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Assessment Of Serum Cathelicidin Level as Potential Roles for Complications in Patients With B-Tm

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ABSTRACT

Introduction: Thalassemia was a genetic defect outcome via human globin gene production conditions, among the most prevalent genotypes were alpha - and beta-thalassemia.In beta-thalassemia, β-globin chain manufacture is impaired, the amount of hemolysis in β-thalassemia has been observed to directly link with the creation of normal alpha-globin chains. Cathelicidins are cationic peptides with amphipathic characteristics, and they are a group that plays a key part in host defense.

Objectives: To assessment serum Cathelicidin level in patients with β-TM predominantly in splenectomy and non-splenectomy group , also find the correlation among Cathelicidin with other parameters of lipid profile and Iron status.

Design: A case-control study design, including of sixty patients with β-TM found in present study, And there patients don't have any chronic diseases. The thalassemia disease was registered in the ((thalassemia unit)) in Al-Zahra teaching hospital in Al Najaf city-Iraq , Implicate children or in aldoescence, Their age was range between 7-20 years.A thirty healthy individuals chosen for the control group based on their proximity in terms of age and gender to the patient groups.

Results: The current result shown that significantly diminished in the serum cathelicidin level as comparing amongst splenectomy ,non-splenectomy ,total patients with control group by definition (11.25±2.462) p= 0.045,(11.419±3.093) p=0.048,(11.35±2.75) p=0.047, vs (14.58±1.311) ,respectively. In this study found a significant positive correlation amidst Cathelicidin and body mass index, TIBC , UIBC, transferrin and total cholesterol (T.C) as well as significantly negative correlated with parameters like ferritin ,IRON , transferrin saturation percentage (TS%) ,TG and VLDL.C.

Conclusions: These AMPs can posses a significant part in immune systems as well as the pathogenesis of these patients. Further studies are necessary so as to appreciate the action of LL37 levels in patients with beta thalassemia major.

Keywords: *Thalassemia ,Beta-thalassemia major, Cathelicidin*

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INTRODUCTION

Thalassemia was a genetic defect outcome via human globin gene production conditions, among the most prevalent genotypes were alpha - and beta-thalassemia (Weatherall, 2001).

The severe form of thalassemia patients are require transfusions and are more likely to experience a number of problems, including iron overload (Badawy & Thompson, 2016), growth impairment (Vogiatzi et al., 2009), bone abnormalities (Toumba & Skordis, 2010), osteoporosis (Perisano et al., 2012) (Jensen et al., 1998), endocrinopathie (Thuret et al., 2010), pulmonary hypertension (Morris & Vichinsky, 2010),splenomegaly (Badawy & Thompson, 2016), and hypercoagulability (M. D. Cappellini et al., 2012).

In beta-thalassemia, β-globin chain manufacture is impaired, the amount of hemolysis in β-thalassemia has been observed to directly link with the creation of normal alpha-globin chains (Vigi et al., 1969).

Ineffective erythropoiesis is caused by beta-diminished TM's or impaired beta-globin production, which also acting a critical part for yield of oxidative stress (Scott et al., 1993). Those with severe anemia who first exhibit symptoms infancy are referred to be TM patients and need lifelong blood transfusions and iron chelation (M.-D. Cappellini et al., 2008).

Splenomegaly caused by means of extramedullary hematopoiesis and persistent passive splenic congestion. Splenectomy was formerly performed to aid in boosting hemoglobin levels and reducing reliance on RBC transfusions. (TAHER et al., 2013). The most detrimental side effect of splenectomy is the patients' elevated hazard of emerging acute infection, especially given that the hazard of post splenectomy sepsis was significantly advanced comparing with the general inhabitants (Singer, 1973).

Infections are frequent side effect of splenectomy, a significant job of spleen that in take away infections from the body. Also, numerous organisms increase in environments with in elevation iron content (Zarina et al., 2010).

Splenectomy is recommended when the kid had previously exhibited splenomegaly in addition to hypersplenism indications. It should be undertaken solitary subsequent six years age as advanced hazards of sepsis in younger age (Choudhry, 2017).

Pneumococcal, influenza, and meningococcal vaccinations should be given to all children who will undergo splenectomy surgery at least three to four weeks before the procedure. The dangers and benefits of a splenectomy should be explained to the family (Choudhry, 2017).

Cathelicidin antimicrobial peptide (AMP), LL-37 (likewise identified as h-CAP18) was a lone cathelicidin create in individuals (Hansson & Johansson, 2010). Neutrophils, keratinocytes, as well as intestinal and respiratory tract epithelial cells all produced LL-37, then secreted from human body peripheral residual in communication together with exterior circumference. The structure and operation of the epithelium are positively affected via cathelicidins (Zhang et al., 2015)(Akiyama et al., 2014).

The cationic peptides known as cathelicidins play a significant role in premature vertebrate host defense versus invasion pathogens (Zasloff, 2002).They were excreted in mucosal surfaces also through infection via leukocytes and epithelial cells across contact with microorganisms. Cathelicidins perform together immunomodulatory and immediate antibacterial activities (Gudmundsson et al., 1996)(Schauber et al., 2003) (Agerberth et al., 2000) (Larrick et al., 1996) (Di Nardo et al., 2003) (Vandamme et al., 2012).

Cathelicidins are cationic peptides with amphipathic characteristics, and they are a group that plays a key part in host defense (Lindow et al., 2016).The N-terminal located in signal peptide with extremely preserved cathelin domain, followed via C-terminal developed peptide with significant structural variability, characterize cathelicidins, which exhibit broad-spectrum antimicrobial activities (Zanetti et al., 1995). Supplement to the immediate antimicrobial effects, cathelicidins have a variety of other defense mechanisms they can activate, including antioxidant, immunomodulatory,

hemolytic, and apoptosis-inhibiting mechanisms (Coorens et al., 2017).

MATERIALS AND METHODS

Study design

A case-control study design, including of sixty patients with β-TM found in present study , And there patients don't have any chronic diseases. The individual were consist of four groups healthy group G1(n=30), splenectomy G2(n=20),non-splenectomy G3(n=40) and total patients G4(n=60).Collecting samples thought period January 2022-March 2022.

The thalassemia disease was registered in the ((thalassemia unit)) in Al-Zahra teaching hospital in Al Najaf city-Iraq , Implicate children or in aldoescence, Their age was range between 7-20 years.A thirty healthy individuals chosen for the control group based on their proximity in terms of age and gender to the patient groups.

Procedures

After being drawn into a gel tube, blood samples were coagulated for 15 minutes at room temperature previously being centrifuged at 3000 X g for the same amount of time. After that, serum samples were stockpiled at 20°C.

Standard enzymatic techniques (kit) were used to analysed the quantities of serum total iron, total cholesterol, high density lipoprotein cholesterol (HDL-C), and triglycerides. Fried Ewald's formula was used to determine the levels of LDL-C.

The levels of serum ferritin, fasting insulin, cathelicidin were detected via enzyme-linked immunosorbent assay (kit). Body mass index were determined through special equation : equally the ratio of weight in to height squared.

Statistical analysis

The information were statistically appreciated via utilize the computer programs microsoft excel 2016 and SPSS-version 26.

Numbers and mean, standard deviation were used to express the results. For two dependent means, the significance of the difference was gauged via employment a paired t-test. Using the pearson correlation coefficient, the parameters were shown to be correlated, a p value of 0.05 would have implied significance.

To compare the variations between the groups under study, the one-way ANOVA and Fishers Least Significant Difference (LSD) were used. Area under the curve (AUC) using receiver operating characteristic (ROC) for diagnosis Cathelicidin.

RESULTS

Sixty subjects were enrolled, whose clinical with biochemical features are reported in Table 1.

This current study demonstrated the comparing between control group (Group1) with three patients group of beta thalassemia major :like splenectomy (Group2),non-splenectomy (Group3), and total patients (Group4).

In table (1) displayed the comparing between splenectomy patients (G2) and control group (G1) and this comparing revealed significantly elevated in iron status such as ferritin, IRON, transferrin saturation percentage (TS%), transferrin and some parameters of lipid profile like this total cholesterol (T.C) and low density lipoprotein cholesterol (LDL.C) (p value of each them : p=<0.001, p=0.001, p=0.001, p=0.01, p=0.001, p=0.003, respectively). However, there was a significant lower in body mass index (BMI), total iron binding capacity (TIBC) ,un saturated iron binding capacity (UIBC), high density lipoprotein cholesterol (HDL.C) ,very low density lipoprotein cholesterol (VLDL.C) and Cathelicidin (p value describe , p=<0.001, p=0.003, p=0.04, p=0.001, p=0.045, p=0.045, respectively), also found no statistical significant differences in age and triglyceride (TG) between in both groups (p=0.57 & p=0.59).

The comparison among non-splenectomy β-TM patients (G3) and control group (G1) were illustrated a significant increased in ferritin, IRON ,TIBC ,TS%, total cholesterol (T.C), TG, LDL.C and VLDL.C (p=0.001, p=0.005,p=0.001, p=0.001,p=0.05, p=0.001, p=0.004,p=0.05, respectively) . Likewise, body mass index (BMI), UIBC, HDL.C and Cathelicidin were found significantly declined

(p=0.001,p=0.001, p=0.001, p=0.048, respectively), excluding age and transferrin which was non significant differences in this groups (p=0.728 & p=0.65).

This present study revealed a significant elevated in TIBC, TG and VLDL.C (p=0.001,p=0.001, p=0.01) as well as lower in age (p=0.046), ferritin (p=0.001), IRON (p=0.005), UIBC (p=0.05), transferrin saturation percentage (TS%) (p=0.05), transferrin (p=0.01), total cholesterol (T.C) (p=0.04), and LDL.C (p=0.04), But found a non-significant difference in body mass index (BMI), HDL.C and Cathelicidin in splenectomy patients (G2) compared with non-splenectomy patients (G3).

Ferritin, IRON, transferrin saturation percentage (TS%), transferrin, total cholesterol (T.C), TG and LDL.C were showed significantly elevated, while body mass index (BMI), UIBC, HDL.C and Cathelicidin were showed a significant decreased, And found non-significantly in age, TIBC, and VLDL.C when comparing total patients group (G4) and control group (G1).

In table (1) and (2) demonstrated the association among serum Cathelicidin level with parameters in β-TM patients in both groups splenectomy and non-splenectomy.

A significant positive correlation between Cathelicidin and body mass index, TIBC , UIBC, transferrin and total cholesterol (T.C) as well as significantly negative correlated with parameters like ferritin ,IRON , transferrin saturation percentage (TS %) ,TG and VLDL.C, except age (r=0.190 , p=0.116) and HDL.C (r=0.221 , p=0.066) have no statistically significant difference with Cathelicidin level in non-splenectomy patients with beta thalassemia major. Figure (1).

TABLE 1: Comparison among biochemical characteristics of splenectomy, non-splenectomy and total patients with control groups

Parameters	Control G1 Mean±SD n=30	Splenectomy G2 Mean±SD n=20	Non-splenectomy G3 *Mean±SD n=40*	*Total Patients G4 Mean±SD n=60*	*P value*
Age(Years)	16.27±4.118	16.80±4.444	14.23±5.066	15.515±4.755	P1=0.046 P2=0.728 P3=0.57 P4=0.06
BMI(kg/m2)	23.85 ±4.059	17.87±5.557	16.27± 4.062	17.07±4.8095	P1=0.190 P2= 0.001 P3=<0.001 P4=0.001
Ferritin (ng/mL)	122.26±45.23	3987±1519.4	2855.1±1416.3	3421±1467	P1=0.001 P2=0.001 P3=<0.001 P4=<0.001
IRON (µmol/L)	22.15±5.16	53.89±17.11	39.09±7.88	46.4±12.49	P1=0.005 P2= 0.005 P3= 0.001 P4=0.001
TIBC (µmol/L)	70.01±9.35	60.98±9.98	84.05±11.13	72.5±10.5	P1= 0.001 P2=0.001 P3=0.003 P4=0.069
UIBC (µmol/L)	46 ±12.87	32.08±16.10	27.75±15.43	29.9 ±15.8	P1=0.05 P2= 0.001 P3=0.04 P4=0.001

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TS%	36.33±12.06	64.74±17.03	61.11±12.45	63.1±14.5	P1=0.05 P2=0.001 P3=0.001 P4=0.001
Transferrin (g/L)	0.18±0.033	0.3±0.01	0.16±0.03	0.21 ±0.02	P1= 0.01 P2=0.65 P3=0.01 P4=0.04
T.C (mg/dL)	114.7±18.87	129.8±12.4	120±12	124.5±12.1	P1=0.04 P2=0.05 P3=0.001 P4=0.03
HDL-C(mg/ dL)	39.33±3.2	23.11 ±2.27	23.48 ±1.46	23.25±1.9	P1=0.54 P2=0.001 P3=0.001 P4=0.001
TG (mg/dL)	64.5±13.77	63.31±12.21	85.99±23.35	75.2±17.5	P1= 0.001 P2=0.001 P3= 0.59 P4=0.04
LDL-C(mg/dL)	70.36±13.22	92.62±11.92	80.2±10.87	85.5±11.4	P1=0.04 P2=0.004 P3=0.003 P4=0.01
VLDL.C(mg/ dL)	12.44±1.84	10±0.7	16.6±3.97	13.4±2.35	P1=0.01 P2=0.05 P3=0.045 P4=0.057
Cathelicidin (ng/mL)	14.58±1.311	11.25±2.462	11.419±3.093	11.35±2.75	P1=0.808 P2=0.048 P3=0.045 P4=0.047

P1 represented the comparison between splenectomy and non-splenectomy group, p2 represented the comparison between non-splenectomy patient and control group, p3 represented as comparing among splenectomy group and control group, p4 symbolised the comparison between total patients and control group,**=significant differences at 1%, NS = non-significant at the threshold of 0.05.

TABLE 2: The relevance of serum Cathelicidin with levels of biochemical parameters in in the group without splenectomy

Parameters	**r**	**P- value**
Age (years)	0.190	0.116
BMI(kg/m2)	0.465**	<0.001
Ferritin (ng/mL)	-0.713**	<0.001
IRON (µmol/L)	-0.652**	<0.001
TIBC (µmol/L)	0.540**	<0.001
UIBC (µmol/L)	0.669**	<0.001
TS %	-0.687**	<0.001

Transferrin (g/L)	0.540**	<0.001
T.C (mg/dL)	0.359**	0.002
HDL.C(mg/dL)	0.221	0.066
TG (mg/dL)	-0.617**	<0.001
LDL.C(mg/dL)	0.447**	<0.001
VLDL.C(mg/dL)	-0.617**	<0.001

TABLE 3: The relevance of serum Cathelicidin with levels of biochemical parameters in the group who had splenectomy

Parameters	**r**	**P- value**
Age (years)	-0.141	0.329
BMI(kg/m2)	0.376**	0.007
Ferritin (ng/mL)	-0.791**	<0.001
IRON (µmol/L)	-0.361*	0.01
TIBC (µmol/L)	-0.133	0.357
UIBC (µmol/L)	0.055	0.703
TS %	-0.222	0.121
Transferrin (g/L)	-0.133	0.357
T.C (mg/dL)	-0.637**	<0.001
HDL.C(mg/dL)	0.457**	0.001
TG (mg/dL)	-0.453**	0.001
LDL.C(mg/dL)	-0.599**	<0.001
VLDL.C(mg/dL)	-0.453**	0.001

This study has found that relationship between serum Cathelicidin level with parameters body mass index (r=0.376 , p=0.007),and HDL.C (r=0.457 , p=0.001) were revealed significantly positive correlation , as well ferritin, IRON, total cholesterol (T.C), TG, LDL.C, and VLDL.C found negative correlated with Cathelicidin. While Age (r=-0.141 , p= 0.329),TIBC (r=-0.133, p=0.357) ,UIBC (r=0.055, p=0.703),TS% (r=-0.222, p=0.121), and transferrin (r=-0.133, p=0.357) have no statistical significant difference with Cathelicidin in splenectomy patients with beta thalassemia major. Figure (2)

As shown in figure 1 and 2 elucidated receiver operating characteristic for cathelicidin. This study revealed cut of value for cathelicidin in splenectomy and non-splenectomy patients group equal (13.3295, 13.1705, respectively). Furthermore, area under curve (AUC) for cathelicidin (0.952) in splenectomy group as well (0.972) in non-splenectomy patients group.The sensitivity of cathelicidin in splenectomy and non-splenectomy (0.9 ,0.967, respectively) ,while specificity (0.875, 1) in both group.

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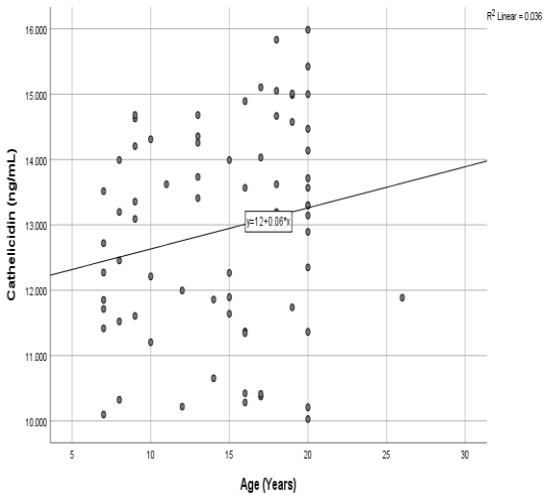

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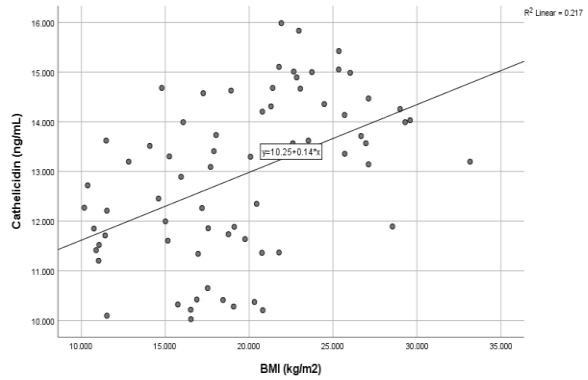

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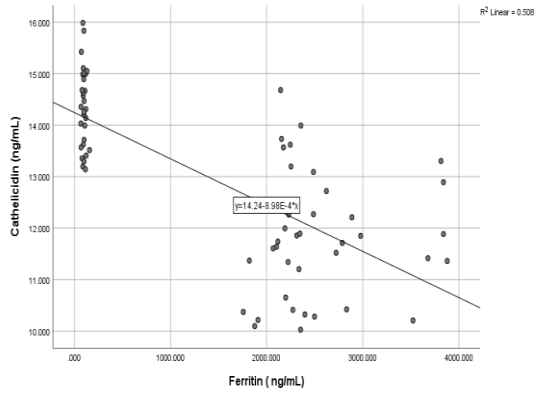

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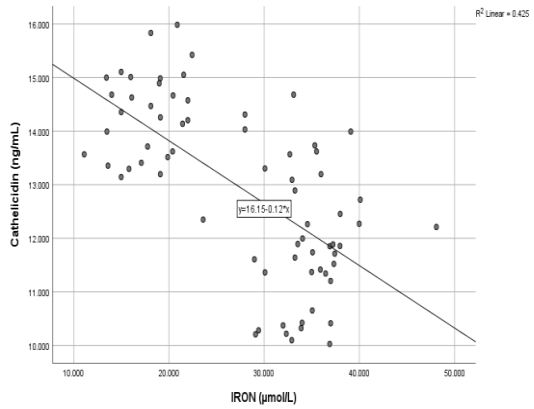

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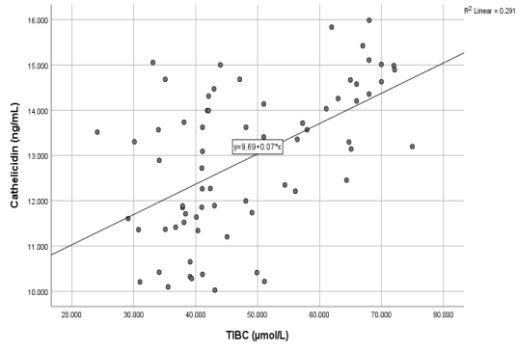

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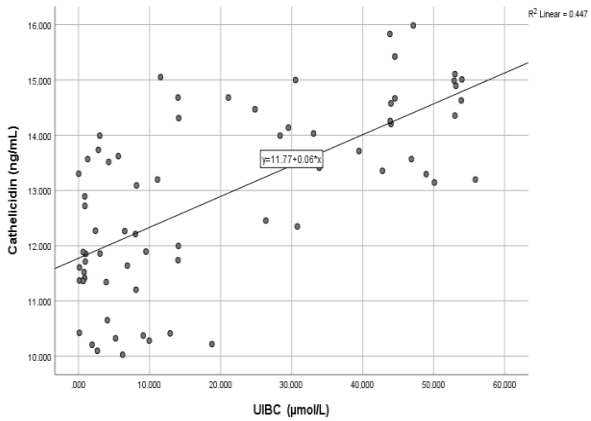

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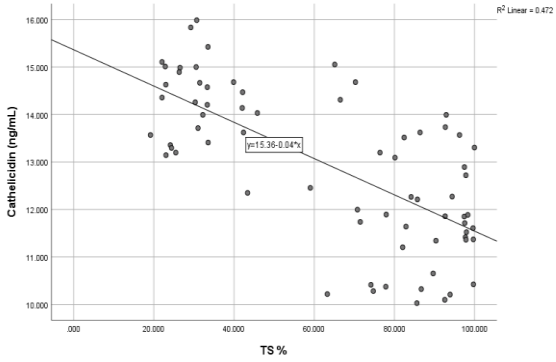

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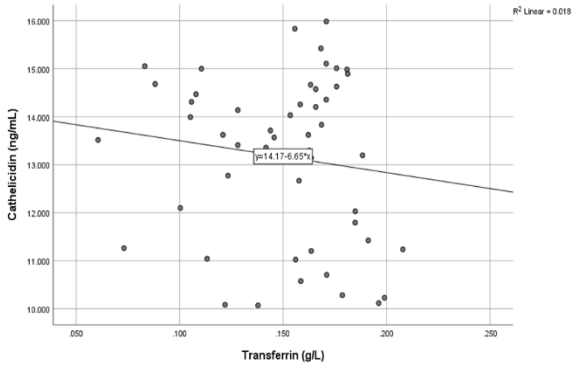

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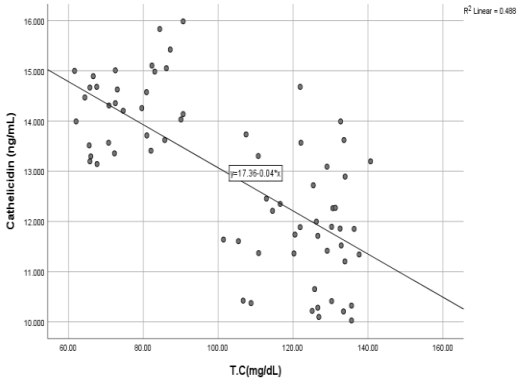

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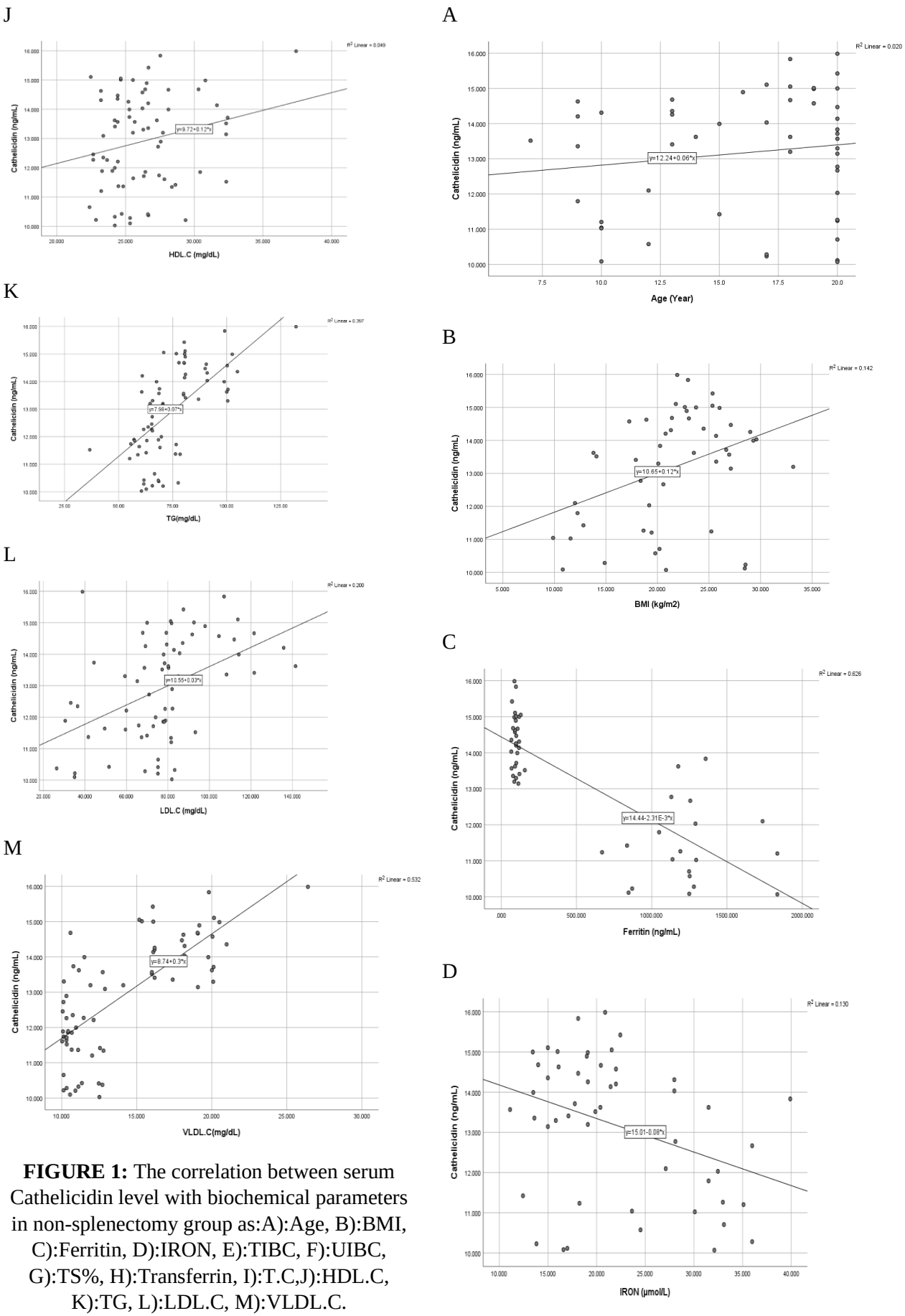

FIGURE 1: The correlation between serum Cathelicidin level with biochemical parameters in non-splenectomy group as:A):Age, B):BMI, C):Ferritin, D):IRON, E):TIBC, F):UIBC, G):TS%, H):Transferrin, I):T.C,J):HDL.C, K):TG, L):LDL.C, M):VLDL.C.

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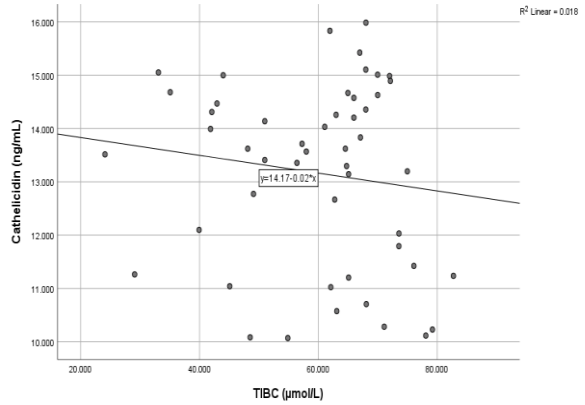

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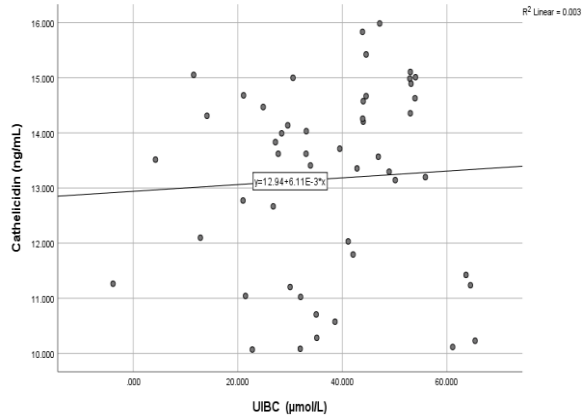

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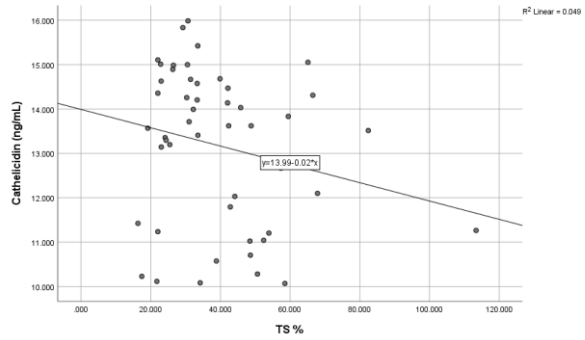

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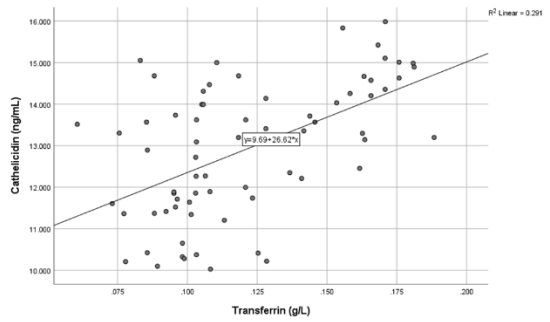

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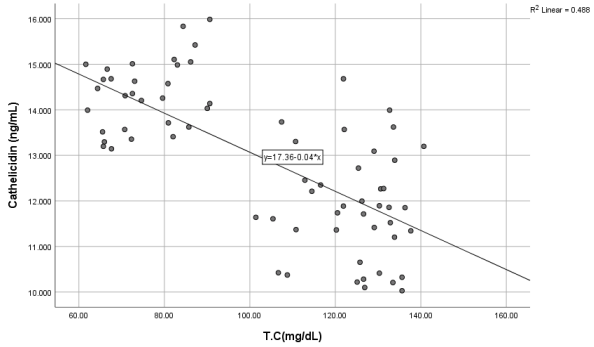

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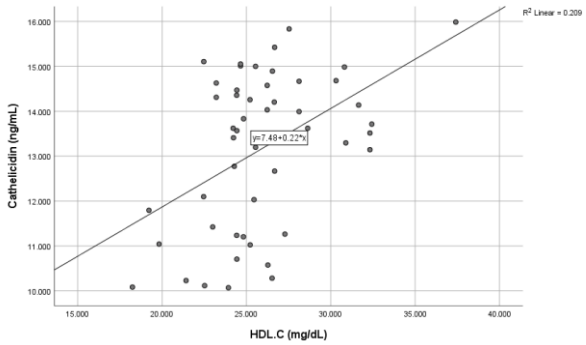

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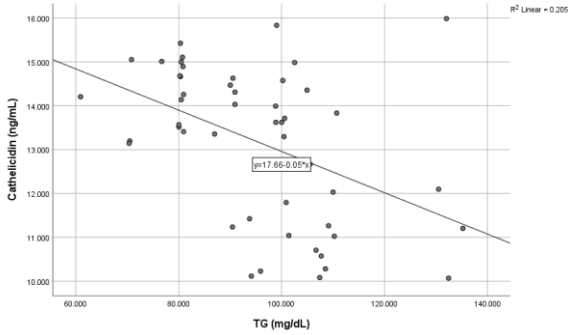

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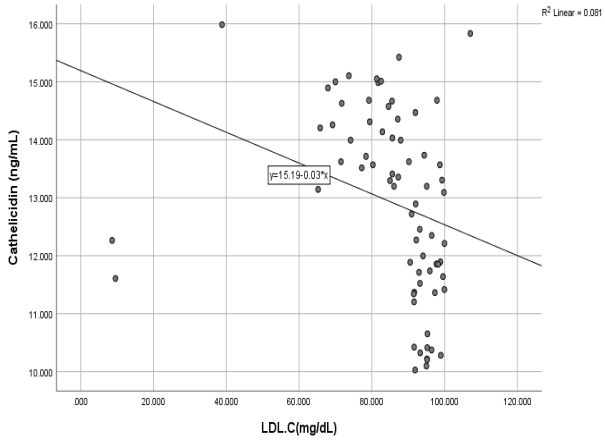

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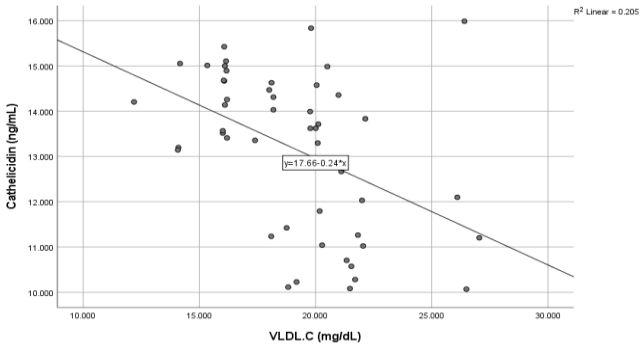

FIGURE 2: The correlation between serum Cathelicidin level with biochemical parameters in splenectomy group as:A):Age, B):BMI, C):Ferritin, D):IRON, E):TIBC, F):UIBC, G):TS%, H):Transferrin, I):T.C,J):HDL.C, K):TG, L):LDL.C, M):VLDL.C.

TABLE 4: Cathelicidin diagnosis using gauged biomarkers: Receiver operating characteristic-area under the curve analysis

Variable	Group	Cut-off concentration	Sensitivity	Specificity	AUC	95% CI of AUC	p-value
Cathelicidin (ng/mL)	Splenectomy	13.3295	0.9	0.875	0.952	0.906-0.998	p=<0.001
	Non-Splenectomy	13.1705	0.967	1	0.972	0.932-1.000	p=<0.001

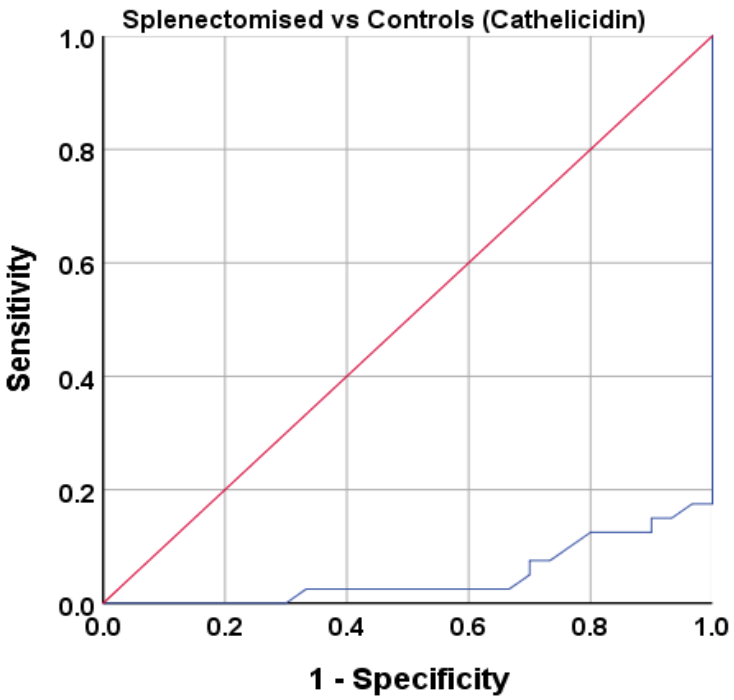

FIGURE 3: Cathelicidin ROC curve demonstration recognition of splenectomised group

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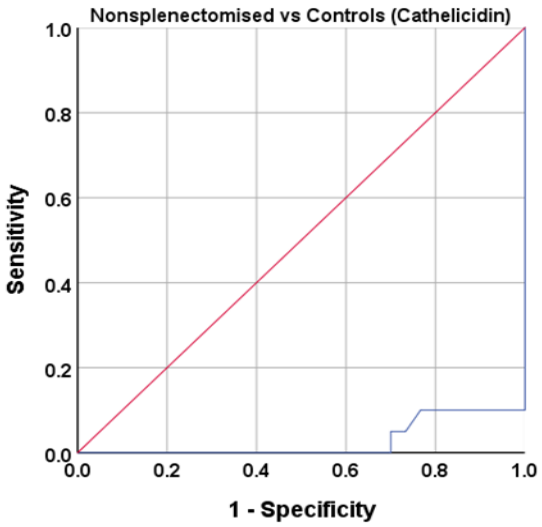

FIGURE 4: Cathelicidin ROC curve demonstration recognition of non-splenectomised group

DISCUSION

As part of this exploration, we looked into the influence of cathelicidin in beta thalassemia major patients ,this patients divided in to three groups splenectomy, non-splenectomy and total patients. Cathelicidin level decreased in this three groups of patients in current study,this results discovered that supposed antimicrobial peptides cathelicidin was a curative cytokines , moreover rises of cathelicidin probability task therapeutic in beta thalassemia major futurity.

This current study found increased in total cholesterol, tri glycerides, low density lipoproteins, very low density lipoproteins and lower in high density lipoproteins of patient groups, and this not good possibility indicates that the patients would exposed infection to heart disease.

Thalassemia was a cluster of congenital anemias that have in common poor creation of one or other globin subunits from normal human hemoglobin (Hbs).The primary deficiency was typically quantitative, comprised of a diminished or skipped production of regular globin chains (Kadhim et al., 2017).

Red blood cells are lost in great amounts from the patient's blood, making it incapable of carrying oxygen. If the body was insufficient production of any sort of protein, the blood cells are not being fully formed and lack of sufficient oxygen transmission ,then the outcome was anemia that develops in childhood and lasts until death (Galanello & Origa, 2010)(Karimi et al., 2009)(Dolai et al., 2012). Analyzing a person's hemoglobin level allows for the diagnosis of thalassemia. People with thalassemia have fewer levels of hemoglobin and red blood cells than average (Peters et al., 2012)(Cao & Galanello, 2010).

Beta-thalassemia consequences from inadequacy in β-globin as well ordinarily produced via point mutations in which gene of β-globin (Shang & Xu, 2017). Severe anemia is a hallmark of beta-thalassemia major, which necessitates frequent blood transfusions and chelation therapy toward survive (Rund & Rachmilewitz, 2005) (Cao & Galanello, 2010).Frequent blood transfusions throughout the course of a person's lifetime cause excessive iron collection, which should be managed by prescription chelator drugs to assist prevent organ failure and death (Tabei et al., 2013).

The unique beta-globin gene deficiency in beta-thalassemia cannot entirely account for the variety of different sequelae like cardiovascular issues or chronic vascular inflammation. Endothelial injury and vascular inflammation are caused by chronic haemolysis, augmented erythrocyte, frequent iron overload, oxidative stress, and platelet adhesion toward endothelial cells. Endothelial cells contribute in atherogenesis in addition anti plus pro

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inflammatory responses lead to capability producing besides identifying cytokines as well as an expression for adhesion molecules below specific conditions (Hartge et al., 2007).

Endothelial dysfunction, damage, and activation can play a role in a variety of disease progressions, involving diabetes, inflammation, atherosclerosis, pulmonary hypertension, and hemoglobinopathies especially beta-thalassemia. This is because endothelial cells perform such a wide range of tasks. There was potent guide from energetic of endothelial cell also weakened endothelial task in patients with β-thalassemia, where vascular problems are common (Hartge et al., 2007)(Taher et al., 2008)(Aggeli et al., 2005).

Iron overload was an inevitable sequel of systematic transfusions as deficiencies mechanism of the human body to expel surplus iron. On the other hand, the greatest general problems linked towards transfusional hemosiderosis, like cirrhosis heart failure, growth retardation, in addition to numerous endocrine abnormalities, an able to avoided and which returned via sufficient iron chelation (Origa, 2017).

Several blood transfusions with lack of hepcidin, a powerful inhibitor of iron intake, cause iron overload at the severe types of beta-thalassemia, which is accompanied by an elevated ferritin serum concentration and transferrin saturation and this agreement with result in current study (Brissot et al., 2008).

Researchers have previously proposed various pathophysiologic explanations for dyslipidemia in thalassemia patients, including anemia-induced plasma dilution, expedited erythropoiesis together with extra cholesterol utilization via reticuloendothelial system's histocytes and macrophages, as well as hormone disruption ,iron overload and macrophage activation with cytokine relief all affect impaired liver's creation task (Amendola et al., 2007)(Shalev et al., 2007), however, diminished extra-hepatic lipolytic action could be responsible from elevated TG in β-thalassemia major patients as agree with result in present study especially in non-splenectomy and total patients (Paganga et al., 1992).

The emergence of premature atherosclerosis in our TM patients was unexpected while having low LDL-C,this finding might be related to the oxidative conversion of LDL-C to turn out "atherogenic LDL" in thalassemia patients with an imbalanced oxidant-antioxidant milieu (Tselepis et al., 2010) (Livrea et al., 1996).

Cathelicidins are host defense peptides with functions in both immunomodulation and antibacterial action. As inefficient precursors, they are created (prepropeptides), reserved in granules, then relief as ripe peptides via proteolytic cleavage when the cell is activated (Kościuczuk et al., 2012). Abundant diverse kinds, including amphibians mammals, fishs, birds and reptiles, have been identified to produce cathelicidins (Hemshekhar et al., 2016)(Van Harten et al., 2018). It's interesting to note that various species have drastically varying numbers of functioning cathelicidin-encoding genes. (Zanetti, 2005). Many variables, including as inflammatory and microbial stimuli, control the expression of cathelicidins (Sunkara et al., 2011).

CONCLUSION

In this study shown that lower serum cathelicidin (LL-37) in patients with beta thalassemia major especially in splenectomised patients compared with non splenectomized than the healthy children group can be a potential predictor for worst prognosis of beta thalassemia major patients. These discoveries upgrade our perception of the task of this peptides in complications and submit that the level of the human cathelicidin (LL-37) could be a novel therapeutic strategy.

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REFERENCES

1. Agerberth, B., Charo, J., Werr, J., Olsson, B., Idali, F., Lindbom, L., Kiessling, R., Jörnvall, H., Wigzell, H., & Gudmundsson, G. H. (2000). The human antimicrobial and chemotactic peptides LL-37 and α-defensins are expressed by specific

lymphocyte and monocyte populations. Blood, The Journal of the American Society of Hematology, 96(9), 3086–3093.
2. Aggeli, C., Antoniades, C., Cosma, C., Chrysohoou, C., Tousoulis, D., Ladis, V., Karageorga, M., Pitsavos, C., & Stefanadis, C. (2005). Endothelial dysfunction and inflammatory process in transfusion-dependent patients with beta-thalassemia major. International Journal of Cardiology, 105(1), 80–84.
3. Akiyama, T., Niyonsaba, F., Kiatsurayanon, C., Ushio, H., Fujimura, T., Ueno, T., Okumura, K., Ogawa, H., & Ikeda, S. (2014). The human cathelicidin LL-37 host defense peptide upregulates tight junction-related proteins and increases human epidermal keratinocyte barrier function. Journal of Innate Immunity, 6(6), 739–753.
4. Amendola, G., Danise, P., Todisco, N., D'urzo, G., Di Palma, A., & Di Concilio, R. (2007). Lipid profile in β-thalassemia intermedia patients: correlation with erythroid bone marrow activity. International Journal of Laboratory Hematology, 29(3), 172–176.
5. Badawy, S. M., & Thompson, A. A. (2016). Management of Thalassemias. Nonmalignant Hematology: Expert Clinical Review: Questions and Answers, 39–51.
6. Brissot, P., Troadec, M.-B., Bardou-Jacquet, E., Le Lan, C., Jouanolle, A.-M., Deugnier, Y., & Loreal, O. (2008). Current approach to hemochromatosis. Blood Reviews, 22(4), 195–210.
7. Cao, A., & Galanello, R. (2010). Beta-thalassemia. Genetics in Medicine, 12(2), 61–76.
8. Cappellini, M.-D., Cohen, A., Eleftheriou, A., Piga, A., Porter, J., & Taher, A. (2008). Management of Fertility and Pregnancy in β-thalassemia. In Guidelines for the Clinical Management of Thalassaemia [Internet]. 2nd Revised edition. Thalassaemia International Federation.
9. Cappellini, M. D., Musallam, K. M., Poggiali, E., & Taher, A. T. (2012). Hypercoagulability in non-transfusion-dependent thalassemia. Blood Reviews, 26, S20–S23.
10. Choudhry, V. P. (2017). Thalassemia Minor and Major: Current Management. Indian Journal of Pediatrics, 84(8), 607–611. https://doi.org/10.1007/s12098-017-2325-1
11. Coorens, M., Scheenstra, M. R., Veldhuizen, E. J. A., & Haagsman, H. P. (2017). Interspecies cathelicidin comparison reveals divergence in antimicrobial activity, TLR modulation, chemokine induction and regulation of phagocytosis. Scientific Reports, 7(1), 1–11.
12. Di Nardo, A., Vitiello, A., & Gallo, R. L. (2003). Cutting edge: mast cell antimicrobial activity is mediated by expression of cathelicidin antimicrobial peptide. The Journal of Immunology, 170(5), 2274–2278.
13. Dolai, T. K., Nataraj, K. S., Sinha, N., Mishra, S., Bhattacharya, M., & Ghosh, M. K. (2012). Prevalance of iron deficiency in thalassemia minor: a study from tertiary hospital. Indian Journal of Hematology and Blood Transfusion, 28, 7–9.
14. Galanello, R., & Origa, R. (2010). Beta-thalassemia. Orphanet Journal of Rare Diseases, 5(1), 1–15.
15. Gudmundsson, G. H., Agerberth, B., Odeberg, J., Bergman, T., Olsson, B., & Salcedo, R. (1996). The human gene FALL39 and processing of the cathelin precursor to the antibacterial peptide LL-37 in granulocytes. European Journal of Biochemistry, 238(2), 325–332.
16. Hansson, G. C., & Johansson, M. E. V. (2010). The inner of the two Muc2 mucin-dependent mucus layers in colon is devoid of bacteria. Gut Microbes, 1(1), 51–54.
17. Hartge, M. M., Unger, T., & Kintscher, U. (2007). The endothelium and vascular inflammation in diabetes. Diabetes and Vascular Disease Research, 4(2), 84–88.
18. Hemshekhar, M., Anaparti, V., & Mookherjee, N. (2016). Functions of cationic host defense peptides in immunity. Pharmaceuticals, 9(3), 40.
19. Jensen, C. E., Tuck, S. M., Agnew, J. E., Koneru, S., Morris, R. W., Yardumian, A., Prescott, E., Hoffbrand, A. V, & Wonke, B. (1998). High prevalence of low bone mass in thalassaemia major. British Journal of Haematology, 103(4), 911–915.
20. Kadhim, K. A., Baldawi, K. H., & Lami, F. H. (2017). Prevalence, incidence, trend, and complications of thalassemia in Iraq. Hemoglobin, 41(3), 164–168.
21. Karimi, M., Bagheri, M. H., Tahmtan, M., Shakibafard, A., & Rashid, M. (2009). Prevalence of hepatosplenomegaly in beta thalassemia minor subjects in Iran. European Journal of Radiology, 69(1), 120–122.
22. Kościuczuk, E. M., Lisowski, P., Jarczak, J., Strzałkowska, N., Jóźwik, A., Horbańczuk, J., Krzyżewski, J., Zwierzchowski, L., & Bagnicka, E. (2012). Cathelicidins: family of antimicrobial peptides. A review. Molecular Biology Reports, 39, 10957–10970.
23. Larrick, J. W., Lee, J., Ma, S., Li, X., Francke, U., Wright, S. C., & Balint, R. F. (1996). Structural,

functional analysis and localization of the human CAP18 gene. FEBS Letters, 398(1), 74–80.
24. Lindow, J. C., Wunder Jr, E. A., Popper, S. J., Min, J.-N., Mannam, P., Srivastava, A., Yao, Y., Hacker, K. P., Raddassi, K., & Lee, P. J. (2016). Cathelicidin insufficiency in patients with fatal leptospirosis. PLoS Pathogens, 12(11), e1005943.
25. Livrea, M. A., Tesoriere, L., Pintaudi, A. M., Calabrese, A., Maggio, A., Freisleben, H. J., D'arpa, D., D'anna, R., & Bongiorno, A. (1996). Oxidative stress and antioxidant status in beta-thalassemia major: iron overload and depletion of lipid-soluble antioxidants.
26. Morris, C. R., & Vichinsky, E. P. (2010). Pulmonary hypertension in thalassemia. Annals of the New York Academy of Sciences, 1202(1), 205–213.
27. Origa, R. (2017). β-Thalassemia. Genetics in Medicine, 19(6), 609–619. https://doi.org/10.1038/gim.2016.173
28. Paganga, G., Rice-Evans, C., Rule, R., & Leake, D. (1992). The interaction between ruptured erythrocytes and low-density lipoproteins. FEBS Letters, 303(2–3), 154–158.
29. Perisano, C., Marzetti, E., Spinelli, M. S., Calla, C. A. M., Graci, C., & Maccauro, G. (2012). Physiopathology of bone modifications in-thalassemia. Anemia, 2012.
30. Peters, M., Heijboer, H., Smiers, F., & Giordano, P. C. (2012). Diagnosis and management of thalassaemia. BMJ, 344.
31. Rund, D., & Rachmilewitz, E. (2005). β-Thalassemia. New England Journal of Medicine, 353(11), 1135–1146.
32. Schauber, J., Svanholm, C., Termen, S., Iffland, K., Menzel, T., Scheppach, W., Melcher, R., Agerberth, B., Lührs, H., & Gudmundsson, G. (2003). Expression of the cathelicidin LL-37 is modulated by short chain fatty acids in colonocytes: relevance of signalling pathways. Gut, 52(5), 735–741.
33. Scott, M. D., Van Den Berg, J. J., Repka, T., Rouyer-Fessard, P., Hebbel, R. P., Beuzard, Y., & Lubin, B. H. (1993). Effect of excess alpha-hemoglobin chains on cellular and membrane oxidation in model beta-thalassemic erythrocytes. The Journal of Clinical Investigation, 91(4), 1706–1712.
34. Shalev, H., Kapelushnik, J., Moser, A., Knobler, H., & Tamary, H. (2007). Hypocholesterolemia in chronic anemias with increased erythropoietic activity. American Journal of Hematology, 82(3), 199–202.
35. Shang, X., & Xu, X. (2017). Update in the genetics of thalassemia: What clinicians need to know. Best Practice and Research: Clinical Obstetrics and Gynaecology, 39(November), 3–15. https://doi.org/10.1016/j.bpobgyn.2016.10.012
36. Singer, D. B. (1973). Postsplenectomy sepsis. Perspectives in Pediatric Pathology, 1, 285–311.
37. Sunkara, L. T., Achanta, M., Schreiber, N. B., Bommineni, Y. R., Dai, G., Jiang, W., Lamont, S., Lillehoj, H. S., Beker, A., & Teeter, R. G. (2011). Butyrate enhances disease resistance of chickens by inducing antimicrobial host defense peptide gene expression. PLoS One, 6(11), e27225.
38. Tabei, S. M. B., Mazloom, M., Shahriari, M., Zareifar, S., Azimi, A., Hadaegh, A., & Karimi, M. (2013). Determining and surveying the role of carnitine and folic acid to decrease fatigue in β-thalassemia minor subjects. Pediatric Hematology and Oncology, 30(8), 742–747.
39. Taher, A. L. I., Vichinsky, E., Musallam, K., Cappellini, M. D., Viprakasit, V. I. P., & Weatherall, S. I. R. D. (2013). For the management of non transfusion dependent thalassaemia (ntdt).
40. Taher, A. T., Otrock, Z. K., Uthman, I., & Cappellini, M. D. (2008). Thalassemia and hypercoagulability. Blood Reviews, 22(5), 283–292.
41. Thuret, I., Pondarré, C., Loundou, A., Steschenko, D., Girot, R., Bachir, D., Rose, C., Barlogis, V., Donadieu, J., & de Montalembert, M. (2010). Complications and treatment of patients with β-thalassemia in France: results of the National Registry. Haematologica, 95(5), 724.
42. Toumba, M., & Skordis, N. (2010). Osteoporosis syndrome in thalassaemia major: an overview. Journal of Osteoporosis, 2010.
43. Tselepis, A. D., Hahalis, G., Tellis, C. C., Papavasiliou, E. C., Mylona, P. T., Kourakli, A., & Alexopoulos, D. C. (2010). Plasma levels of lipoprotein-associated phospholipase A2 are increased in patients with β-thalassemia. Journal of Lipid Research, 51(11), 3331–3341.
44. Van Harten, R. M., Van Woudenbergh, E., Van Dijk, A., & Haagsman, H. P. (2018). Cathelicidins: immunomodulatory antimicrobials. Vaccines, 6(3), 63.
45. Vandamme, D., Landuyt, B., Luyten, W., & Schoofs, L. (2012). A comprehensive summary of LL-37, the factotum human cathelicidin peptide. Cellular Immunology, 280(1), 22–35.
46. Vigi, V., Volpato, S., Gaburro, D., Conconi, F., Bargellesi, A., & Pontremoli, S. (1969). The correlation between red-cell survival and excess

of α-globin synthesis in β-thalassaemia. British Journal of Haematology, 16(1), 25–30.
47. Vogiatzi, M. G., Macklin, E. A., Trachtenberg, F. L., Fung, E. B., Cheung, A. M., Vichinsky, E., Olivieri, N., Kirby, M., Kwiatkowski, J. L., & Cunningham, M. (2009). Differences in the prevalence of growth, endocrine and vitamin D abnormalities among the various thalassaemia syndromes in North America. British Journal of Haematology, 146(5), 546–556.
48. Weatherall, D. J. (2001). Phenotype—genotype relationships in monogenic disease: lessons from the thalassaemias. Nature Reviews Genetics, 2(4), 245–255.
49. Zanetti, M. (2004). Cathelicidins, multifunctional peptides of the innate immunity. Journal of Leukocyte Biology, 75(1), 39–48.
50. Zanetti, M. (2005). The role of cathelicidins in the innate host defenses of mammals. Current Issues in Molecular Biology, 7(2), 179–196.
51. Zanetti, M., Gennaro, R., & Romeo, D. (1995). Cathelicidins: a novel protein family with a common proregion and a variable C-terminal antimicrobial domain. FEBS Letters, 374(1), 1–5.
52. Zarina, A. L., Norazlin, K. N., Hamidah, A., Aziz, D. A., Zulkifli, S. Z., & Jamal, R. (2010). Spectrum of infections in splenectomised thalassaemia patients. The Medical Journal of Malaysia, 65(4), 283–285.
53. Zasloff, M. (2002). Antimicrobial peptides of multicellular organisms. Nature, 415(6870), 389–395.
54. Zhang, H., Xia, X., Han, F., Jiang, Q., Rong, Y., Song, D., & Wang, Y. (2015). Cathelicidin-BF, a novel antimicrobial peptide from Bungarus fasciatus, attenuates disease in a dextran sulfate sodium model of colitis. Molecular Pharmaceutics, 12(5), 1648–1661.