



شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكرو فيلم

بسم الله الرحمن الرحيم



HANAA ALY



شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكروفيلم



شبكة المعلومات الجامعية التوثيق الإلكتروني والميكروفيلم



HANAA ALY



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



HANAA ALY



Follistatin Level as a Prognostic Marker of Allogenic HSCT in Haematological Disease

Thesis

*Submitted for Partial Fulfilment of Master Degree
in Clinical Haematology*

By

Omar Mohamed Mahmoud Abouelhassan

M.B.B.ch.

Under Supervision of

Prof. Dr. Mohamed Osman Azzazi

*Professor of Internal Medicine-Clinical Haematology and BMT
Faculty of medicine, Ain Shams University*

Prof. Dr. Walaa Ali Elsalakawy

*Professor of Internal Medicine-Clinical Haematology and BMT
Faculty of Medicine, Ain Shams University*

Dr. Haydi Sayed Mohamed

*Lecturer of Internal Medicine-Clinical Haematology and BMT
Faculty of Medicine, Ain shams university*

*Faculty of Medicine
Ain shams university
2020-2021*

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قَالَ

سَبِّحْ اِنَّكَ لَا تَعْلَمُ لَنَا
اِلَّا مَا عَلَّمْتَنَا اِنَّكَ اَنْتَ
الْعَلِيمُ الْعَظِيمُ

صدق الله العظيم

سورة البقرة الآية: ٣٢

Acknowledgment

*First and foremost, I feel always indebted to **ALLAH**,
the Most Kind and Most Merciful.*

*I'd like to express my respectful thanks and profound
gratitude to **Prof. Dr. Mohamed Osman Azzazi**,
Professor of Internal Medicine-Clinical Haematology and BMT
Faculty of medicine, Ain Shams University for his keen
guidance, kind supervision, valuable advice and continuous
encouragement, which made possible the completion of this work.*

*I am also delighted to express my deepest gratitude and
thanks to **Prof. Dr. Walaa Ali Elsalakawy**, Professor of
Internal Medicine-Clinical Haematology and BMT Faculty of
Medicine, Ain Shams University, for her kind care, continuous
supervision, valuable instructions, constant help and great
assistance throughout this work.*

*I am deeply thankful to **Dr. Haydi Sayed
Mohamed**, Lecturer of Internal Medicine-Clinical
Haematology and BMT Faculty of Medicine, Ain shams
university, for her great help, active participation and guidance.*

Omar Mohamed

List of Contents

Title	Page No.
List of Abbreviations.....	i
List of Tables	iv
List of Figures	vii
Introduction	1
The Aim of the Study.....	3
Review of Literature	
Stem Cell Transplantation.....	4
Graft-Versus-Host Disease.....	31
Diagnostic Biomarkers of GVHD.....	60
Patients and Methods.....	82
Results	97
Discussion	136
Summary and Conclusion.....	147
Recommendations	151
References	152
Arabic Summary	—

List of Abbreviations

Abb.	Full term
AHSC.....	Allogeneic hematopoietic stem cell transplant
ALP.....	Alkaline phosphatase
ALT.....	Alanine aminotransferase
AML.....	Acute myeloid leukemia
ANC.....	Absolute neutrophil count
ANG2.....	Angiopoetin-2
ANOVA.....	One-way analysis of variance
APCs.....	Antigen presenting cells
AST.....	Aspartate aminotransferase
ATG.....	Antithymocyte globulin
ATG.....	Antithymocyte globulin
BM CTN.....	The Blood and Marrow Transplant Clinical Trials Network
BM.....	Bone marrow
Bregs.....	Regulatory B cells
CBT.....	Cord blood transplantation
CIBMTR.....	The Center for International Blood and Marrow Transplant Research
CSA.....	Cyclosporine
CXCR4.....	Chemokine receptor 4
DAMPs.....	Danger associated molecular pattern molecules
DNA.....	Deoxyribonucleic acid
DRI.....	Disease risk index
dUCB.....	Double unit umbilical cord transplant
EBMT.....	The European Group for Blood and Marrow Transplantation
ELISA.....	Enzyme-linked immunosorbent assay
FI.....	Full intensity
FP.....	False Positive

List of Abbreviations Cont...

Abb.	Full term
FS	Follistatin
FSH.....	Follicle-stimulating hormone
FSP	FSH-suppressing protein
GC.....	Granulosa cells
G-CSF.....	Granulocyte colony-stimulating factors
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GVHD.....	Graft versus host disease
HCT	Hematopoietic cell transplant
HGF	Hepatocyte growth factor
HSCT.....	Hematopoietic stem cell transplant
IFN- γ	Interferon- γ
IL	Interleukin
iNKT cells.....	Invariant natural killer T cells
ISC.....	Immune stem cells
IV	Intravenously
LGVHR.....	Lymph hematopoietic graft-versus-host reactions
LLC.....	Large lutein cells
MA	Myeloablative
MDSCs	Myeloid derived suppressor cells
M-MDSCs	Monocytic MDSCs
MMF	Mycophenolate mofetil
MPR.....	Melphalan, prednisone, lenalidomide
MTX.....	Methotrexate
NIH.....	National Institutes of Health
NK	Natural killer cells
NRM	Non-relapse mortality
OD.....	Optical densit

List of Abbreviations Cont...

Abb.	Full term
PAMPs.....	Pathogenic associated molecular pattern molecules
PBSC	Peripheral blood stem cells
PBSCTs	Peripheral blood stem cells transplant
PCV	Pneumococcal conjugate
P-MDSCs	Promyelocytic MDSCs
PS	Performance state
REG3 α	Regenerating islet-derived 3-alpha
RIC	Reduced intensity chemotherapy
ROC	Receiver Operating Characteristic
SCID.....	Severe combined Immunodeficiency
SD	Standard deviation
SDF-1.....	Stromal cell-derived factor-1-alpha
sIL-2R.....	Soluble IL-2 receptor
SNPs.....	Single-nucleotide polymorphisms
SOS.....	Sinusoidal obstruction syndrome
ST2.....	Stimulation 2
T reg	T regulatory cells
TAC.....	Tacrolimus
TBI.....	Total body irradiation
TGF.....	Transforming growth factor
TMP-SMX.....	Trimethoprim-sulfamethoxazole
TNF α	Tumor necrosis factor α
TP	True Positive
UCB	Umbilical cord transplant
UD SD	Sibling donors
UD	Unrelated donors
UDCA.....	Ursodeoxycholic acid
VOD	Veno occlusive disease

List of Tables

Table No.	Title	Page No.
Table (1):	Stages and grades of actue GVHD.....	40
Table (2):	Common GVHD prophylaxis medications with associated regimens and their way of action.	43
Table (3):	Clinical manifestations of chronic GVHD.	55
Table (4):	Demographic data of the study group.....	97
Table (5):	Laboratory data of the study groups.....	104
Table (6):	Acute GVHD severity distribution in the study group	106
Table (7):	Chronic GVHD distribution in the study group.....	107
Table (8):	CMV distribution in the study group.....	108
Table (9):	Overall survival (OS) distribution by Kaplan meire survival cure analysis.....	109
Table (10):	Cumulative incidence of relapse	110
Table (11):	Non relapse mortality (NRM) distribution in the study group.....	111
Table (12):	Disease free survival (DFS) distribution by Kaplan meire survival cure analysis.....	112
Table (13):	Follstatin level distribution in the study group.....	113
Table (14):	Infection distribution in the study group.....	114
Table (15):	Relation between Follistatin level and Age in the study group.....	115
Table (16):	Relation between Follistatin level and sex in the study group by ANOVA test.....	116

List of Tables Cont...

Table No.	Title	Page No.
Table (17):	Relation between Follistatin level and incidence of Acute GVHD in the study group by ANOVA test.....	117
Table (18):	Relation between Follistatin level and severity of GVHD in the study group by ANOVA test	118
Table (19):	Relation between Follistatin level and acute GVHD grade in the study group by ANOVA test and pairwise comparisons	119
Table (20):	Relation between Follistatin level and chronic GVHD in the study group by ANOVA test	120
Table (21):	Relation between Follistatin level and VOD in the study group by ANOVA test.....	121
Table (22):	Relation between Follistatin level and CMV in the study group by ANOVA test	123
Table (23):	Relation between Follistatin level and Engraftment of neutrophils in the study group by ANOVA test and pairwise comparisons.....	124
Table (24):	Relation between Follistatin level and CRP in the study group by ANOVA test	125
Table (25):	Relation between Follistatin level and Infection in the study group by ANOVA test.....	126
Table (26):	Pearson Correlation (R) between Follistatin level at day 28 and other variables in the study group	127

List of Tables Cont...

Table No.	Title	Page No.
Table (27):	Pearson Correlation (R) between Follistatin level at day zero and other variables in the study group	128
Table (28):	Predictive value of Follistatin level at day zero for outcome by Receiver Operating Characteristic Curve (ROC)	129
Table (29):	Predictive value of Follistatin level at day 28 for outcome by Receiver Operating Characteristic Curve (ROC)	130
Table (30):	Comparing overall survival (OS) according to cut off follistatin level at day 28 by Kaplan meire survival curve analysis	131
Table (31):	Comparing DFS according to cut off follistatin level at day 28 by Kaplan meire	133
Table (32):	Comparing NRM according to cut off follistatin level at day 28 by Kaplan meire survival curve analysis	135

List of Figures

Fig. No.	Title	Page No.
Figure (1):	Pathophysiology of acute GVHD.....	35
Figure (2):	Pathophysiology of chronic GVHD.	54
Figure (3):	Sex distribution.....	99
Figure (4):	Engraftment.	99
Figure (5):	HLA tissue typing.	100
Figure (6):	Conditioning distribution.	100
Figure (7):	Diagnosis distribution.	101
Figure (8):	Veno-occlusive disease distribution.	101
Figure (9):	Actue GVHD distribution.	102
Figure (10):	Actue GVHD grades distribution.....	102
Figure (11):	Chronic GVHD distribution.	103
Figure (12):	ABO recipient distribution.	103
Figure (13):	Follistatin level day zero and day 28.	105
Figure (14):	Laboratory study.	105
Figure (15):	Acute GVHD severity distribution in the study group.	106
Figure (16):	Chronic GVHD.	107
Figure (17):	CMV distribution in the study group.....	108
Figure (18):	Overall survival (OS) distribution by Kaplan meire survival cure analysis.	109
Figure (19):	Cumulative incidence of relapse.	110
Figure (20):	Non relapse mortality (NRM) distribution in the study group.	111
Figure (21):	Disease free survival (DFS) distribution by Kaplan meire survival cure analysis.....	112
Figure (22):	Follstatin level distribution in the study group.....	113
Figure (23):	Infection distribution in the study group.....	114

List of Figures Cont...

Fig. No.	Title	Page No.
Figure (24):	Relation between Follistatin level and sex in the study group by ANOVA test.....	116
Figure (25):	Relation between Follistatin level and incidence of Acute GVHD in the study group by ANOVA test	117
Figure (26):	Relation between Follistatin level and severity of GVHD in the study group by ANOVA test.	118
Figure (27):	Relation between Follistatin level and acute GVHD grade in the study group by ANOVA test and pairwise comparisons.	119
Figure (28):	Relation between Follistatin level and chronic GVHD in the study group by ANOVA test.	120
Figure (29):	Relation between Follistatin level and VOD in the study group by ANOVA test.	122
Figure (30):	Relation between Follistatin level and CMV in the study group by ANOVA test.	123
Figure (31):	Relation between Follistatin level and Engraftment of neutrophils in the study group by ANOVA test and pairwise comparisons.	124
Figure (32):	Relation between Follistatin level and CRP in the study group by ANOVA test.	125
Figure (33):	Relation between Follistatin level and Infection in the study group by ANOVA test.	126
Figure (34):	Pearson Correlation (R) between Follistatin level at day 28 and other variables in the study group.	127