% were above 4%. In 20 % patients reflux could not be detected visually and this fact was supported by values of RI% which were below 4%. So in 67% patients GERD was not confirmed.

### 3.5. Statistical Analysis of Correlation between Visual and RI% Analysis

The calculated value of Chi-Square for the correlation between visual analysis and RI% is 5.347. For one degree of freedom and at p value equals to 0.05 the tabulated Chi-statistic is 3.84. So our calculated Chi-square value is bigger than the tabulated value so we reject our null hypothesis i.e. there is no correlation between the results of visual analysis and RI%, at the level of 0.05 significance. Hence correlation is present between visual and RI% analysis. All statistical data is summarized in table 4.

Results of some abnormal and normal patients through TAC, Visual analysis between different region ratios and RI%.

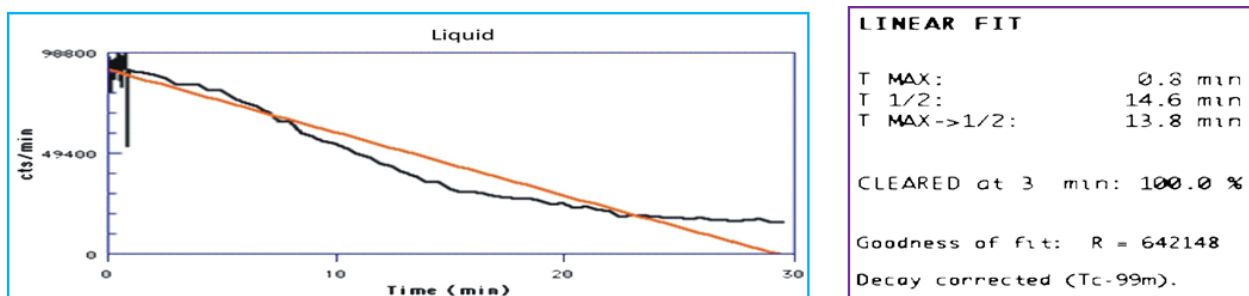


Figure 1: Shows Normal TAC (Time Activity Curve) analysis with milk

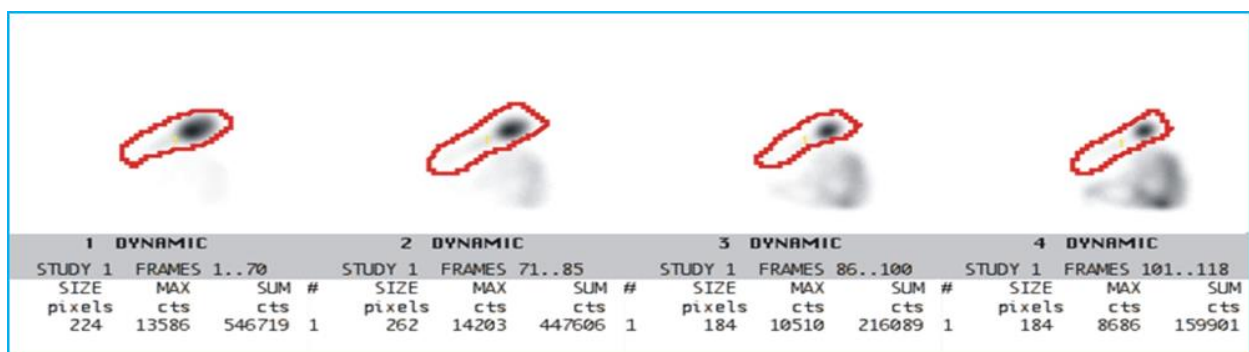


Figure 2: Shows radioactive counts in upper region of esophagus in different frames [visual Normal]

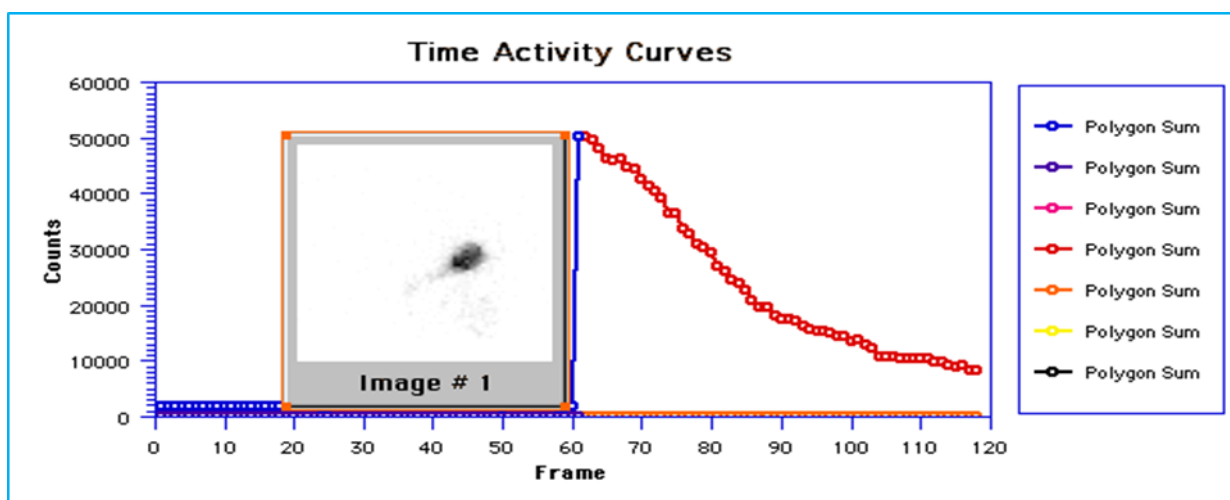


Figure 3: Shows Normal [TAC]

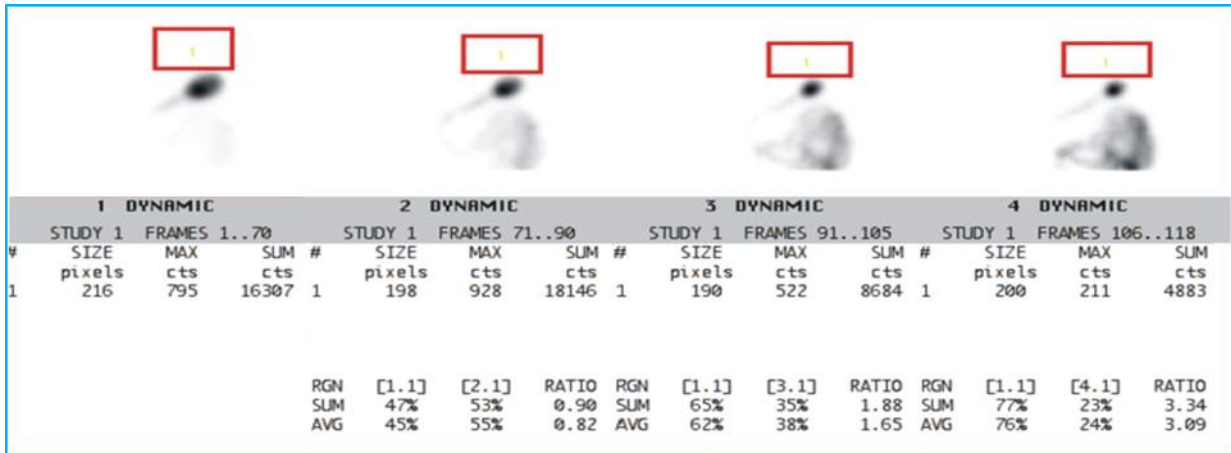


Figure 4: Shows Nuclear counts between different upper regions of normal patient [visual]

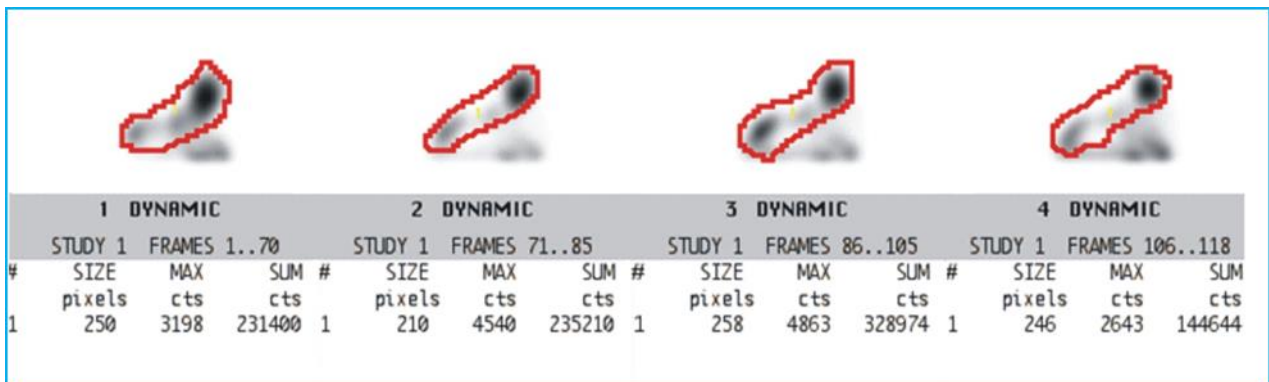


Figure 5: Shows counts in different region of abnormal study [visual analysis]

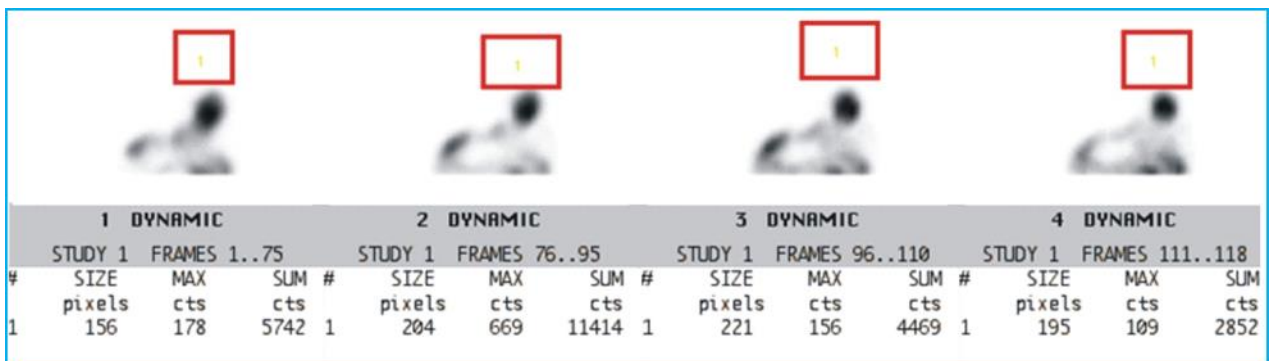


Figure 6: Shows abnormal study [visual]

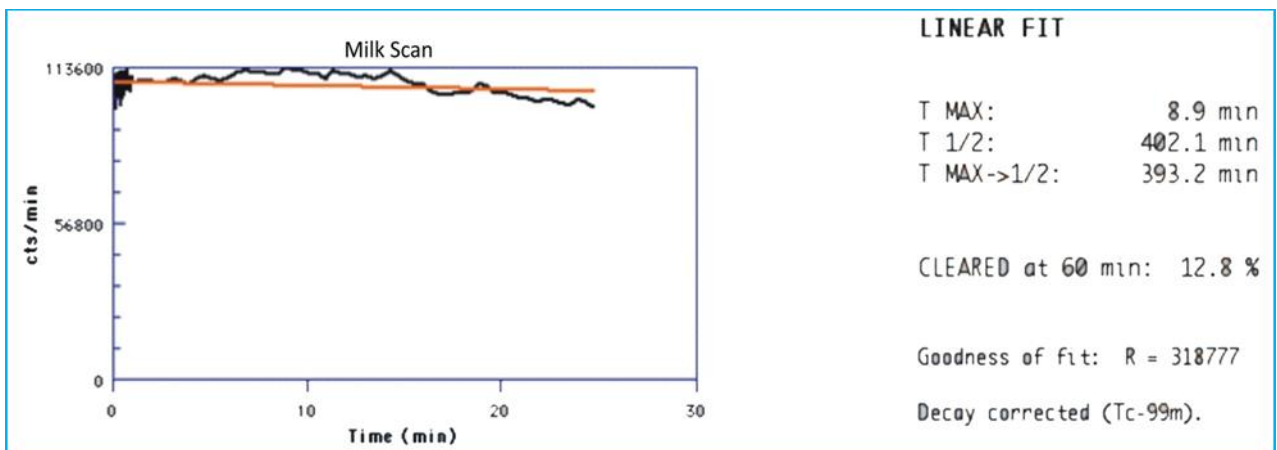


Figure 7: Shows Abnormal milk study [TAC]

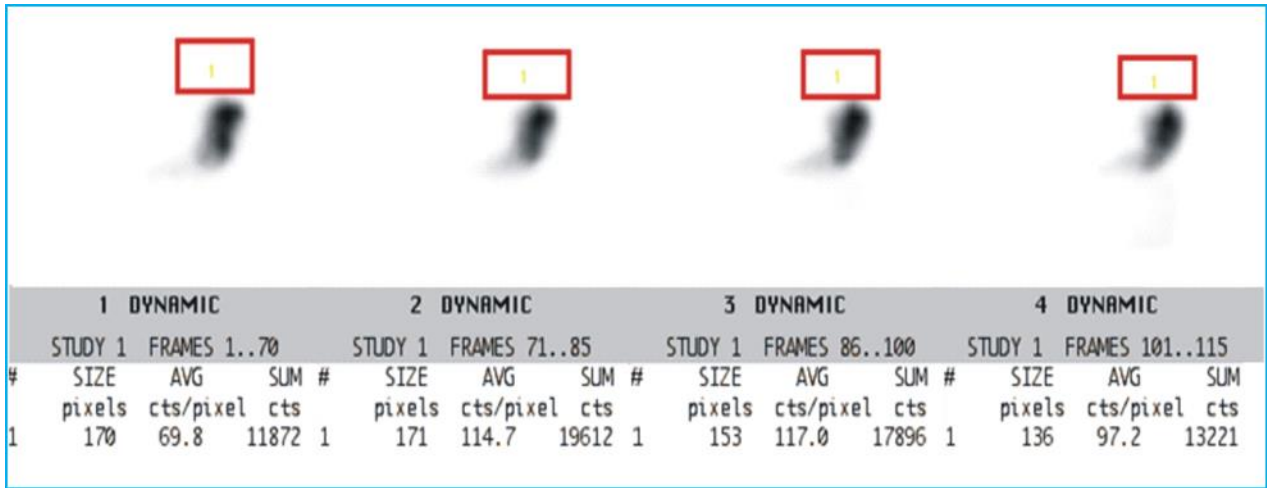


Figure 8: Shows abnormal study [visual analysis]

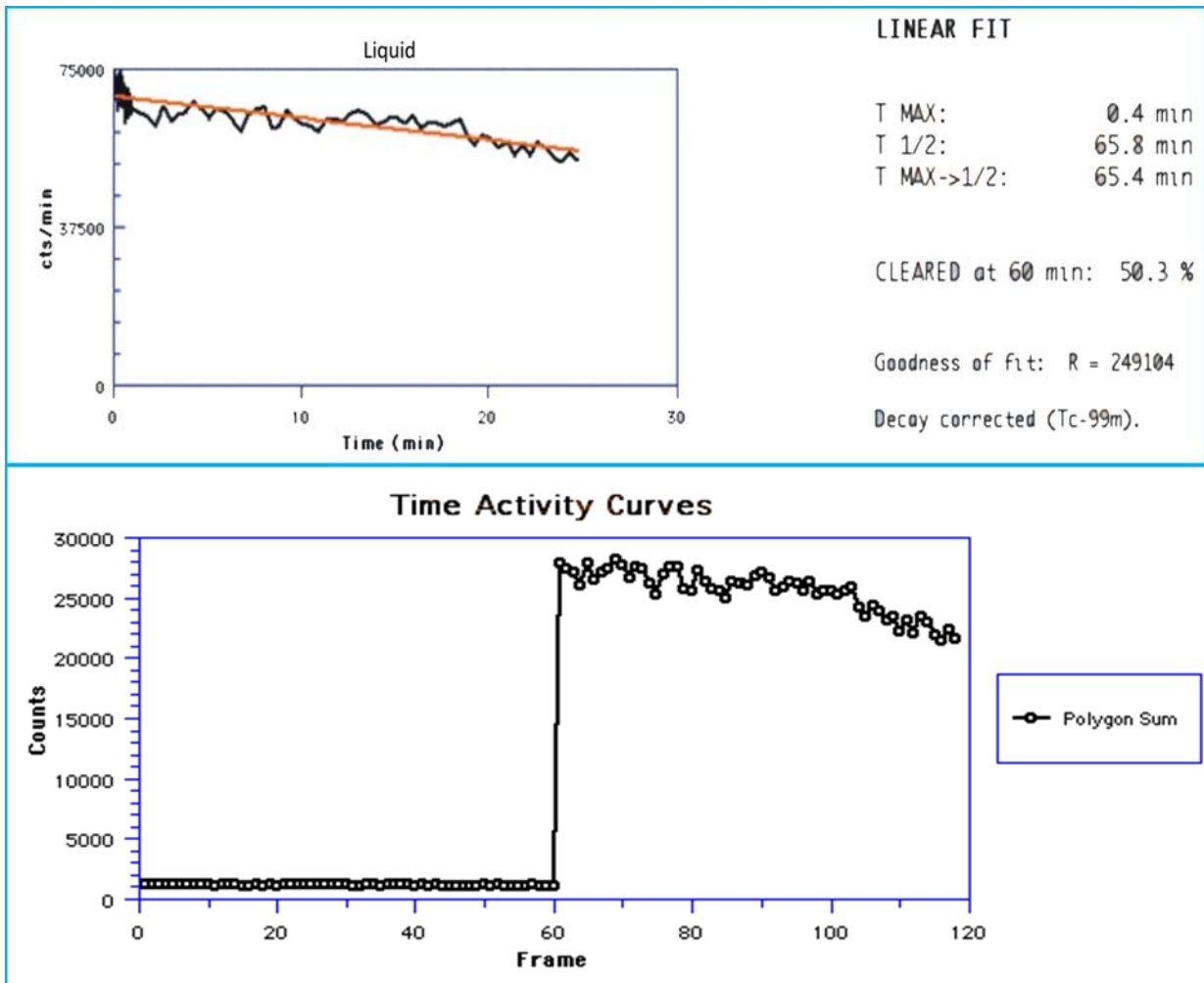


Figure 9: Shows poor milk study [TAC]

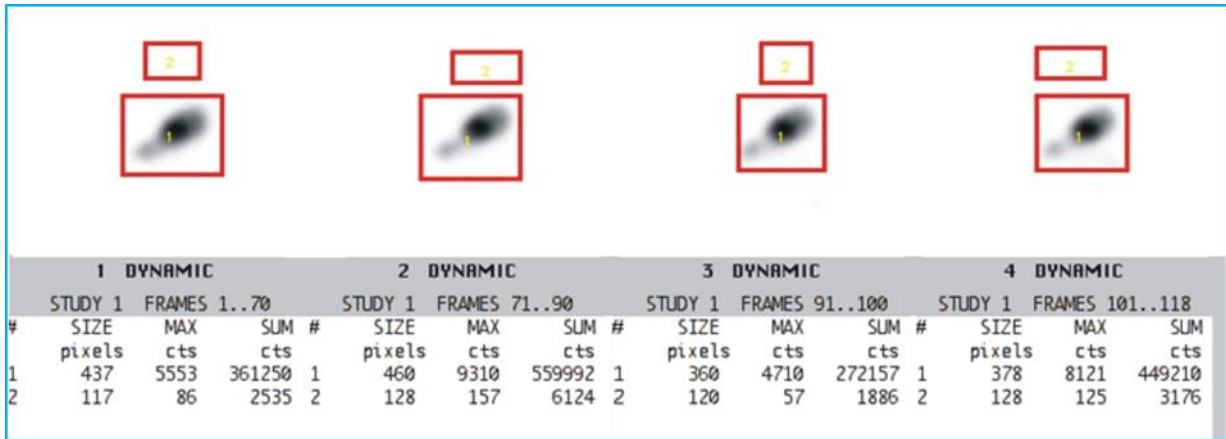


Figure 10: Shows poor study [visual]

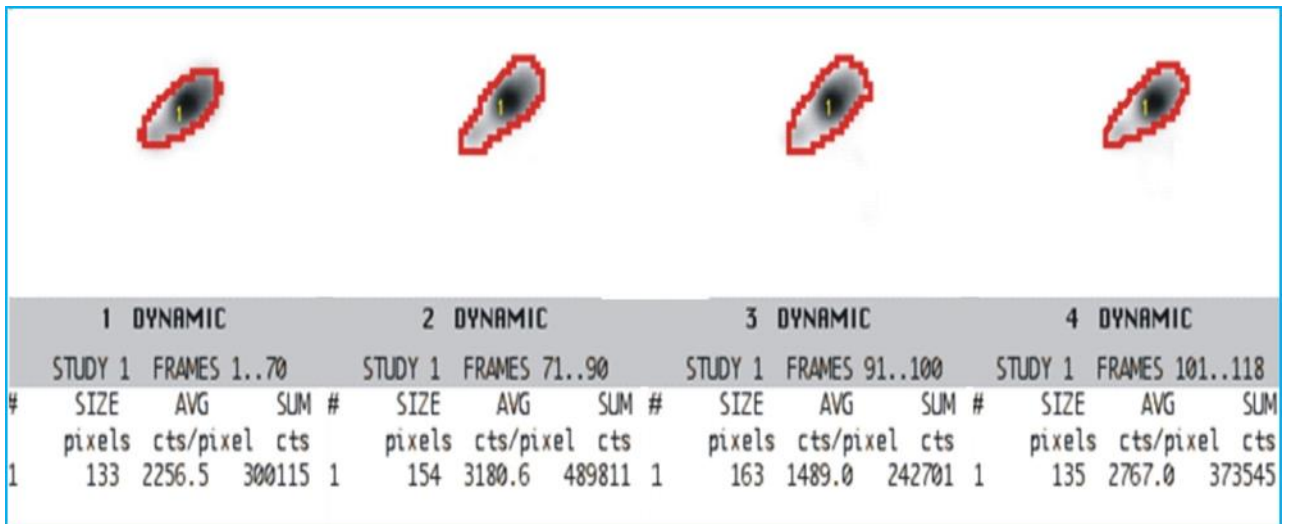


Figure 11: Shows poor study [visual]

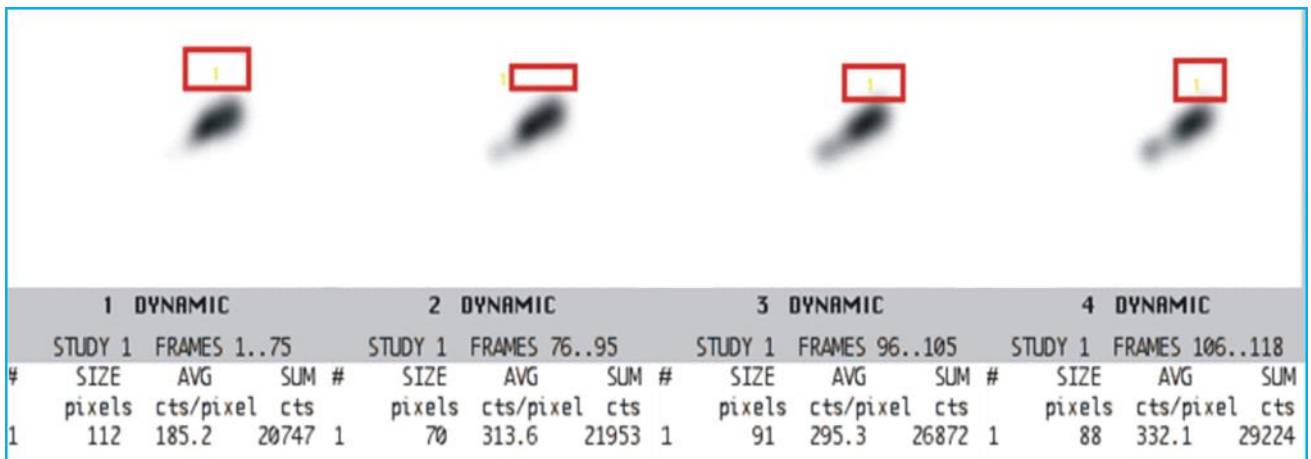


Figure 12: Shows abnormal child study [visual]



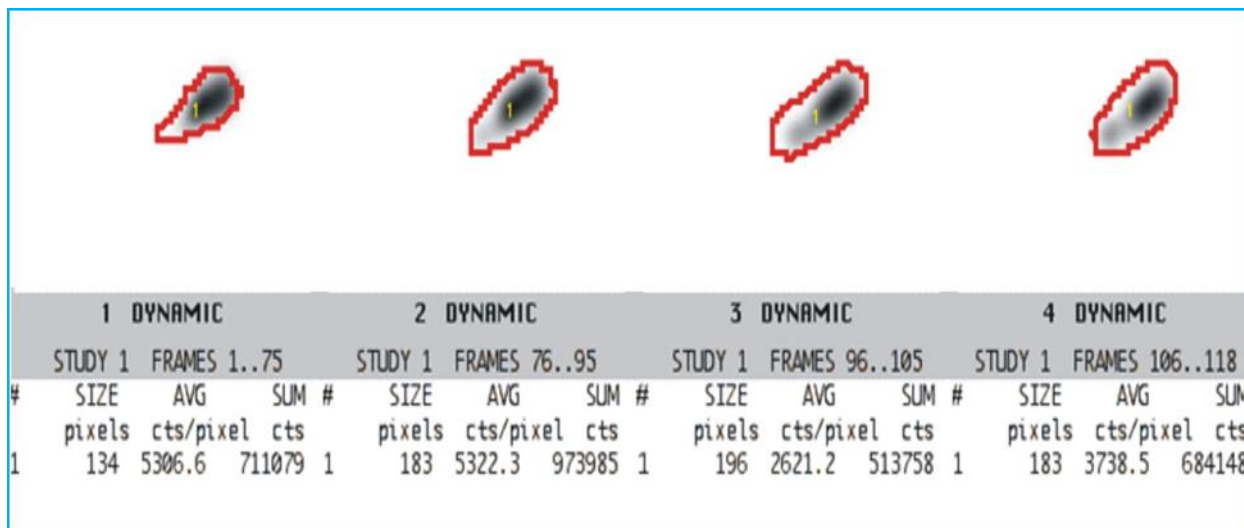


Figure 13: Shows abnormal study [visual]

#### 4. Discussion

GER is common physiological phenomenon in neonates, infants, children and adults. It is most frequently seen postprandial. GER normally appears by the age of 2 months (Haber & Lopez, 1999; Piepsz, 1995). In most of the children this process is self-controlled comes to an end by the end of infancy. GER prevalence in different age groups varies and reported spontaneously at the age of 12-18 month in 55-90 % patients, (Gilger, 2003; Haber & Lopez, 1999; Piepsz, 1995). In the majority of the patients GER is harmless and self-limiting and considered as physiological phenomenon rather than disease. Only a small proportion of these, suffer complication which, by implication, render the gastro esophageal reflux pathological (Zeevenhooven, Koppen, & Benninga, 2017).

The spectrum of problems caused by GERD has expanded in the last decade far beyond the traditional heart burn, a concept of a generation ago (Quigley, 2007). In recent years the concept of GERD has been broadened to include not only the effects of GER on esophageal mucosa but also the role of acid in reflux in laryngeal and pulmonary symptoms (Quigley, 2007; Zeevenhooven et al., 2017). The manifestations of pathological GER are diverse and may involve gastrointestinal, respiratory, and neuro-behavioral symptoms (Czinn & Blanchard, 2013; Fouad, Katz, Hatlebakk, & Castell, 1999; Piepsz, 1995). GERD has been implicated as a cause of recurrent respiratory infection i.e. pneumonia, asthma cough and vomiting (Caglar, Volkan, & Alpar, 2003).

Carre stated in his study that 1 in 500 infants requiring hospital consultations suffer from GER and in the absence of treatment 10% of children developed complications (Ehsan, Ahmad, Qadeer, Abdullah, & Ayesha, 2010; Rudolph et al., 2001). Hence GERD is common and recurrent problem and deserve effective therapy and care to improve quality of life (Thrall & Zeisman, 2001). It is now well recognized that vomiting is not necessarily present in severe GER, this symptoms may even be completely missing in recurrent lung infection directly related to GER (Ehsan et al., 2010). It is mandatory to investigate a possible GERD in case of chronic or recurrent lung pathology without any other clear explanation. Awareness of non-gastro esophageal symptoms and high index of suspicion when they are present may allow timely identification and formulation of treatment strategy (Falk et al., 2015). The study of this relationship still is an area of active research.

GER scintigraphy study was analyzed qualitatively (visual) as well as quantitatively (TAC and RI %). The final results were made after taking into account all these three factors. In our study 22(20%) patients out of 60 showed reflux, while 48(80%) showed no reflux. GER was observed in all age groups and there was no evidence of particular sex preponderance. (Bar-Sever, 2017; Deeb, Al-Hakeem, & Dib, 2010; Ehsan et al., 2010; Katz, Gerson, & Vela, 2013; Rubenstein & Chen, 2014; Tsoukali & Sifrim, 2013). It was reported in the literature that 38%-51% of the patients having positive GER are suffering from recurrent respiratory tract infections, while 40%-50% of GER positive patients are asthmatics and suffering from acidic peptic disease (Kling, 2012; Tsoukali & Sifrim, 2013).

Our findings are similar to previously reported incidence of GER in such patients. Slight variation from individual studies do exist due to many reasons explained below.

Patient having severe and difficult to control asthma/respiratory manifestations show high prevalence of GER compared to the patients which respiratory symptoms are well controlled (Ehsan et al., 2010; Patra, Singh, Chandra, Kumar, & Tripathi, 2011; Thakkar, Boatright, Gilger, & El-Serag, 2010). Severity of the upper respiratory tract infection has also been compared with degree of reflux (Patra et al., 2011).

It is documented in the literature that 22-25 % of reflux may be missed by limiting the study to 30 minutes in children (Caglar et al., 2003; S Heyman, 1997; Manini, Camilleri, Grothe, & Di Lorenzo, 2018). So if study is limited to 30 minutes (children), the prevalence of GER may be decreased. One-hour acquisition of images along with rapid frames of shorter duration i.e. 61sec/frame, can increase the detection rate of GER (Caglar et al., 2003; Sydney Heyman, 1995; S Heyman, 1997; Manini et al., 2018). Our dynamic acquisition time was 30 minutes due to difficulty in implying one-hour acquisition protocol.

From this study we observed that on the basis of visual analysis 22 (40%) patients out of 60 (60%) were found to have reflux. There were 12 (21.81%) patients in which GER was positive visually but negative on TAC analysis Chi square statistics shows that no correlation is present between visual and TAC analysis.

TAC is very good quantitative method for verification of visual analysis. By seeing the TAC graph one can immediately find the abnormal frame which then can be viewed in detail later 61. In various studies on GER scintigraphic, TAC analysis was also done along with visual analysis (Bestetti, Carola, Carnevali-Ricci, Sambataro, & Tarolo, 2000; Caglar et al., 2003; Orenstein, Klein, & Rosenthal, 1993; Piepsz, 1995). Utilization of scintigraphic time activity curves has been proposed by Heyman et al (Bestetti et al., 2000). According to Caglar M et al scintigraphic reflux event is defined as peaks which displays a 2 fold or more increment in esophageal counts over the base line and this peak coincided with the point where the GER is visible using quantitation technique (Contran, Kumar, & Robbins, 1994). In our study the results of visual and TAC analysis tally with each other fulfilling the definition of Caglar M et al (Caglar et al., 2003).

TAC analysis proves very useful against visual analysis for detection of presence of minimal refluxes, in the presence of gastric scatter as it is very difficult to distinguish distal esophageal reflux from gastric scatter (Caglar et al., 2003).

Hence it is concluded that TAC is a very sensitive and valuable supplementary way to analyze presence, duration of reflux episode and its esophageal clearance. Visual images integrate all esophageal activity during the given frame period while TAC displays continuous value of esophageal counts at any given movement (Caglar et al., 2003). TAC is simple to use and more objective than the images, provided motion artifact is ruled out. So it is concluded that the use of curve is potentially inaccurate in infants and children who are difficult to keep still for half an hour during GER study. Hence image is probably more appropriate than curves to use in case of young children (Orenstein et al., 1993). In conclusion visual and TAC analysis can detect GER and the most useful when used in combination as also concluded by Ciglar M et al (Orenstein et al., 1993).

## **5. Conclusion**

Single Photon Emission Computed Tomography is the versatile and state of the art technique to explain the percentage function of any organ of human body. It helps the medical professional for the proper treatment of the patients. SPECT also explain the peacefully purposes of an atom and radioactivity for the betterment of mankind. SPECT is able to explain the working ability of any organ e.g. heart, stomach, bones, kidneys, thyroid uptake, brain, liver, lungs, breasts cancer and even severe infections.

SPECT also explain the use of different radioactive isotopes for imaging different organs. During the study, it uses every small amount of radioactivity because safety from radiation exposure is important.

Gastric SPEC represents a significant advance in the diagnosis and quantitation of GER. It is one of the simplest radionuclide investigations which can be conducted with least patient inconvenience at a considerable low radiation burden. It can detect GERD with great accuracy even after physiologic neutral pH meal. This can be used for determination of gastric emptying and detection of aspiration. Its disadvantages include its insensitivity for late postprandial reflux and the requirement for immobilization for half an hour and 2 hours. Each GER scan was assessed by visual, TAC and RI% analysis GER was diagnosed by this technique was present in 40% of patient. This appears to be a remarkably low incidence of GER. This also helps the medical professional for poor diagnostic of GERD that is actually not GERD every time further studies are required to confirm the present observations. At follow up after 3 months of anti-reflux treatment, the clinical condition of majority of the patients improved, validating the initial diagnosis of GERD and proving that GER is amenable to treatment. The incidence of heart burn and asthma can be reduced by treating GER, helping to reduce cost of health care of these patients. This study proves to be a very beneficial as far as the diagnosis and management of patients suffering from heartburn asthma, lower and upper respiratory tract infections are concerned.

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