Table of contents

| Contents | Page |
|---|------|
| Introduction | 1 |
| Aim of the work | 4 |
| Review | |
| Introduction to liver transplantation | 5 |
| Indications of liver transplantation | 7 |
| • Hepatitis C in liver transplantation | 12 |
| Primary hepatic malignancy | 25 |
| • Contraindications to liver transplantation | 35 |
| Role of liver biopsy in liver transplantation | 37 |
| Principles in deceased liver biopsy | 44 |
| Living donor liver transplantation | 38 |
| Complications of liver transplantation | 46 |
| - Preservation reperfusion injury | 49 |
| - HCV recurrence | 51 |
| - Liver allograft rejection | 57 |
| - Rejection versus recurrent hepatitis | 62 |
| Prognostic factors in liver transplantation | 86 |
| • Cluster of differentiation (CD) | 89 |
| cluster of differentiation (CD) | 99 |
| | |
| Materials and methods | 112 |
| Results | 118 |
| Discussion | 160 |
| Summary and conclusion | 170 |
| References | 174 |
| Arabic summary | |

List of Abbreviations

Abbreviation Full name

ACR Acute cellular rejection
ADP Adenosine Di phosphate

AFB1 Aflatoxins B1

AIDS Acquired Immune deficiency syndrome

AMP Adenosine Mono phosphate

APC Antigen presenting cell
AR Androgen Receptor

AR Acute rejection

LRLT Living Related liver transplantation

ATP Adenosine Tri phosphate

BMI Body mass index C4d Complement 4 d.

CD4 Cluster of differentiatian 4
CD8 Cluster of differentiatian 8

CIN Carcinoma insitu

CLD Chronic liver disease
CNS Central nervous system

CMV Cytomegalo virus

CT Computerized tomography

CTP Child – Turoctte pugh

DAB **Diaminobenzidine**DP **Double positive**

EBV Epestien Barr Virus

EDC Extended Donor criteria

EDTA Ethylenediaminetraacetic acid

ESLD End Stage liver disease

Fas L Fas ligand
FK 506 Tacrolimus

HAI Hepatitis Activity Index

HBcAb Hepatitis B core antibody

HBsAb **Hepatitis B Surface antibody**

HBsAg Hepatitis B Surface antigen

HBV Hepatitis B virus

HCC HepatoCellular Carcinoma

HCV Hepatitis C Virus

H&E **Hematoxylin & eosin stain**

HIV Human Immune deficiency virus

HLDA Human leukoyte Differentiatian Antigens

HPF High power field

 $\begin{array}{ll} ICU & \textbf{Intensive care unite} \\ IFN \ \gamma & \textbf{Interferon gamma} \\ IgG & \textbf{Immunoglobulin G} \end{array}$

IgV Immunoglobulin variable
IHC Immunohistochemistery

IL2 Interleukin 2

IMC International Medical Centre

IPF Initial poor function

LB Liver biopsy

LDLT Living donor liver transplantation

Leu-3 Leukotrien 3

LRLD Living Related liver Donor

M ab Monoclonal Antibody

MELD Model for End Stage liver Disease
MHC Major histocompatabitily complex

MRI Magnetic resonance Image

NAFLD Non – alcoholic fatty liver disease

NF κb **Nuclear Factor κb**

NHBDS Non heart beating donors

OKT3 Muromonab-CD3

OLT Orthotropic liver transplantation

OPTN Organ Procurement and Transplantation Network

P value **Probability factor**

PBC Primary biliary cirrhosis
PBS Phosphate buffer saline
PDF Primary dysfunction

PNF **Primary non function**

PSC **Primary sclerosing cholangi**tis

RAI Rejection activity Index
Rec. hep C Recurrent hepatitis C
ROS Reactive oxygen species

Sd Standard deviation
SECs Sub Endothelial Cells

SPSS Statistical package for social séances

TCRS T cell receptors

TH1 Thelper 1
TH2 Thelper 2

TH17 **T helper 17**

TNF α Tumor necrosis factor α

UW University of Wisconsin

UK United Kingdom

UNOS United Network of Organ Sharing

List of tables

| Table | Title | page |
|--------|---|------|
| number | | |
| 1 | Child- Turcotte Pugh (CTP) Scoring System to Assess Severity of Liver Disease | ١. |
| ۲ | Morphologic Features of Viral Hepatitis | 16 |
| ٣ | Histological Grading of Chronic Viral Hepatitis | 19 |
| ٤ | Histological staging of Chronic Viral Hepatitis | 21 |
| ٥ | Algorithm for Evaluation of Histological Activity | 22 |
| ٦ | Entry criteria for liver transplantation in patients with cholangiocarcinoma | ٣ ٤ |
| ٧ | Major indications for re-transplantation, frequency and approximate timing after liver transplantation | 37 |
| ٨ | Main pathological changes occurring in the liver allograft | 43 |
| 4 | European grading system for acute liver allograft rejection | 70 |
| 1. | Banff schema for grading liver allograft rejection—global assessment of overall rejection grade | 71 |
| 11 | Banff schema for grading liver allograft rejection—rejection activity index | 72 |
| ١٢ | Histopathological features characteristically seen during the early and late stages of chronic rejection | 79 |
| ١٣ | Main criteria used in diagnosis of acute and chronic liver allograft rejection | 81 |
| 1 £ | Comparison of histological changes occurring in hepatitis C infection and acute cellular rejection of the liver allograft | 87 |
| 10 | Grades of steatosis | 92 |
| ١٦ | Uses of CDS as cell markers | 101 |

| 1 7 | Relation between steatosis of donors and post transplant complications | 120 |
|-----|--|-----|
| ١٨ | Relation between spotty necrosis of donors and post transplant complications | 121 |
| ١٩ | Age distribution of the recipients | 122 |
| ۲. | Correlation between mean CD8 +ve cells/ all lymphocytes in portal tracts and severity of acute rejection in donors | 170 |
| ۲۱ | Correlation between mean CD8 +ve cells/ all lymphocytes in hepatic lobules and severity of acute rejection in donors | 127 |
| * * | Correlation between mean CD4 +ve cells/ all lymphocytes in portal tracts and severity of acute rejection in donors | 128 |
| 77 | Correlation between mean CD4 +ve cells/ all lymphocytes in hepatic lobules and severity of acute rejection in the donors | 129 |
| 7 £ | Correlation between mean CD8 +ve cells/ all lymphocytes in portal tracts and severity of acute rejection in the donors | ١٣. |
| Y 0 | Correlation between mean CD8 +ve cells/ all lymphocytes in hepatic lobules and severity of acute rejection in recipients | 131 |
| 77 | Correlation between mean CD4 +ve cells/ all lymphocytes in portal tracts and severity of acute rejection in the recipients | 132 |
| ** | Correlation between mean CD4 +ve cells/ all lymphocytes in hepatic lobules and severity of acute rejection in recipients | 133 |
| ۲۸ | Correlation between mean CD8 +ve cells/ all lymphocytes in portal tracts and grade of recurrent hepatitis in donors | 134 |
| 44 | Correlation between mean CD8 +ve cells/ all lymphocytes in hepatic lobules and grade of recurrent hepatitis in donors | 136 |
| ٣. | Correlation between mean CD4 +ve cells/ all lymphocytes in portal tracts and grade of recurrent hepatitis in donors | 137 |
| ٣١ | Correlation between mean CD4 +ve cells/ all lymphocytes in hepatic lobules and grade of recurrent hepatitis in donors | 138 |
| ٣٢ | Correlation between mean CD8 +ve cells/ | 139 |

| | all lymphocytes in portal tracts and grade of recurrent hepatitis in recipients | |
|----|--|-------|
| 44 | Correlation between mean CD8 +ve cells/ all lymphocytes in hepatic lobules and grade of recurrent hepatitis in recipients | 1 2 . |
| ٣٤ | Correlation between mean CD4+ve cells/ all lymphocytes in portal tracts and grade of recurrent hepatitis in recipients | 1 £ 1 |
| 40 | Correlation between mean CD4 +ve cells/ all lymphocytes in hepatic lobules and grade of recurrent hepatitis in recipients) | 1 2 7 |
| ٣٦ | Ratio between CD4 and CD8 in pre transplant cases (donors) | 1 20 |
| ٣٧ | Ratio between CD4 and CD8 in post transplant cases | 1 £ 7 |
| 38 | Correlation between studied cases and (MEAN CD4 &CD8) | 147 |

List of figures

| Figure number | Title | page |
|------------------|---|------|
| 1 | Preservation reperfusion injury in liver allograft show necrosis consist of focal necrosis of hepatocytes and accumulation of clusters of neutrophil (H&Ex400) | 56 |
| ۲ | A case of chronic rejection show bile duct loss (H&Ex400) | 77 |
| ٣ | Multiple pathways of CD4+ cell | 85 |
| ŧ | Cluster of differentiation as cell markers | 100 |
| ٥ | CD8 receptor | 104 |
| ٦ | A liver biopsy of donor show minimal steatosis (<5%)& minimal portal inflammation (H&E x200) | 148 |
| ٧ | A liver biopsy from donor show focus of spotty necrosis (H&E x200) | 148 |
| ٨ | A post transplant biopsy from recipient; moderate ACR of score 4/9 show endotheliitis, bile duct changes (double arrow) and portal inflammation (H&Ex200) | 149 |
| ٩ | A post transplant biopsy from recipient; recurrent hepatitis of severe activity of Ishak score 15/18 show interface hepatitis, portal inflammation, confluent necrosis and spotty necrosis (H&E x200) | 150 |
| 1. | A post transplant biopsy from recipient; recurrent hepatitis of moderate activity of Ishak score 11/18 show interface hepatitis, portal inflammation and spotty necrosis (H&E x200) | 150 |
| 11 | A post transplant biopsy from recipient; recurrent hepatitis, mild activity of Ishak score 6/18 show mild portal inflammatino, spotty necrosis and mild interface hepatitis (H&Ex100) | 151 |

| ١٢ | Anti- CD8 immunostain in a donor of a case of ACR show CD8+ cells in portal tract (strept-Avidin Biotin, DAB chromogenx400 | 152 |
|-----|---|-----|
| ١٣ | Anti-CD4 immunostain in a donor of a case of ACR show CD4+ cells in portal tract (strept-Avidin Biotin, DAB chromogenx400) | 107 |
| 1 £ | Anti- CD8 immunostain in a donor of a case of ACR show CD8+ cells in hepatic lobule(strept -Avidin Biotin,DAB chromogenx400) | 153 |
| 10 | Anti- CD4 immunostain in a donor of a case of ACR show CD4+ cells in hepatic lobule (strept-Avidin Biotin, DAB chromogenx400) | 153 |
| 17 | Anti- CD8 immunostain in a recipient case of ACR show CD8+ cells portal tract (strept-Avidin Biotin, DAB chromogenx200) | 154 |
| 1 V | Anti-CD4 immunostain in a recipient case of ACR show CD4+ cells in portal tract (strept-Avidin Biotin, DAB chromogenx200) | 154 |
| ١٨ | Anti CD8 immunostain in a recipient case of ACR show CD8+ cells in hepatic lobule(strept-Avidin Biotin,DAB chromogenx400) | 155 |
| 19 | Anti- CD4 immunostain in a recipient case of ACR show CD4+ cells in hepatic lobule with increase number than CD8(strept-Avidin Biotin,:DAB chromogenx400) | 155 |
| ۲. | Anti- CD8 immunostain in a donor of a case of recurrent hepatitis CD8 + cells in portal tract (strept-Avidin Biotin,:DAB chromogenx400) | 156 |
| ۲۱ | Anti-CD4 immunostain in a donor case of recurrent hepatitis show CD4+ cells in portal tract (strept- Avidin Biotin, DAB chromogenx400) | 107 |
| * * | Anti-CD8 immunostain in a donor of a case of recurrent hepatitis show CD8 negative cells s in hepatic lobule (strept-Avidin Biotin, DAB chromogenx400) | 157 |

| 77 | Anti-CD4 immunostain in a donor of a case of recurrent hepatitis show CD4+ cells in hepatic lobule (strept -Avidin Biotin, DAB chromogenx400) | 157 |
|-----|--|-----|
| 7 £ | Anti- CD8 immunostain in a recipient case of recurrent hepatitis show CD8+ cells in portal tract (strept-Avidin Biotin, DAB chromogen CD8x200) | 158 |
| 70 | Anti- CD4 immunostain in a recipient case of recurrent hepatitis show CD4+ cells in portal tract (strept- Avidin Biotin,DAB chromogenx200) | 158 |
| 77 | Anti- CD8 immunostain in a recipient case of recurrent hepatitis show CD8+ cells in hepatic lobule (strept -Avidin Biotin, DAB chromogenx400) | 159 |
| ** | Anti-CD4 immunostain in a recipient case of recurrent hepatitis show CD4+ cells in hepatic lobule (strept-Avidin Biotin,DAB chromogenx400) | 159 |

List of graphs

| Graph number | Title | page |
|-----------------|--|------|
| 1 | Distributions of studied cases | 118 |
| ۲ | Relation between steatosis of donors and post transplant complications | 120 |
| ٣ | Relation between spotty necrosis of donors and post transplant complications | 121 |
| ٤ | Age distribution of recipient cases | 122 |
| ٥ | Gender distribution in post transplant cases | 125 |
| ٦ | Correlation between mean CD8 +ve cells/ all lymphocytes and severity of acute rejection in donors | 126 |
| ٧ | Correlation between mean CD8 +ve cells/ all lymphocytes in hepatic lobules and severity of ACR in donors | 127 |
| ٨ | Correlation between mean CD4 +ve cells/ all lymphocytes in portal tracts and severity of acute rejection in donors | 128 |
| ٩ | Correlation between mean CD4 +ve cells/ all lymphocytes in hepatic lobules and severity of acute rejection in donors | 129 |
| ١. | Correlation between mean CD8 +ve cells/ all lymphocytes and severity of acute rejection in recipients | 130 |
| 11 | Correlation between mean CD8 +ve cells/ all lymphocytes in hepatic lobules and severity of ACR in recipients. | 131 |
| 17 | Correlation between mean CD4 +ve cells/ all lymphocytes in portal tracts and severity of acute rejection in recipients | 132 |
| ١٣ | Correlation between mean CD4 +ve cells/ all lymphocytes in hepatic | 133 |

| | lobules and severity of acute rejection in the recipients | |
|-----|---|-------|
| 1 £ | Correlation between mean CD8 +ve cells/ all lymphocytes in portal tracts and grade of recurrent hepatitis in donors | 170 |
| 10 | Correlation between mean CD8 +ve cells/ all lymphocytes in hepatic lobules and grade of recurrent hepatitis in donors | 1 7 7 |
| 17 | Correlation between mean CD4 +ve cells/ all lymphocytes in portal tracts and grade of recurrent hepatitis in donors | 1 4 4 |
| 1 V | Correlation between mean CD4 +ve cells/ all lymphocytes in hepatic lobules and grade of recurrent hepatitis in donors | ۱۳۸ |
| ١٨ | Correlation between mean CD8 +ve cells and grade of recurrent hepatitis of portal tract in recipients. | 1 7 9 |
| 19 | Correlation between mean CD8 +ve cells/ all lymphocytes of hepatic lobules and grade of recurrent hepatitis in recipients | 1 & . |
| ۲. | Correlation between mean CD4+ve cells/ all lymphocytes in portal tracts and grade of recurrent hepatitis in recipients | 1 £ Y |
| *1 | Correlation between mean CD4 +ve cells/ all lymphocytes in hepatic lobules and grade of recurrent hepatitis in recipients | 1 £ £ |
| * * | Ratio between CD4 and CD8 in donors | 1 20 |
| 7 7 | Ratio between CD4 and CD8 in recipients | 1 £ 7 |

Acknowledgements

First of all, many thanks to my God for helping me, guiding me and providing me all the help from my supervisors to finish this work.

I am particularly honored to have been graciously supervised by *Prof. Dr. Hala A. Agina*, Professor and Head of Pathology Department, Benha Faculty of Medicine, Benha University -for I have always inspired by her sparkling enthusiasm and spending much of her valuable time to provide me with a wide scope of knowledge in all essential aspects of this study.

I would like to express my profound gratitude to *Prof. Dr. Abd El-Latif M. El-Balshy*, Professor of Pathology, Benha Faculty of Medicine, Benha University, for his skillful pathological advice, fruitful discussions and who devoted much of his time in guiding me throughout this study.

My sincere unlimited appreciation and gratitude go to *Dr. Rasha M. El-Sawy*, Lecturer of Pathology, Benha Faculty of Medicine, Benha University, who sacrificed a great deal of her valuable time in the correction of this work and for whom no words or praise are sufficient.

I am also sincerely grateful to *Dr. Amr F. El-Sebaaie*, Consultant and Head of Pathology Department, International Medical Centre, Cairo, who gave me a lot of his constructive guidance, constant encouragement and generous help throughout this work; to him I am greatly indebted.

Special thanks to **Dr.Ghada A. Abd-Elfatah** for her help and support during this work.

Finally special thanks to my husband and all my family members for their help and generous support.