بسم الله الرحمن الرحيم

MONA MAGHRABY

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

MONA MAGHRABY

شبكة المعلومات الجامعية

التوثيق الإلكتروني والميكروفيلم

جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها
علي هذه الأقراص المدمجة قد أعدت دون أية تغيرات

يجب أن

تحفظ هذه الأقراص المدمجة بعيدا عن الغبار

MONA MAGHRABY

Exploring The Clinical Significance Of Serum Angiopoietin-2 In Breast Cancer Patients

Thesis

Submitted for Partial Fulfillment of Master Degree in Clinical Pathology

Presented by

Seham Kamal Mohamed

M.B., B.Ch. Faculty of Medicine- Alazher University

Supervised by

Professor. Abeer Ibrahim Abd Elmagid

Professor of Clinical Pathology

Faculty of Medicine, Ain Shams University

Professor. Hala Abdel Al Ahmed

Professor of Clinical Pathology

Faculty of Medicine, Ain Shams University

Dr. Wessam El-Sayed Saad

Assistant Professor of Clinical Pathology

Faculty of Medicine, Ain Shams University

Faculty of Medicine

Ain Shams University

2020

في استكشاف الأهمية الاكلينيكية للأنجيوبويتين-٢ □الدم لدى مرضى سرطان الثدي

رسالة

توطئة للحصول علي درجة الماجستير في الباثولوجيا الاكلينيكية

مقدمة من

□ سهـام كمـال محمـد موسـى/الطبيبة

بكالوريوس الطب والجراحة - كلية الطب- جامعة الأزهر

تحت إشراف

الأستاذ الدكتور/ عبيـــرإبراهيـــم عبد المجيـــد

أستاذ الباثولوجيا الاكلينيكية

كلية الطب- جامعة عين شمس

الأستاذ الدكتور / هالـة عبد العـــال أحمـــــد

أستاذ الباثولوجيا الاكلينيكية

كلية الطب- جامعة عين شمس

□د/ وسام السيد سعد

أستاذ مساعد الباثولوجيا الإكلينيكية

كلية الطب- جامعة عين شمس

كلية الطب

جامعة عين شمس

٢٠٢٠

سورة البقرة الآية: ٣٢

Acknowledgement

First and foremost thanks to ALLAH, the Most Merciful.

I wish to express my deep appreciation and sincere gratitude to ***Prof. Abeer Ibrahim Abd Elmagid,*** *Professor of Clinical Pathology, Ain Shams University, for her close supervision, valuable instructions, continuous help, patience, advices and guidance. She has generously devoted much of her time and effort for planning and supervision of this study. It was a great honor to me to work under his direct supervision.*

I find no words by which I can express my deepest thanks and appreciation to ***Prof. Hala Abdel Al Ahmed,*** *Professor of Clinical Pathology, Ain Shams University, for greet support, valuable supervision and continuous encouragement throughout the whole work.*

I wish to express my great thanks and gratitude to ***Dr. Wessam El-Sayed Saad,*** *Assistant Professor of Clinical Pathology, Ain Shams University, for her kind supervision, indispensable advice and great help in this work.*

Last and not least, I want to thank all my family and my colleagues for their valuable help and support.

Finally I would present all my appreciations to my patients without them, this work could not have been completed.

CONTENTS

List of Abbreviations

ANG	: Angiopoietin
ATM	: Ataxia telangiectasia mutated gene
AUC	: Area under curve
BRCA	: Breast cancer gene
CA	: Cancer antigen
	:
CEA	: Carcino embryonic antigen
CT	: Computed tomography
ECs	:Endothelial cells
Eff	: Efficacy
EGF	: Endothelial growth factor
ELISA	: Linked immunosorbent assay-enzyme
ER	: Estrogen receptor
FAK	: Focal adhesion kinase
FN	: False negative
FOXO1	: Forkhed box protein 1
FP	: False positive
HER2/neu	: Human epidermal growth factor receptor 2/ neuro-glioblastoma
HIF	: Hypoxia-inducible factor
ICAM1	: Intercellular adhesion molecule 1
Ig	: Immunoglobulin
IHC	: Immunohistochemistry
IQR	: Interquartile range
JAM	: Jancutinoal adhesion molecule
KDR	: Kinase domain region
MAb	: mono clonal antibody
mL	: milliliter
MRI	:Magnetic resonance imaging
NPV	: Negative predictive value
OR	: Odd ratio
P value	: Probability value
p53	: The 53 kda protein
PAF	: Platelet-activating factor
PAI	: Plasminogen activator inhibitor
PCR	: Polymerase chain reaction
PECAM	: Platelet endothelial cell adhesion molecule
PH	: Prolyl hydroxylase

PI3K/AKT	: Phosphatidyl inositide-3- oh kinase and protein kinase b
PPV	: Positive predictive value
PR	: Progesterone receptor
PTEN	: Phosphatase and tensin gene,
ROC	: Receiver operating chart
Rs	: Reference snp
RT	: reverse transcription
rTKs	: Receptor tyrosine kinases
SBR	: Scarff-bloom-richardson
	:
SD	: Standard deviation
Ser	: Serine
SMCs	: Smooth muscle cells
SN	: Sensitivity
SP	: Specificity
TEM	: Tie2-expressing monocytes
TGF	: Tumor growth factor
Tie2	: Tyrosine kinase with immunoglobulin-like and EGF-like domains 2
Tis	: Tumor in situ
TN	: True negative
TNFα	: Tumor necrosis factor-α
TNM	: Tumor-node-metastasis
TP	: True positive
Tyr	: Tyrosin
UPA	: Urokinase plasminogen activator
uPA	: urokinase plasminogen activator
uPAR	: uPA membrane bound receptor
US	: Ultrasonography
VCAM1	: Vascular cell-adhesion molecule 1
VE-cadherin	: Vascular endothelial
VEGF	: Vascular endothelial growth factor
Ẋ	: Mean
z	: Mann-whitney test
χ2	: Chi square

List of Tables

List of Figures

ABSTRACT

Background: Breast cancer is the most common cancer among women and one of the most important causes of death among them.Angiogenesis is an important step for primary tumor growth, invasiveness, and metastases. Angiopoietins are well-recognized endothelial growth factors that are involved in angiogenesis associated with tumors.

Aim: To explore the diagnostic significance of serum angiopoietin-2 (Ang-2) in breast cancer and to evaluate its prognostic efficacy through studying the degree of its association with the TNM staging of the disease.

Patients and Methods: This study was conducted on (35) Egyptian female patients who were diagnosed as breast cancer according to histopathological examination of breast biopsy (Group 1, Breast Cancer Patients) and (25) female patients with benign breast diseases (Group II, Pathological Control Patients), in addition to (20) age - matched apparently healthy, free mammogram, females serving as healthy controls (Group III, Healthy Controls). For all participants, measurement of serum Ang-2 was done using enzyme linked immunosorbent assay (ELISA) technique.

Results: A highly significant increased levels of Ang-2 was observed in breast cancer patients when compared to healthy control group ($Z= 4.95$, $p<0.01$). However, no significant difference was observed in Ang-2 levels between breast cancer patients group and pathological control group ($Z=3.37$, $p>0.05$). No significant difference was detected in Ang-2 levels in relation to TNM stage and histological grade. No significant correlation was found between Ang-2 levels and serum levels of CA15-3, hormone receptors, HER2/new receptor status ($p>0.05$, respectively).

Conclusion: This study revealed that Ang-2 serum levels were significantly increased in patient with breast cancer compared with healthy controls, indicating that high Ang-2 level is a promising non invasive biomarker for breast cancer diagnosis. However, no significant difference of Ang-2 levels was detected in relation of breast TNM staging in the population studied.

. **Keywords:** Breast cancer, Angiopoietins, Ang-2, ELISA

INTRODUCTION

Breast cancer is the most common cancer in women worldwide where it represents 25% of all cancers ***(Ferlay et al., 2015),*** and ranks second as a cause of cancer related death in females ***(Oak et al., 2016).*** Nearly 1.2 million new cases are diagnosed annually; this represents about 12% of all new cancer cases ***(Ferlay et al., 2015).***

Mammography is the gold standard for screening of early stage breast cancer, with a limited sensitivity of 37.5% ***(Riedl et al., 2015)***. The false positive rate of mammography is too high to be tolerated, resulting in additional unnecessary follow-up testing or biopsy recommendations. Moreover, the achilles' heel of this technique is the risk of radiation-induced breast cancer during mammography ***(Ali et al., 2015).***

The two most widely applied serum tumor markers for breast cancer are carcinoembryonic antigen (CEA) and cancer antigen 15-3 (CA15-3). However, these two markers have a sensitivity of 54.4% and 48.6%, respectivily and a specificity of 77.6% and 89.8%, respectivily ***(Park et al., 2014)***. Moreover, their serum levels are not correlated with staging of the breast cancer and their use is only limited to the breast cancer recurrence ***(Moazzezy et al., 2014 and Di Gioia et al., 2016).*** Therefore, there is an urgent need for a diagnostic marker that allows the accurate early diagnosis of breast cancer.