Serum Soluble Triggering Receptor Expressed on Myeloid Cells versus 16s rRNA genes detection in early diagnosis of bacteremia in malignant febrile neutropenic patients

thesis

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Presented by

Omima Sayed Mohammed

Master degree of Medical Microbiology and Immunology

Under supervision of

Dr. Manal Mohamed Yassin

Professor of Medical Microbiology and Immunology

Faculty of Medicine, Ain Shams University

Dr. Nehad Mohamed Sayed

Professor of Medical Microbiology and Immunology

Faculty of Medicine, Ain Shams University

Dr. Lamiaa Abd EL Monem Adel

Assistant professor of Medical Microbiology and Immunology

Faculty of Medicine, Ain Shams University

Faculty of Medicine

Ain Shams University

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مستوى المستقبل المحفز الموجود على الخلايا الميلوديه الذائب فى المصل بالمقارنه بالكشف عن جينات الحامض النووى الريبوزى البكتيرى ذي الترميز ١٦إس فى التشخيص المبكر لوجود البكتيريا فى دم مرضى قلة العدلات الحموية الناتجة من الاورام الخبيثة

رسالة

توطئة للحصول على درجة الدكتوراه

فى الميكروبيولوجيا الطبية والمناعة مقدمة من

الطبيبة/ اميمـــــة سيـــــد محمـــــد

ماجستير الميكروبيولوجيا الطبية والمناعة

كلية الطب جامعة عين شمس

تحت اشراف

د / منـــال محمـــد ياسيـــن

استاذ الميكروبيولوجيا الطبية والمناعة

كلية الطب جامعة عين شمس

د / نهـــاد محمـــد سيـــد

استاذ الميكروبيولوجيا الطبية والمناعة

كلية الطب جامعة عين شمس

د/ لميـــاء عبـــد المنعـــم عـــادل

استاذ مساعد الميكروبيولوجيا الطبية والمناعة

كلية الطب جامعة عين شمس

كلية الطب

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Omima Sayed

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List of Abbreviations

A	**ACCP**	**A**merican **C**ollege of **C**hest **P**hysicians
	ACEP	**A**merican **C**ollege of **E**mergency **P**hysicians
	ALL	**A**cute **L**ymphoblastic **L**eukemia
	AML	**A**cute **M**yeloid **L**eukemia
	ANC	**A**bsolute **N**eutrophil **C**ount
	APPT	**A**ctivated **P**artial **P**hromboplastin **T**ime
	ARDS	**A**cute **R**espiratory **D**istress **S**yndrome
	AUC	**A**rea **U**nder **C**urve
B	**BAL**	**B**roncho **A**lveolar **L**avage
	BP	**B**ase **P**air
	BCLL	**B**-cell **C**hronic **L**ymphocytic **L**eukemia
	BSI	**B**lood **S**tream **I**nfections
C	**CARD**	**Ca**spase-**R**ecruitment **D**omain protein
	CBC	**C**omplete **B**lood **C**ount
	CD	**C**luster **D**ifferentiation
	CDC	**C**enters of **D**iseases **C**ontrol and prevention
	CFU	**C**olony **F**orming **U**nit
	CI	**C**onfidence **I**nterval
	CLL	**C**hronic **L**ymphocytic **L**eukemia
	CMV	**C**yto**m**egalo**V**irus
	CNS	**C**entral **N**ervous **S**ystem
	CO2	**C**arbon dioxide
	CPG	**C**ytosine- **P**hosphate- **G**uanine
	CRP	**C**-**R**eactive **P**rotien
	CSF	**C**olony **S**timulating **F**actor

	CT	**C**omputed **T**omography
D	**DAG**	**D**i**a**cyl**g**lycerol
	DAP-12	**D**nax-**A**ctivation **P**rotein-12
	DC	**D**endritic **C**ells
	DEAE	**D**i**E**thyl**A**mino**E**thyl
	DIC	**D**isseminated **I**ntravascular **C**oagulopathy
	DNA	**D**eoxy**N**ucleic **A**cid
	DNTP	**D**eoxy **N**ucleotide **T**ri**P**hosphate.
E	**EAE**	**E**xperimental **A**utoimmune **E**ncephalomyelitis
	ELISA	**E**nzyme **L**inked **I**mmuno**S**orbent **A**ssays
	EDTA	**E**thylene**D**iamine**T**etra**A**cetic acid
	ERK	**E**xtracellular signal **R**egulated **K**inase
	ERM	**E**zrin, **R**adixin and **M**oesin
	ESBL	**E**xtended **S**pectrum **B**-**L**actamase
	ESICM	**E**uropean **S**ociety **o**f **I**ntensive **C**are **M**edicine
	ESR	**E**rythrocyte **S**edimentation **R**ate
F	**FA**	**F**anconi **A**nemia
	FERM	**F** domain of **E**zrin, **R**adixin and **M**oesin
	FISH	Fluoresent **I**n **S**itu **H**ybridization
	FN	**F**ebrile **N**eutropenia
G	**G-CSF**	**G**ranulocyte **C**olony-**S**timulating **F**actor
	GM-CSF	**G**ranulocyte **M**onocyte **C**olony-**S**timulating **F**actor
	GRB	**G**rowth factor **R**eceptor **B**inding protein
H	**HCC**	**H**epatocellular **C**ancenoma
	HCL	**H**airy **C**ell **L**eukemia
	HCV	**H**epatitis **C** **V**irus
	HHM	**H**umoral **H**ypercalcemia of **M**alignancy
	HIV	**H**uman **I**mmunodeficiency **V**irus

	HL	**H**odjkin **L**ymphoma
	HLA	**H**uman **L**eukocyte **A**ntigen
	HSV	**H**erpes **S**implex **V**iruses
	HTLV-1	**H**uman **T**-**l**ymphotropic **V**irus-1
	ICU	**I**ntensive **C**are **U**nit
	IG	**I**mmuno **G**lobulin
	IL	**I**nterleukin
	ITAM	**I**mmunoreceptor **T**yrosine-based **A**ctivation **M**otif
	ITIM	**I**mmunoreceptor **T**yrosine-based **I**nhibition **M**otif
	ITS	**I**nternal **T**ranscribed **S**pacer
	IV	**I**ntra **V**enous
	IVIG	**I**ntra **V**enous **I**mmuno **G**lobulin
J	**JAK2**	**J**anus **K**inase 2
K	**KPC**	**K**lebsiella **P**neumoniae **C**arbapenemase
L	**LCBI**	**L**aboratory-**C**onfirmed **B**loodstream **I**nfection
	LPS	**L**ipo **P**oly **S**accaride
M	**MAPK**	**M**itogen-**A**ctivated **P**rotein **K**inase
	MBI-LCBI	**M**ucosal **B**arrier **I**njury **L**aboratory-**C**onfirmed **B**loodstream **I**nfection
	MDS	**M**yelo **D**ysplastic **S**yndromes
	ML	**M**illi **L**iter
	µL	**M**icro **L**iter
	MM	**M**ultiple **M**yeloma
	MMP	**M**atrix **M**etallo-**P**roteinases
	MPN	**M**yelo **P**roliferative **N**eoplasms
	MRSA	**M**ethicillin **R**esistant **S**taphylococcus **A**ureus
	MS	**M**ultiple Sclerosis
N	**N**	**N**umber

	NCCN	**N**ational **C**omprehensive **C**ancer **N**etwork
	NF-κB	**N**uclear **F**actor **κB**
	NHL	**N**on **H**odjkin **L**ymphoma
	NPV	**N**egative **P**redictive **V**alue
O	**O2**	**O**xygen
	PAMP	**P**athogen-**A**ssociated **M**olecular **P**attern
	PAO2	**A**rterial **O**xygen **T**ension
	PAP	**P**ulmonary **A**lveolar **P**roteinosis
	PAS	**P**eriodic **A**cid–**S**chiff
	PCR	**P**olymerase **C**hain **R**eaction
	PCT	**P**roalcitonin
	PDC	**P**lasmacytoid **D**endritic **C**ell
	PG	**P**ico**G**ram
	PGLYRP1	**P**eptido**Gly**can **R**ecognition **P**rotein 1
	PI3K	**P**hosphatidyl**I**nositol 3-**K**inase
	PKC	**P**rotein **K**inase **C**
	PMNs	**P**oly**M**orpho**N**uclear cells
	PNA	**P**eptide **N**ucleic **A**cid
	PNL	**P**olymorph **N**uclear **L**eukocytes
	PLC	**P**hospho **L**ipase **C**
	PPV	**P**ositive **P**redictive **V**alue
	PT	**P**rothrombin **T**ime
	PTH	**P**ara **T**hyroid **H**ormone
	PTHrP	**P**ara **T**hyroid **H**ormone **r**elated **P**rotien
R	**rRNA**	**R**ibosomal **R**ibo**n**ucleic **A**cid
	ROC	**R**eceiver **O**perating **C**haracteristic
S	**SCCM**	**S**ociety of **C**ritical **C**are **M**edicine
	SD	**S**tandaed **D**eviation

	Siglec H	**Si**alic acid binding**I**immuno**G**lobulin-like **Lec**tin **H**
	SIRS	**S**ystemic **I**nflammatory **R**esponse **S**yndrome
	SLE	**S**ystemic **L**upus **E**rythrematosis
	SPS	**S**odium **P**olyanethole**S**ulfonate
	Src	**S**arcoma **k**inase
	Syk	**S**pleen **T**yrosine **K**inase
T	**sTLT-1**	**S**oluble TLT-1
	sTREM	**S**oluble **T**riggering **R**eceptor **E**xpressed on **M**yeloid cells
	TAE	**T**ris-**A**cetate-**E**DTA
	TLR	**T**oll-**L**ike **R**eceptor
	TLT	**TREM L**ike **T**ranscript
	TNF-α	**T**umor **N**ecrosis **F**actor – **α**
	TREM	**T**riggering **R**eceptor **E**xpressed on **M**yeloid cells
	TREM-1L	**T**REM-1 **L**igand
	T- test	Student **t- test**
U	**US**	**U**nited **S**tates
	UTI	**U**rinary **T**ract **I**nfection
	UV	**U**ltra**V**iolet
V	**VRE**	**V**ancomycin **R**esistant **E**nterococcus
	VZV	**V**aricella-**Z**oster **V**irus
W	**WBCs**	**W**hite **B**lood **C**ells
	WHO	**W**orld **H**ealth **O**rganization.
Z	**ZAP**	ζ- chain-**A**ssociated **P**rotein

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INTRODUCTION

Infections are the leading cause of morbidity and mortality in neutropenic patients with hematological malignant disease. Those immunocompromised patients are at high risk of infection as a result of the underlying malignancy or due to chemotherapy ***(Arzanian et al., 2011)***.

For many years, fever has been recognized as a major sign of infection in patients with hematological malignancy during neutropenia. Unfortunately many non infectious processes may be responsible for fever , and the etiology of fever in most of neutropenic patients is unknown .So diagnosis of infection in those patients is still problematic because clinical signs are often vague , and laboratory parameters are non specific ***(Soreng, 2010).***

Conventional blood culture is considered the gold standard for confirmation of bacterial sepsis, but it requires a minimum of 48–72 hours and yield a positive results in only 30-40% of cases ***(Heininger et al., 2004).***

To overcome these difficulties it is necessary to advise new rapid diagnostic tests to help in early diagnosis and therefore may prevent unnecessary usage of broad-spectrum antibiotic ***(Connel et al., 2007).***

Automated blood culture is more sensitive than conventional one, and gives significantly faster results ***(Yu and Black, 2003).***

Recently, polymerase chain reaction (PCR) based assays have the potential to provide an early and accurate diagnosis of bacterial pathogens

especially the culture resistant, fastidious, inactivated or slow-growing bacteria ***(Al Mousawi and Kadhim, 2011).***

16S rRNA genes are common and conserved in all bacteria .Those universal or broad range PCR primers are considered new and effective methods of detection of bacterial pathogens in normally sterile body fluids ***(Kalghatgi et al., 2008).***

One of the new methods for detecting sepsis is Soluble Triggering Receptor Expressed on Myeloid Cells (sTREM-1) test. sTREM-1 is a superfamily of immunoglobulins produced by phagocytes, especially macrophages that are stimulated by microbial products and therefore its level will be increased when and where macrophages accumulate ***(Miedema et al., 2010).***

It has been described that the molecule (sTREM-1) can be further up regulated by stimulation of the cells by bacteria and their products. Triggering of the receptor will result in the release of pro-inflammatory cytokines and chemokines and the up regulation of surface activation markers and in that respect is thought to be amplifying inflammatory responses to bacterial infections and potentiate septic shock ***(Collins et al., 2008)***.

Although sTREM-1has recently been suggested as a marker for bacterial infection, only a few studies have been published before in patients with hematological malignancy during neutropenia ***(Arzanian et al., 2011)***.

AIM OF THE WORK

This study aims to evaluate the utility of measuring sTREM-1 level; compared to 16S rRNA gene detection; in early diagnosis of bacteremia in febrile neutropenic patients with hematological malignancie.

HEMATOLOGICAL MALIGNANCIES

Hematological malignancies comprise a collection of heterogeneous conditions, all originating from cells of the bone marrow and the lymphatic system. There are three major groups: leukemia, lymphoma, and plasma cell neoplasms ***(Burns et al., 2010).***

Hematological neoplasms are comparatively common, accounting for around 9% of all cancers and being the fourth most frequently diagnosed cancer in both men (after prostate, lung, and colorectum) and women (after breast, lung, and colorectum) in developed regions of the world ***(Westlake, 2009).***

In 2001 the WHO produced, for the first time, a consensus classification that defined disease entities in terms of immunophenotype, genetic abnormalities and clinical features ***(National Cancer Intelligence Network, 2009; Jemal et al., 2011).***

Types of hematological malignancies:

A-Leukemia is a set of diseases of the blood or bone marrow, involving an abnormal proliferation of blood cells ***(Horner et al., 2009)***

1-Acute myeloid leukemia (AML), also known as acute myelogenous leukemia or acute non lymphocytic leukemia, is a cancer of the myeloid line of blood cells, characterized by the rapid growth of abnormal white blood cells (WBCs) that accumulate in the bone marrow and interfere with the production of normal blood cells. AML is the most common acute leukemia affecting adults, 30% of all leukemias, and its incidence increases with age ***(Jemal et al., 2011).***