Open Access Maced J Med Sci **electronic publication ahead of print, published on December 14, 2019 as https://doi.org/10.3889/oamjms.2019.592**

ID Design Press, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences.
https://doi.org/10.3889/oamjms.2019.592
eISSN: 1857-9655
Clinical Science

Vitamin D Status in Neonatal Pulmonary Infections: Relationship to Inflammatory Indicators

Ghada M. El-Kassas[1], Maged A. El Wakeel[1], Mona A. Elabd[1*], Alyaa H. Kamhawy[1], Mohamed Abdel Atti[1], Shereen A. Abd El-Gaffar[2], Salwa Kamal Hanafy[3], Eman Awadallah[4]

[1]Child Health Department, Medical Division, National Research Centre, Cairo, Egypt; [2]Pediatric Department, Banha Teaching Hospital, Banha, Egypt; [3]Neonatal Intensive Care Unit, El-Galaa Maternity Teaching Hospital, Cairo, Egypt; [4]Department of Clinical and Chemical Pathology, National Research Centre, Cairo, Egypt

Citation: El-Kassas GM, El Wakeel MA, Elabd MA, Kamhawy AH, Atti MA, El-Gaffar SAA, Hanafy SK, Awadallah E. Vitamin D Status in Neonatal Pulmonary Infections: Relationship to Inflammatory Indicators. Open Access Maced J Med Sci. https://doi.org/10.3889/oamjms.2019.592

Keywords: Vitamin D; Pneumonia; Neonates; Pentraxin 3

***Correspondence:** Mona A. Elabd. Child Health Department, Medical Division, National Research Centre, Cairo, Egypt. E-mail: mona_elabd@yahoo.com

Received: 05-Nov-2019; **Revised:** 03-Dec-2019; **Accepted:** 04-Dec-2019; **Online first:** 14-Dec-2019

Funding: This research did not receive any financial support

Competing Interests: The authors have declared that no competing interests exist

Abstract

AIM: The study aimed to evaluate serum vitamin D concentrations among neonates with pneumonia.

METHODS: This case-control study enrolled 33 neonates with pneumonia in addition to 30 healthy controls. CBC, CRP, Serum vitamin D and Pentraxin 3 levels were measured for all participants.

RESULTS: There was significant difference between patients and controls regarding Hemoglobin levels, TLC and CRP (p value < 0.01, = 0.002, < 0.01 respectively). Patients with pneumonia showed significant lower levels of Vit. D (9 ± 2.1) compared to controls (14.1 ± 2.8), P value < 0.01. However, patient group had significant higher levels of Pentraxin 3 (29.1 ± 4.8) compared with controls (12.6 ± 3), P value < 0.01. Moreover, mechanically ventilated patients revealed significant lower vit D (7.7 ± 1.8) and higher pentraxin 3 (32.2 ± 2.6) compared to patients on free oxygen (9.1 ± 2.1, 26.4 ± 3.7 respectively), P value = 0.05, 0.02 respectively. Regarding hospital stay, it had significant positive correlation with serum pentraxin 3 (r = 0.6, P value < 0.01) and significant negative correlation with serum vit D (r = -0.4, P value = 0.04). Finally a significant negative correlation between serum levels of vitamin D and Pentraxin 3 was found (r = -0.4, P value = 0.01).

CONCLUSION: Lower concentration of serum vitamin D may be significantly associated with neonatal pneumonia. It also can predict the need for mechanical ventilation and duration of hospital stay in neonatal pneumonia. Similarly, higher levels of Pentraxin 3 may be used as an indicator for mechanical ventilation need and a longer hospital stay in neonates with pneumonia.

Introduction

Pneumonia is broadly defined as lung inflammation induced by an infectious agent who stimulates a response resulting in lung tissue damage [1]. Globally pneumonia accounts for nearly one in five deaths among children > 5 years of age [2]. Etiological factors for pneumonia vary according to age, source of infection (community or hospital-acquired pneumonia) and underlying host defects as immunodeficiency [3]. In neonatal periods, the underdeveloped immune system predisposes newborns, especially preterm to pulmonary infections, which is a major cause of death [4].

Vitamin D is a steroid hormone that has a great role in calcium and phosphorus homeostasis, bone metabolism and bone development [5], [6]. Recently the role of vitamin D on glucose homeostasis, cardiovascular diseases, immune system and cancer has been reported [7], [8].

In adults, deficiency of vitamin D is associated with higher risks for many cancers, diabetes mellitus (DM), rheumatoid arthritis and multiple sclerosis [9]. In children and infants, Vitamin D insufficiency was reported to be associated with type 1 DM, allergies and atopic diseases (10). Also, children who manifested vitamin D deficiency as rickets were reported to have pneumonia [11].

Indeed, multiple reports suggested the vital role of vitamin D in immune system function and regulation since 1, 25 dihydroxy vitamin D can promote the innate immature response to the

pathogen [12]. Besides, multiple studies have identified an association of respiratory infectious disease and inadequate serum vitamin D in non-rachitic children [13], [14]. Biomarkers, applied in synergy with clinical signs and symptoms of pneumonia may provide extra data on disease severity and the differentiation between bacterial and viral aetiology [15], [16]. Pentraxin 3 is known as an acute-phase mediator that rapidly increases in inflammatory and infectious disorders [17], [18].

However, few studies regarding this link among neonates have been found. Given that this study was designed to evaluate the serum level of 25 hydroxy-vitamin D in neonates with pneumonia and to assess its correlation with serum levels of Pentraxin 3 as a mediator of acute inflammation.

Subjects and Methods

Thirty-three neonates diagnosed to have late-onset pneumonia were recruited from NICU in El Galaa Teaching Hospital.30 healthy neonates of matched age and sex were enrolled as a control group. Parental written informed consent was obtained from all study participants and the study was approved by the medical ethical committee of the National Research Center, Cairo, Egypt.

The inclusion criteria were as follows: age between day one and one month, clinical signs suggestive of pneumonia such as tachypnea, abnormal breath sounds, and radiological confirmation of pneumonia according to the WHO criteria for the standardised interpretation of pediatric chest radiographs for pneumonia diagnosis. Infants with underlying chronic respiratory disease were excluded from this study.

All participants were subjected to full history taking and full clinical examination. Culture and sensitivity test was done to confirm the aetiology whether bacterial or nonbacterial pneumonia. Venous blood samples (3 cm) were taken from each infant participating in the study and were divided into two aliquots. The first aliquot 1 ml of venous blood was used for determination of CBC. The second aliquot 2ml of venous blood was left to clot, and then the serum was separated by centrifugation and stored at −20°C for detection of serum vitamin D, Pentraxin 3 and CRP levels.

Statistical analysis

Analysis of data was performed by using Statistical Package for the Social Science SPSS version 16.G. Data were presented as a mean and standard deviation. Chi-square test was conducted for detecting the significant difference in the distribution between categorical variables at P-value < 0.05. Continuous variables were compared by t-test (for normally distributed data). Spearman correlation was used to assess the correlations between non-normally distributed qualitative variables.

Results

The study group comprised 33 neonates with pneumonia aged 24.8 ± 4.6 days. They were 12 (36.4%) males and 21 (63.6%) females. The mean of their gestational age was 37.5 ± 1.8 weeks and 11 of them (33.3%) delivered normally and 22 (66.7%) by caesarian section (CS). The study also included 30 controls matched for age and sex with the patient group as delineated in Table 1. Regarding blood culture of cases, 22 neonates had positive blood cultures for bacteria: *Staphylococcus aureus* (30%), *Klebsiella pneumonia* (25%), *Pseudomonas* (20%), *Acinetobacter* (15%), *E. coli* (10%).

When it comes to laboratory findings of both patient and control group, haemoglobin levels were significantly lower while TLC and CRP levels were higher in cases in comparison to controls. Patients with pneumonia also showed significantly lower levels of vitamin D compared to controls; however, the patient group had significantly higher levels of Pentraxin 3 compared to controls, (Table 1).

Table 1: Demographic and laboratory data of the studied groups

Descriptive data Items	Cases n = 33 (Mean ± SD) (Range) n (%)	Control n = 30 (Mean ± SD) (Range) n (%)	Statistical test	P-value
Gestational age (Wks)	37.5 ± 1.8	37.7 ± 1.1	*t* = -0.5	0.6
Age (days)	24.8 ± 4..6	26.1 ± 6.1	*t* = -0.7	0.5
Mode of delivery				
NVD	11 (33.3%)	10 (33.3%)	$\chi^2 = 0$	1.0
CS	22 (66.7%)	20 (66.7%)		
Sex				
Male	12 (36.4%)	14 (46.7%)	$\chi^2 = 0.7$	0.4
Female	21 (63.6%)	16 (53.3%)		
Hemoglobin (g/dl)	9.8 ± 1.4	13.3 ± 1.8	*t* = 4.2	< 0.01*
TLC (× 10^9/L)	12.2 ± 3.5	6.9 ± 1.6	*t* = 3.3	0.002*
Serum CRP (mg/dl)	29.7 ± 4.2	4.1 ± 1.0	*t* = 5.1	< 0.01*
Serum 25 (OH) D (µg/L)	9 ± 2.1	14.1 ± 2.8	*t* = -8	< 0.01*
Serum Pentraxin3 (µg/L)	29.1 ± 4.8	12.6 ± 3	*t* = 3.7	< 0.01*

*(P ≤ 0.05) is significant.

According to Table 2, mechanically ventilated patients revealed significantly lower vitamin D and higher pentraxin 3 compared to free oxygen patients.

Table 2: Comparison between serum vitamin D and Pentraxin3 in mechanically ventilated patients and patients on free oxygen

Variable	Mechanically ventilated patients N = 14 (Mean ± SD)	Patients on free oxygen N = 19 (Mean ± SD)	P-value
Serum 25 (OH) D (µg/L)	7.7 ± 1.8	9.1 ± 2.1	0.05*
Serum Pentraxin3 (µg/L)	32.2 ± 2.6	26.4 ± 3.7	0.02*

*(P ≤ 0.05) is significant.

Regarding hospital stay, it had significant negative correlation with serum vit D (r = -0.4, P value = 0.04) and significant positive correlation with serum pentraxin 3 (r = 0.6, P value < 0.01) and as delineated in Figure 1 (top), (middle) respectively. Finally a significant negative correlation between serum Vitamin D and Pentraxin 3 was found (r = -0.4, P value = 0.01) (Figure1: bottom).

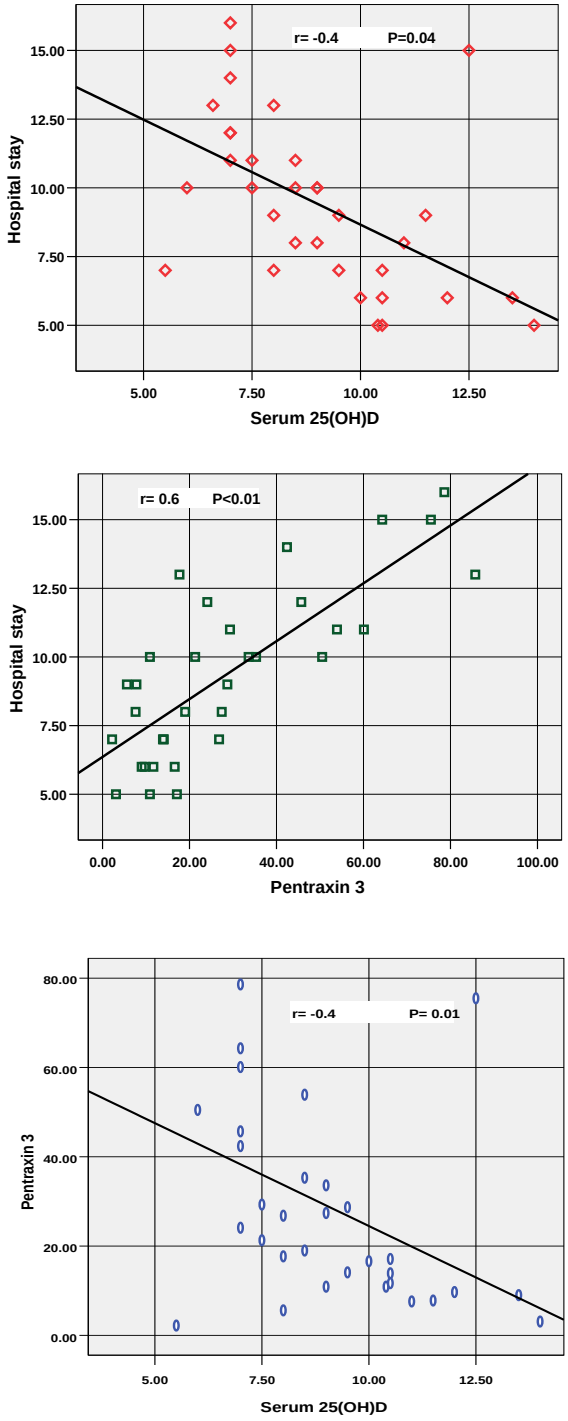

Figure 1: Correlation between serum vitamin D and a hospital stay of neonates with pneumonia (top); Correlation between serum Pentraxin 3 and hospital stay of neonates with pneumonia (middle); Correlation between serum vitamin D and Pentraxin 3 (bottom)

Discussion

The current case-control study aimed to study vitamin D in neonates with pneumonia, and the results showed that serum vitamin D was significantly lower among patients with pneumonia compared to controls and in patients on mechanical ventilation compared to patients on free oxygen. Also, serum vitamin D was negatively correlated with the duration of hospital stay. Similarly, (Lezhenko et al., 2016) reported that children at an early age with low levels of vitamin D are at risk for pneumonia since significant lower concentrations of 25-hydroxyvitamin D were detected in children with community-acquired pneumonia compared with healthy controls [19]. (Dinlen et al., 2016) Also assessed serum 25 (OH) D levels in newborns with pneumonia and their mothers and observed a lower concentration compared to healthy newborns and their mothers [20]. In the same point of view (Mohamed and Al-Shehri, 2013) tested cord blood of 206 newborns for 25 (OH) D and reviewed their medical records during the early 2 years of life and noticed that lower level of 25 (OH) D in cord blood was associated with higher risk for acute lower respiratory tract infection (LRTI) in early life [21]. Indeed, deficiency of vitamin D in pregnant women has been reported to rise respiratory tract infection risk in their offspring as vitamin D can modulate the expression of specific tolerogenic genes during pregnancy that related to diseases other than congenital rickets [22], [23].

The current hypothesis of lower vitamin D is a risk factor for neonatal pneumonia, and its poor prognosis can also be confirmed by the meta-analysis of (Charan et al., 2012) which showed that Vitamin D supplementation could decrease the events related to respiratory tract infections [24]. Besides the systematic review of (Christensen et al., 2017) reported that supplementation of vitamin D during pregnancy could prevent respiratory tract infection of offspring [25]. A more recent systematic review and meta-analysis of (Jat, 2017)showed a significant correlation between vitamin D concentrations and both the incidence and severity of LRTI [26].

In contrast to the current findings, (McNally et al., 2009) did not observe a difference in vitamin D levels between the children with LRTI and controls but vitamin D deficiency was noticed to be significantly associated with admission to the pediatric ICU [27].

Regarding pentraxin 3, it was significantly elevated in patients with pneumonia compared with controls and in mechanically ventilated patients compared to free oxygen ones. Moreover, it was positively correlated with the duration of hospital stay. Similarly, (Tekerek et al., 2018) detected higher levels of Pentraxin 3 among patients with ventilator-associated pneumonia (VAP) compared to controls. [28]. By the same way, (Lin et al., 2013) reported that pentraxin 3 is a biomarker for VAP that correlated with

sepsis severity and was an independent predictor for VAP mortality by multivariate Cox regression analysis [29].

Finally, the present study was able to delineate a significant negative correlation between serum vitamin D and serum Pentraxin 3. Pentraxin 3 is known as an inflammatory biomarker that can be easily used to assess the severity of lung injury [30], [31] and this noticed correlation can confirm the role of vitamin D in neonatal pneumonia.

In conclusion, from the above results, it is now clear that inadequate concentrations of vitamin D in neonates may be associated with higher risks for pneumonia. Also, lowers levels can be a predisposing factor for the need for mechanical ventilation and longer hospital stay. So we can conclude that maternal prenatal/postpartum vitamin D supplementation may be a feasible primary preventive strategy to reduce pulmonary infections in the neonatal period.

Acknowledgement

The authors are grateful to El-Galaa Maternity Teaching Hospital, the administrators, the laboratory team and the nurses of the Medical Research Centre of Excellence (MRCE). Also, we appreciate all infants participated in the study and their parents.

References

1. Organization WH: Revised WHO classification and treatment of pneumonia in children at health facilities: evidence summaries. 2014.

2. Walker CLF, Rudan I, Liu L, Nair H, Theodoratou E, Bhutta ZA, et al. Global burden of childhood pneumonia and diarrhoea. The Lancet. 2013; 381:1405-16. https://doi.org/10.1016/S0140-6736(13)60222-6

3. Rudan I, Boschi-Pinto C, Biloglav Z, Mulholland K, Campbell H. Epidemiology and etiology of childhood pneumonia. Bull World Health Organ. 2008; 86:408-16. https://doi.org/10.2471/BLT.07.048769 PMid:18545744 PMCid:PMC2647437

4. El-Wakeel MA, El-Kassas GM, Fathy GA, El-Wakkad AS, Sebaii HM, El-Zayat SM. Diagnostic and prognostic values of high sensitive c-reactive protein, tumor necrosis factor and interleukin-1β in neonatal sepsis. Aust J Basic Appl Sci. 2012; 6:224-8.

5. DeLuca HF. Overview of general physiologic features and functions of vitamin D. Am J ClinNutr. 2004; 80:1689S-96S. https://doi.org/10.1093/ajcn/80.6.1689S PMid:15585789

6. El Wakeel MA, Shehata MA, El-Kassas GM, Mostafa HH, Galal EM, El-Zayat SR, Mohammed NA. Bone Health in Relation to Vitamin-D Status and Serum Adipokines in Obese Egyptian Children. Biomedical & Pharmacology Journal. 2019; 12(3):1379-88. https://doi.org/10.13005/bpj/1766

7. Holick MF. Vitamin D deficiency. N Engl J Med. 2007; 357:266-81. https://doi.org/10.1056/NEJMra070553 PMid:17634462

8. El-Shaheed AA, El-Arab AE, El-Kassas GM, El Wakeel MA, Abou-Zekri M, El-Banna M. An Innovative Effective Nutritional Therapy for Vitamin D Deficiency in Children with Celiac Disease. Biomedical and Pharmacology Journal. 2019; 12(3):1481-90. https://doi.org/10.13005/bpj/1778

9. Gharehbaghi MM, Ghergherechi R, Karimi B. Vitamin D Deficiency and Lower Respiratory Tract Infections in Newborn Infants. HONG KONG JOURNAL OF PAEDIATRICS. 2018; 23(1):20-4.

10. Bener A, Alsaied A, Al-Ali M, et al. High prevalence of vitamin D deficiency in type 1 diabetes mellitus and healthy children. ActaDiabetol. 2008; 46:183-9. https://doi.org/10.1007/s00592-008-0071-6 PMid:18846317

11. Zittermann A, Dembinski J, Stehle P. Low vitamin D status is associated with low cord blood levels of the immunosuppressive cytokine interleukin-10. Pediatr Allergy Immunol. 2004; 15:242-6. https://doi.org/10.1111/j.1399-3038.2004.00140.x PMid:15209957

12. El-Shaheed AA, Sallam SF, El-Zayat SR, Sibaii H, Mahfouz NN, Moustafa RS, Ibrahim SM. Vitamin D level in children and its relation to immunity and general health condition. Bioscience Research. 2017; 14(2):143-8.

13. Walker VP, Modlin RL. The vitamin D connection to pediatric infections and immune function. Pediatr Res. 2009; 65:106R-13R. https://doi.org/10.1203/PDR.0b013e31819dba91 PMid:19190532 PMCid:PMC2925470

14. Sibaii H, El-Zayat SR, El-Shaheed AA, Mahfouz NN, Sallam SF, El Azma MH. The hidden function of vitamin D. Open access Maced J Med Scis. 2016; 4(4):591. https://doi.org/10.3889/oamjms.2016.134 PMid:28028396 PMCid:PMC5175504

15. Siljan WW, Holter JC, Michelsen AE, Nymo SH, Lauritzen T, Oppen K, Husebye E, Ueland T, Mollnes TE, Aukrust P, Heggelund L. Inflammatory biomarkers are associated with aetiology and predict outcomes in community-acquired pneumonia: results of a 5-year follow-up cohort study. ERJ Open Research. 2019; 5(1):00014-2019. https://doi.org/10.1183/23120541.00014-2019 PMid:30863773 PMCid:PMC6409082

16. El Wakeel MA, El-Kassas GM, Hashem SA, Abouelnaga MW, Elzaree FA, Hassan M, Abdelrahman AH, Mohammed NA. Potential role of oxidative stress in childhood obesity and its relation to inflammation. Bioscience Research. 2018; 15(4):3791-9.

17. Bilgin H, Haliloglu M, Yaman A, Ay P, Bilgili B, Arslantas MK, Ture Ozdemir F, Haklar G, Cinel I, Mulazimoglu L. Sequential Measurements of Pentraxin 3 Serum Levels in Patients with Ventilator-Associated Pneumonia: A Nested Case-Control Study. Canadian Journal of Infectious Diseases and Medical Microbiology. 2018; 2018. https://doi.org/10.1155/2018/4074169 PMid:29861799 PMCid:PMC5971295

18. Luo Q, He X, Ning P, Zheng Y, Yang D, Xu Y, Shang Y, Gao Z. Admission Pentraxin-3 Level Predicts Severity of Community-Acquired Pneumonia Independently of Etiology. PROTEOMICS-Clinical Applications. 2019; 13(4):1800117. https://doi.org/10.1002/prca.201800117 PMid:30557448

19. Lezhenko G, Pashkova O, Kraynya H. The vitamin D deficiency as a marker of risk of pneumonia among children under 3 years. Biol Markers GuidTher. 2016; 3:99-106. https://doi.org/10.12988/bmgt.2016.638

20. Dinlen N, Zenciroglu A, Beken S, et al. Association of vitamin D deficiency with acute lower respiratory tract infections in newborns. J Matern Fetal Neonatal Med. 2016; 29:928-32. https://doi.org/10.3109/14767058.2015.1023710 PMid:25786473

21. Mohamed WAW, Al-Shehri MA. Cord blood 25-hydroxyvitamin D levels and the risk of acute lower respiratory tract infection in early childhood. J Trop Pediatr. 2013; 59:29-35. https://doi.org/10.1093/tropej/fms042 PMid:23022743

22. Principi N, Bianchini S, Baggi E, et al. Implications of maternal vitamin D deficiency for the fetus, the neonate and the young

infant. Eur J Nutr. 2013; 52:859-67. https://doi.org/10.1007/s00394-012-0476-4 PMid:23224056

23. Esposito S, Lelii M. Vitamin D and respiratory tract infections in childhood. BMC infectious diseases. 2015; 15(1):487. https://doi.org/10.1186/s12879-015-1196-1 PMid:26521023 PMCid:PMC4628332

24. Charan J, Goyal JP, Saxena D, et al. Vitamin D for prevention of respiratory tract infections: A systematic review and meta-analysis. Journal of Pharmacology and Pharmacotherapeutics. 2012; 3:300-303. https://doi.org/10.4103/0976-500X.103685 PMid:23326099 PMCid:PMC3543548

25. Christensen N, Søndergaard J, Fisker N, et al. Infant Respiratory Tract Infections or Wheeze and Maternal Vitamin D in Pregnancy: A Systematic Review. Pediatr Infect Dis J. 2017; 36:384-391. https://doi.org/10.1097/INF.0000000000001452 PMid:27977549

26. Jat KR. Vitamin D deficiency and lower respiratory tract infections in children: a systematic review and meta-analysis of observational studies. Trop Doct. 2017; 47:77-84. https://doi.org/10.1177/0049475516644141 PMid:27178217

27. McNally JD, Leis K, Matheson LA, et al. Vitamin D deficiency in young children with severe acute lower respiratory infection. Pediatr Pulmonol. 2009; 44:981-8. https://doi.org/10.1002/ppul.21089 PMid:19746437

28. Tekerek NU, Akyildiz BN, Ercal BD, et al. New Biomarkers to Diagnose Ventilator Associated Pneumonia: Pentraxin 3 and Surfactant Protein D. Indian J Pediatr. 2018; 85:426-432. https://doi.org/10.1007/s12098-018-2607-2 PMid:29396775

29. Lin Q, Fu F, Shen L, Zhu B. Pentraxin 3 in the assessment of ventilator-associated pneumonia: an early marker of severity. Heart & Lung: The Journal of Acute and Critical Care. 2013; 42(2):139-45. https://doi.org/10.1016/j.hrtlng.2012.11.005 PMid:23273657

30. El Wakeel MA, Sabry RN, El-kassas GM, El-Gaffar SA, Galal EM, Azmy A, Awadallah E. Pentraxin 3: A Potential Novel Predictor for Neonatal Pulmonary Hypertension. Open Access Maced J Med Sci. 2019; 7(15). https://doi.org/10.3889/oamjms.2019.638 PMid:31666840 PMCid:PMC6814462

31. Mauri T, Coppadoro A, Bellani G, et al. Pentraxin 3 in acute respiratory distress syndrome: an early marker of severity. Crit Care Med. 2008; 36:2302-8. https://doi.org/10.1097/CCM.0b013e3181809aaf PMid:18596636