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Prevalence of *H pylori* among patients with Mitral Valve prolapse

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Abstract
Helicobacter pylori is one of a pathogenic bacteria that prevalent a wide on the world ,It is found around 50% from population in different region , it is colonized on stomach ,it is have ability to adapted itself to acidic media on it , ,It is responsible of many gastric cancer Colorectal cancer ,Ulcers ,Gastritis and have an important role in increased severity of Chronic disease such as Diabetic ,Autoimmune ,Coronary Heart diseases and Arthrosclerosis .In this current study ,We are working to study a prevalence *H pylori* in M VP patients by three methods ,estimate INF-γ & IL-6 ,detect genes .At first ,All participation patients are from the gastro-intestinal and Cardiology department of Al Fallujah General Hospital and Al Ramadi General Hospital , From period 1st September in 2020 to 1st April 2021 .A total of cases are 100 case ,50 case with Mitral Valve prolapse (pre-diagnosed with Mitral Valve Prolapse) ,Other 50 case are normal patients used as a control, their ages range from 10 to 70 year .All patients are suffered from gastric inflammation ,bloating ,nausea and burping, All patients don't have any drugs before tested. The diagnosis by three method , estimate INF-γ ,IL-6 by ELISA , All positive stool in MVP kept deep freezing for gene detect by Real Time PCR. The results are in SAT and U B T (identical result), positive in M V P patients high than N patients, Urban are a high positive results than urban. While in S Ab T are high positive in MVP than N patients ts. Also the results are positive in INF-γ and IL-6 are high values in MVP than N patients .the results of detect *H pylori* genes by real time PCR , 16sr RNA gene is positive for all MVP only, Cag-A gene is (12) positive (54%) , Vac A gene is (6) positive (27.5%)

Keywords: Arthrosclerosis , Coronary Heart Diseases, Mitral Valve Prolapse , 16s rRNA ,Cag-A, Vac-A *Helicobacter pylori* ,Interferon- gamma-γ , Interleukin-6 ,Stool Antigen Test , Serum Antibody Test and Urea Breath Test .

1. Introduction:

Helicobacter pylori is gram positive bacteria ,motile by(3-6) flagellum ,spiral shape ,It is belong to family *(Heilcobacteraceae)*.Genus Helicobacter have many species and *H pylori* one of these species is colonized on stomach ,At first ,It is discovered by two Australian physician ,Barry Marshall and Robin warren in 1982 ,they were identified *H pylori* of patient was suffering from gastric ulcer and abdominal pain .The prevalence of it is probably (44.3%) of the individuals on the wide world ,It is about (34.7%) prevalence in developed countries and about (50.8%) prevalence in developing countries(1) .Many of patients on the world have no clearly symptoms but only appeared gastritis under the endoscopic examination and the other patients have several symptoms such as nausea ,bloating ,burning pain , frequent burping and abdominal pain when stomach is empty For that ,the asymptomatic patients are occurring to them many changes and developing on their diseases to more severe that including : peptic ulcer (PU), gastric cancer (GC), and mucosa associated lymphoid tissue (MALT). Therefore, It has been classified by WHO as a class 1 carcinogenic (2) . *H pylori* bacterium have many virulence factors such as Cag-A ,Vac- A, Urec and OMPs ,This factors are play an important role on support pathogenesis of *H pylori*, they are provides adaptive conditions for *H pylori* colonized on the gastric mucosal layer ,invasion from immune system and produced urease enzyme to change pH to a high level and that make to be it survive in stomach .also *H pylori* have characterized to resistance for many antibiotic ,because of It is have ability to mutant to be more resistance that explain the difficult to eradicate it (3). .*H pylori* is have many mechanisms to evasion from immune response , The chronic active gastritis occurred when these initial responded are failure to eradication the infection of *H pylori* ,therefore the gastric mucosa accumulation of the cells such as neutrophils, B cells, T cells and macrophages, the cells refers to a characteristic histological of this disease , chronic stimulation of the inflammatory responses are n 't effected with gut and gastric organ only but caused dyslipidemia by increased levels of fibrinogen, stimulating the release of C-reactive proteins (CRP), increased blood leukocyte, the creation of hypercoagulability, stimulation the cross-reactivity, increased their proinflammatory Cytokines and at last the cytotoxic agents(of bacteria) (4) this sequence of happened that arise after a production of a variant proinflammatory and inflammatory metabolites are affected on the blood vessel elasticity and induced the endothelial dysfunction, which result of that by blocking arteries that way increased the chances of a heart attack. In C- reactive proteins it's considered as a potential

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indicator of the diseases that related with the heart and it is have a crucial role a vessel elasticity (5). B and T lymphocytes that way these caused a heart diseases or a heart attack. The toxins Cag A and Vac A increased inflammation and cellular damage that considered as third and autoimmune reaction could be imposed that and including across reactivity between an anti-Cag A (Antibodies) and a vascular wall antigen. these antibodies may contributed to activation of their inflammatory cells with the atherosclerotic lesion (6) *H pylori* infection make a high disturbances in the lipid metabolism and lipoprotein, The level of triglyceride usually rises and the level of HDL ,Cholesterol decreases and all that may be a reason of cytokines, especial the tumor necrosis factor-α that inhibition the lipoprotein lipase and enhanced a generation of a free radical which facilitated the oxidation of LDL, and it also affected to in the atherosclerosis and heart disease therefore that make many tissue and organs damaged.therefore, there are many studies to find the associated of it with many physiological disorder diseases such as Diabetic Mellitus type 2, Gastric Adenocarcinoma ,Arteriosclerosis and Coronary Heart Disease(7) In this study ,we proved the prevalence of *H pylori* among Mitral Valve Prolapse.

1.2 Mitral Valve Prolapse:

MVP is a type of the myxomatous valve diseases .The leaflets tissue of mitral valve and the chordae are a abnormally stretchy therefore ,when the heart beats the mitral valve flops or bows in to the left atrium. The symptoms of prolapse of mitral valve may be not have any regurgitation or have of severity from a mild leak to a very floppy leaky valve (8). The prevalent of valvular heart disease is a high around the world yet , (MVP) is one of it either syndrome with person from born or acquired with life and it will stay with patients for all their lifespan, may be increased or decreased (MVP) is the most popular valvular heart disease, it is affected about (93%) of people that as 75 years in old, it is a evaluation about (15–20%) (5 million) of the people in the world, and all the patients are diagnosed by heart failure diseases, which the heart failure is from mile to severe degree, most of the symptoms of (MVP) are bursts of rapidly heart beat as known (palpitations), chest discomfort, shortness of breath, dizziness, easily tired (9). Many of them may be not have any regurgitation or they may have a range of leak to a very floppy (Leaky valve) and the majority of people have no leak or a mild leak, a small percentage of people of them have severe MVP and require a treatment. MVP are affected with females are twice as from males, and it can be observed children, the teens and last in the adults (10) MVP is usually diagnosed from the routine physical exam, also is called the click-Mur Mur sound because of a doctor can hear a click and Mur Mur as result of abnormal blood flowing through the mitral value as that leaflet of a valve bow back into the left atrium with each heartbeat and that make sound .there are other testes used for diagnosis maybe more accuracy include :Echocardiography (ECHO) .Trans esophageal Echocardiography ,Cardiac Catheterization (Cardiac Cathoangiogram) Electrocardiogram (ECG) , Coronary Angiogram .and Chest –X-ray. All these are methods to detect MVP in peoples and each one have a different technical working , they give different results but they are act in one direction which it to detect MVP (11).

2.1 Study Subjects:

A total of one hundred patients an age range of (10-70) years (50) patients are normal as control and (50) patients are with MVP .In current study are interested in the Gastroenterology and Cardiology department in Ramadi teaching Hospital and Fallujah Central hospital, From. 15th September 2020 to first April 2021. All these individuals have suffering from nausea ,bloating ,frequent burning, loss of appetite ,a stomach ache ,burning ,abdominal pain , ,constipation , weight less unintentionally, when stomach empty frequent burping , and not bleeding in stool. diagnosed by three methods for *H pylori* , estimate (IL-6 ,IF-γ and detect PCR). All patients of study are divided into (2) groups as the following Group 1: this group are 50 patients group includes (29 male and 21 female) which are pre-diagnosis provisionally with M.VP already by stethoscope and ECG . Group 2: this group are (50) patients (34 male and 16 female) . all the patients have a period of antibiotic taken treatment less than 4 weeks from the time of test and collection. all these compounds may give false test .

2.2 Stool and Serum Samples Collection Test and Storage :

For collection stool samples from patients and make test for stool as it is described by manufactured company LUGENE Germany, all positive results of MVP patients keep freezing at -20°C for detect PCR . while for serum collection and make test for serum Abs test as it is described by manufactured company LUGENE Germany, all positive results of all patients keep freezing at -20°C for , estimate INF-γ ,IL-6 by ELISA .

3.2 ^{14}C Urea Breath Test:

This is consider as a gold standard method which is used for detect *H pylori* in patients when a recent disease and bacteria is survive and activity. This test is described as manufactured company Breath Test Kit from Mindray China and measured by ^{14}C Urea Breath Instrument.

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3.3 Detection of *H pylori* from Stool by Real Time PCR:

PCR is considered important method to detect *H pylori* in many sources of samples such as culture, saliva, dental plaque and stool, for that we need DNA extraction from stool to detect *H pylori* 16s rRNA ,Cag-A ,Vac-A genes.

A. DNA Extraction**:** All samples are preparing , freezing and keeping , they are freezing at -20Cº until PCR . DNA extraction by using a manual which is provided from the company that makes it Zymo Research Corp. Quick DNA fecal/soil microbe micropep kit produced in USA, protocol of extraction are performed according to manufactured company. at last, measure the concentration of extract DNA by Nanodrop microvalume at wave length 260-280 nm and with range (1.8-2.0µL) and now the filtered DNA is suitable for PCR

B. Primers preparation: These primers were supplied by MICROGENE Company in USA and lyophilized form. lyophilized primers are dissolved in a nuclease free water to get a required concentration .*primer sequences as (12).

C. Reaction set up and thermal cycling protocol as the devise of PCR .We take 22 samples of MVP patients with positive of *H pylori* proved by AST and UBT,. Make that by of many of working steps of manufactured company Go Tag Q pcr Master Mix Nuclease Free Water. Promega , USA detect Real Time by PCR program: Make a program in Mic qPCR Cycler Bio Molecular System ,Australia .

3.4 Enzyme – linked Immune Sorbent Assay:

A. Estimate Human Interferon Gamma (INF_γ) and Human Interleukin- 6 (IL-6) by ELISA in all patients :This sandwich kit is for the accurate quantitative detection of Human (INF_γ and IL-6) in serum, plasma, etc. Kit is provided from Bioassay Company, China. measured by Microplate ELISA Reader, all results (INF-γ >5 ng/L) consider positive and all results (IL-6 >10 ng/L) consider positive too. result calculation: The results are calculate recently by Microplate ELISA Reader,

4.1 Results and Discussion :

In this study is including to detect prevalence and associated of *H pylori* infection with chronic diseases, cytokines ,MVP , normal patients and their residency ,the depending tests are SAT and UBT because they are identical in this study . The results are high significant (p <0.005) observed positive for: M V P patient with : (16%) Urban and (6 %) Rural , while N patient with (4%) Urban and (4%) Rural .The results are negative for : M V P patients with (18%) Urban and (9%) Rural ,while N patients with (31%) Urban and (12%) Rural, In this study observed different data between males and females .males are about (20%) positive and (43 %) negative .While females are about (10%) positive and (27%) negative , also The patients of age groups are observed high in (30-40 ,40-50) age groups than other . The results are performed by two tests AST and UBT .The results of them are identical to all patients. IL-6 and INF-γ are high value with MVP patients than normal patients when all of them positive with *H pylori* . The results of all patients when tested with Antibody test are : positive in(29%) in M V P ,(28%) in N patients , negative (21 %) in M V P patients ,(22%) in N patients and they are different with AST & UBT when compared .all MVP patients(22) are positive with detect 16s rRNA gene (22) (100%) , Cag-A (12) (54%) and Vac - A (6) (27.5%). The results of Interferon gamma are : positive to (27%) in MVP patients ,(17%) in N patients while negative to (23%) in M V P patients , (33%) in N patients. As well as ,The results of Interleukin-6 are : positive to (22%) in M V P Patients , (15%) in N patients while negative to (28%) in M V P patients ,(35%) in N patients .

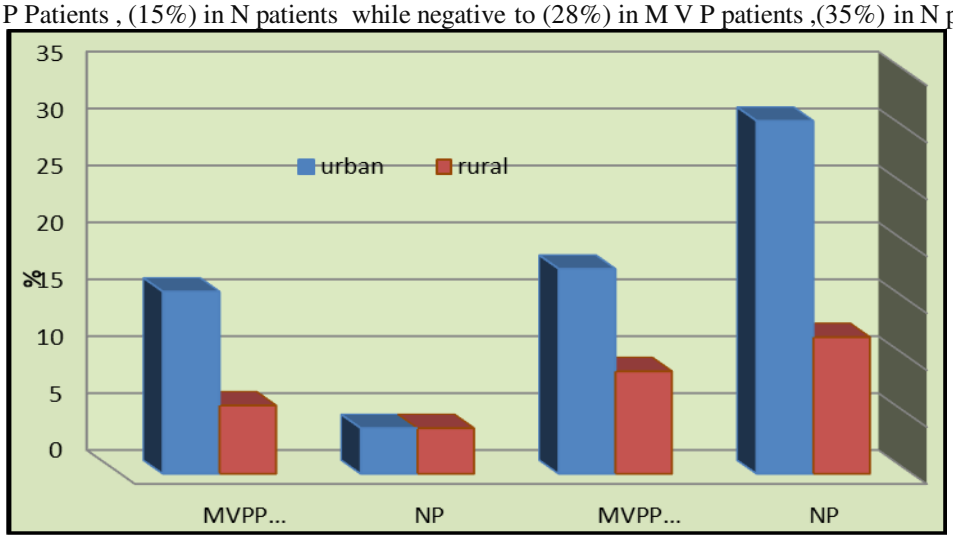

Table (1) Distribution of *Helicobacter pylori* infections among MVP and N patient according to residency .

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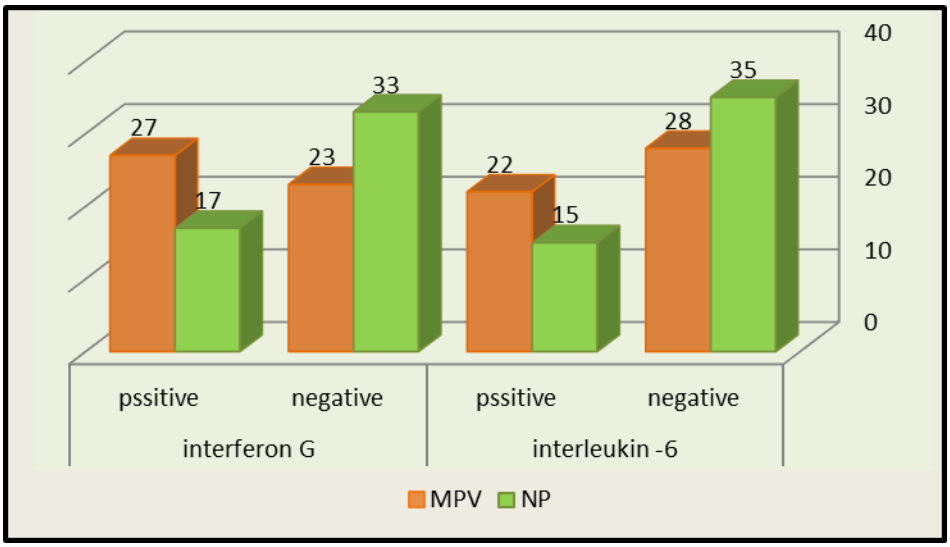

Table (2) Distribution of *Helicobacter pylori* infections (diagnosis by AST ,UBT) among M V P and N patient and related with high value of INF-γ and IL-6.

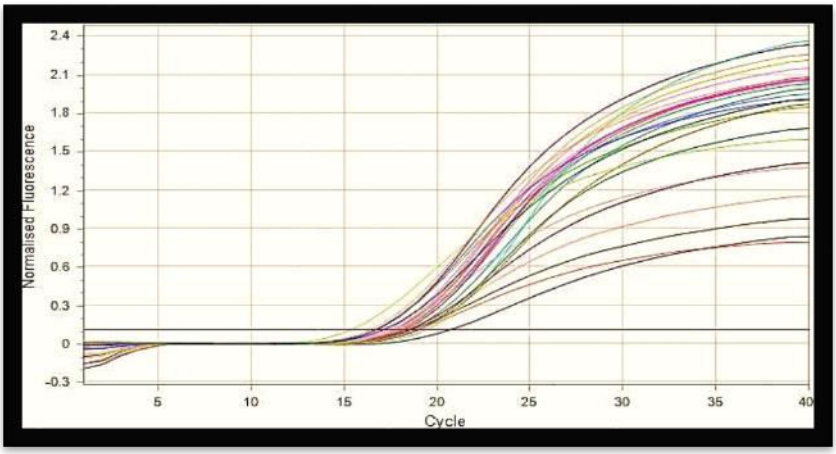

Figure (1) Detect 16s rRNA in MVP patients that positive with *H pylori* tested by (AST & UBT)

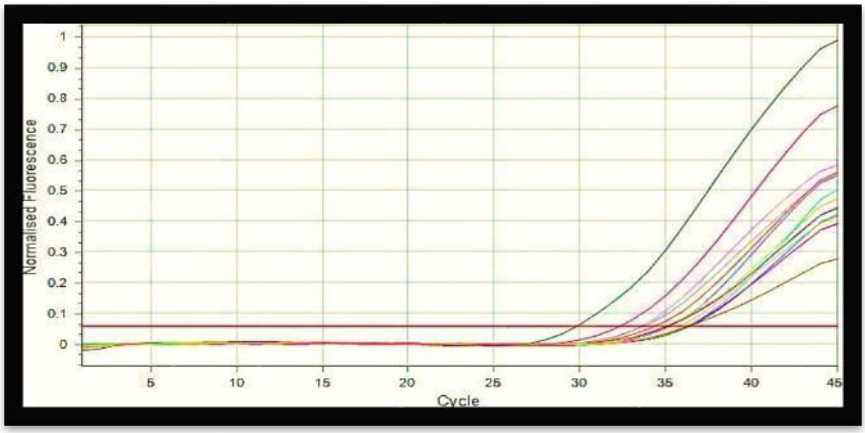

Figure (2) Detect Cag-A in MVP patients that positive with *H pylori* tested by (AST & UBT).

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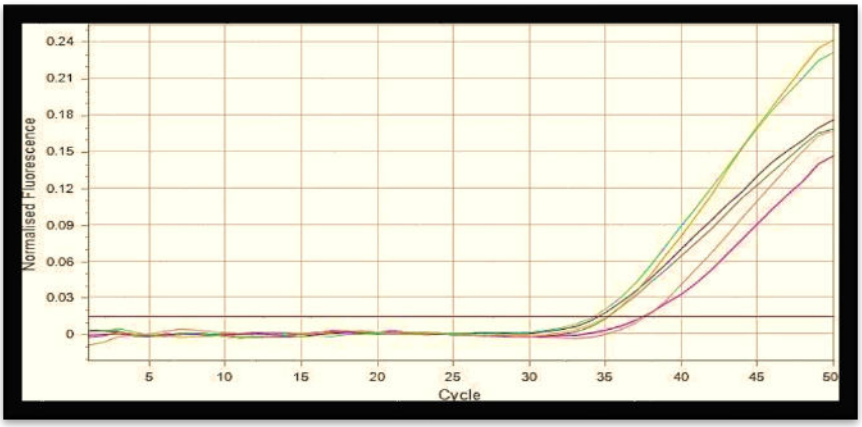

Figure (3)) Detect Vac-A in MVP patients that positive with *H pylori* tested by (AST & UBT).

Discussion

These results are appear differences of infection between MVP patients and normal patients , MVP patients are high results with *H pylori* infection , value INF-γ and IL-6 ,also infection with this bacterium are high in rural than urban , the infections are high in male than female ,infections are high in (30-40),(40-50) than the other age groups .All that are belong to: socioeconomic ,nutrition status, ecological contamination, personal cleanliness and prevalence range of infection in geographic spot , overcoming in city , more mixing among population , working environment and more hospitals ,all that increased transmission of infection in population .As well as , personal factors hygiene , dietary habits ,differences on host genetic, and also environment factors : supply with clean water, sanitary wastewater ,geographic area and cultural awareness These factors are different from one population to another, one place to another and one time to another , so many biologic factor are effected, chronic diseases (Diabetic Mellitus ,CHD and Arthosclorosis) , lowly immune responses , gender , hormones and bacterial infections.. that proved prevalence of infection among some groups (13). These results are appear differences between SAT and S Abs T while SAT and UBT are identical and that belong to : in serum antibody test is not specific for active or no active infections , *H pylori* strains stimulate variant levels of antibodies , variant with host genetic, many pathogenic microorganisms have similar virulence factor, a long period to used antibiotic give false positive and gastritis ,bleeding also give false positive for that ,the Abs test is used for clinical participates and to detect a prevalence of bacteria .While stool antigen test and Urea Breath Test are more accuracy to detect for infection , , these tests are using to detect a current and survive infection of bacteria which it is making a stimulating and disorder . But also S A T effected with antibiotic ,PPI , NASID , and diarrhea, bleeding therefore , to reduced false result may be prevent patients from all drugs for two weeks before test (14) ,(15). the levels of each Interferon gamma and Interleukin -6 are associated with diversity of *H pylori* genotypes. In addition , Cytokines is related with host immune ,age ,gender ,have or no chronic disease , lifestyle and nutrition .In fact released cytokines refer to dangerous order but not give real value of infection ,Also all studied of CHD, Atherosclerosis and Myocardial Infarction were identical . *H pylori* is responsible of many disorders: Iron and B_{12} deficiency, metabolism disorder , Increased Cytokines , Increased activity of other bacteria , Increased Triglyceride and the first reason of gastric cancer .All that disorders may be belong to the mechanisms that used from it to invasion , colonized , virulence factor , immune responses, difficult to eradicated it and high resistance to antibiotic , therefore it prevalence in patients with Chronic or Syndrome diseases (11). 16s rRNA gene is a specific to detect *H pylori* consider as a housekeeping gene which different from microorganisms and it used as a closely molecular to recognize between closely species because of sequences from distantly related bacterial lineages are showed to have similar functionalities in many countries for many studies including differentiation the gut microbiota in gastric dyspasia in U S A by George et al (16). The differences in the current result and other study in Iraq when used different samples to detect 16s rRNA may be a false tested used ,mistake in primer sequences , type of specimens , a false keeping method , and diversity of *H pylori* genetic compare with geographic area when it located . In cases of saliva normal flora secreted bacitracin against *H pylori* growth ,effect yeasts and short life a reason to O_2 exposure(3) . *H pylori* has many genotypes of Cag A gene , therefore the effect on host may be different from one to other ,Cag A gene positive have secretion system island (T4SS) is responsible on gastric cancer by increased the inflammation and induced to high level of Interferon gamma (INF-γ) make to induced pre-new plastic changes in mucosa layer of gastric and Cag A is make to increase the level of COX 1 and COX 2 in vascular endothelium which is due to generate prostacyclin and caused platelets aggregation and the arise of cytokines is effected with atherosclerosis therefore infections are more

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virulence in CHD and Atherosclerosis .As well as several patients with asymptotic or moderate gastritis are negative to Cag A . diversity in genetic, ethics , geographic region and chronic disease of host as co factor in virulence of *H pylori* (11) All strains of *H pylori* have Vac A gene but the differences in result belong to the diversity in genotype of Vac A gene It is polymorphic alleles are (s1a ,s1b, s1c ,s2 and m1, m2) the Vac A s1m1 strain is more virulence, Vac A is responsible about vacoulation , a ptosis and reduced proliferation ,it has many receptors on host cell which support a binding with trans membrane, it is make to damage tissue therefore it is increased Heart diseases and autoimmune diseases (16). to identify the genotype more common ,proved Vac A s1 m1 is the high level and it related with increased Cytokines also other genotype induced Cytokines but Lesley amount ,the result of study may be contrary not related with infected genotype only but also effected with primer sequences , sample type, geographic area (3)(17).

Conclusion: The MVP patients are more infection with bacteria than normal patients. The levels of INF γ and IL-6 are more value in M V P patients than normal patients that refer to associated of bacteria with immunity of patients and increase with chronic diseases The patients with *H pylori* have a high Levels of INF γ and IL-6 especially when strains have Cag A & Vac A genes .*H pylori* is more prevalence in persons have chronic disease ,The test is more accuracy to diagnosis *H pylori* is Urea Breath Test and Stool Antigen Test than Serum Antibody Test but high value of INF-γ & IL-6 related with S Abs t than SAT or UBT, when patients are prevent from drugs which is give a false positive May be to detect h pylori in stool in Real time PCR dependent on 16s rRNA as a House keeping gene. There are many strains of *H pylori* ,therefore not all infection may be dangerous.

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Ethical Approval : All patients were examined according to the ethical standards of the responsible committee on human in the Ramadi city Institutions of Health, Ministry of Health. Informed consent was gained from all patients for their involvement in the study.

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