INDIVIDUAL PATIENT PROFILING USING CLINICAL AND NEURORADIOLOGICAL BIOMARKERS IN ACUTE ISCHEMIC STROKE: APPLICATION OF ADVANCED MULTIMODAL NEUROIMAGING

SONU BHASKAR
Mismatch showing salvageable tissue (penumbra) and dead tissue (core) in an acute ischemic stroke patient.
INDIVIDUAL PATIENT PROFILING USING CLINICAL AND NEURORADIOLOGICAL BIOMARKERS IN ACUTE ISCHEMIC STROKE: APPLICATION OF ADVANCED MULTIMODAL NEUROIMAGING

SONU BHASKAR

Department of Neurology, John Hunter Hospital
Priority Research Centre for Translational Neuroscience and Mental Health
Hunter Medical Research Institute (HMRI), Hunter Stroke Services
School of Medicine & Public Health, and School of Health Sciences
Faculty of Health & Medicine
University of Newcastle

A Thesis by Publication Submitted for the Degree of

Doctor of Philosophy (Medicine)

School of Medicine & Public Health
School of Health Sciences
Faculty of Health and Medicine
University of Newcastle, Australia
SUPERVISORS

A/PROF PETER STANWELL, PHD
Associate Professor
School of Health Sciences
Faculty of Health and Medicine
Convenor Imaging Section, Priority Research Centre for Translational Neuroscience & Mental Health, Hunter Medical Research Institute (HMRI), University of Newcastle, Callaghan, NSW, Australia

PROF CHRISTOPHER LEVI, MD
Senior Staff Neurologist, Comprehensive Stroke Centre, Department of Neurology, John Hunter Hospital
Director of Clinical Research and Translation, Hunter New England Local Health District, New South Wales (NSW)
Conjoint Professor of Medicine (Neurology), School of Public Health & Medicine, University of Newcastle
Practitioner Fellow, National Health & Medical Research Council (NHMRC), Australia

PROF MICHAEL NILSSON, MD, PHD
Director, Hunter Medical Research Institute (HMRI)
Professor, School of Medicine & Public Health, Faculty of Health and Medicine, University of Newcastle, Australia
Burges Professor of Medical Science, Department of Clinical Neuroscience, Institute of Neuroscience and Physiology, Sahlgrenska University Hospital, University of Gothenburg, Sweden

PROF JOHN ATTIA, MD, PHD, FRCPC, FRACP
Professor of Medicine and Clinical Epidemiology, University of Newcastle
Director, Clinical Research Design, IT, and Statistical Support Unit, Hunter Medical Research Institute
Academic Director, Department of General Medicine, John Hunter Hospital

DR ANDREW BIVARD, PHD
Hunter Medical Research Institute (HMRI), University of Newcastle
Kookaburra Circuit, New Lambton Heights, Australia
STROKE – NO POSTCODE UNTOUCHED IN AUSTRALIA*

*Based on the 2014 report of Deloitte Access Economics, commissioned by National Stroke Foundation, to estimate the impact of stroke across Australia.
DECLARATIONS

Statement of Originality
I, Sonu Bhaskar, hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. I give consent to this copy of my thesis, when deposited in the University Library, being made available for loan and photocopying subject to the provisions of the Copyright Act 1968.

Statement on Thesis by Publication
I, Sonu Bhaskar, hereby certify that this thesis is submitted in the form of a series of published papers of which I am a joint author. I have included as part of the thesis a written statement from each co-author and endorsed by the Faculty Assistance Dean (Research Training), attesting to my contribution to the joint publications.

Statement of Collaboration
I, Sonu Bhaskar, hereby certify that the work, embodied in this thesis, have been done in collaboration with other researchers. I have included as part of the thesis a statement clearly outlining the extent of collaboration, with whom and under what auspices.

Signed

Date
ACKNOWLEDGEMENTS

“Attention is the rarest and purest form of generosity.”
- Simone Weil

First, and foremost, I would like to start by expressing my gratitude towards my clinical and academic supervisors A/Professor Peter Stanwell, Professor Christopher (Chris) Levi, Professor Michael Nilsson, and Dr Andrew Bivard. I am also grateful to Professor John Attia for his generous guidance and feedback on research methodology and statistical analyses. Thank you, John, for your advice and support. I would like to acknowledge Professor Mark Parsons for his overall guidance gratefully. Special thanks to A/Professor Neil Spratt for his critical feedback, valuable edits to my “confirmation thesis”. I could not have asked for better scientific mentors at this early stage of my career.

Chris, I have been incredibly lucky to have a supervisor like you, and I sincerely want to express my utmost gratitude for everything you’ve done for me – for giving me the opportunity to work with you, for believing in me, and for making me realise my potential. Your breadth and depth of clinical knowledge about stroke and neurology, in general, have been inspirational and invaluable. Thank you for being a great mentor, guide and a teacher; and for inspiring me to pursue this doctoral project (at a time when going was tough!). The best part of Chris has been his attention to details, inexhaustible patience, and generosity. Every time I have had an opportunity to meet him, I was assured that he is there to look after me. Thank you, Chris, for all that you have done. I am not sure this section would do justice to the enormous gratitude I owe to you for your continued support. I will always remember our chats regarding new ideas and coming up with so many that could change the world but quickly having to get back on track and focus on the achievable goals for the short-term. I hope I can come up with as many excellent ideas throughout my career. You have been a role model to me - one who I look up to with reverence, and shall always, for your humility, kindness, and awesomeness in every way. I hope, in you, I have a mentor and friend for life. Gracias!

Peter, thank you for being an excellent mentor. Your passion for radiology/neuroimaging is infectious. I could not have succeeded without your care and patience in guiding me through the radiological analyses. I have many fond memories of the catch-ups over coffee at cafeterias located at the Bar on the Hill, and the Hunter Building. Thank you for agreeing to meet me at short notices, for your critical feedback, and discussions on the manuscripts under revision. Your humility, forthrightness and grace have been truly inspirational that I would like to imbibe within me for the rest of my life. Thank you for just being there for me and helping me take my mind off research when I needed to. Beyond research, you have also been a great friend who taught me how to strike a much-needed work and family-life balance.
I owe special thanks to Professor Robert (Bob) Callister, the Deputy Head of the Faculty of Health & Medicine and Assistant Dean Research Training, for his support during the initial stages of my study, and to Shirley Savy, Alli Johns, Kristy Brooks, and Annalese S. Johnson for their continued administrative support and encouragement. Thank you to the Hunter Stroke team at the Lodge, and at the Department of Neurology, John Hunter Hospital. Clinical research is a collaborative endeavour, and I have been fortunate enough to collaborate with all of you on a daily basis. In particular, I would like to thank Louise-Anne Jordan, Malcolm Evans, Christine Selmes, Erin Kerr, Kristy Morris, Nicole Starkie, Rhonda Walker, Heidi Janssen, Shelagh Garfield, and Gemma Kitsos who I have had the privilege of working closely with. Louise has been supportive, both as a colleague and as a friend. She has been a kind mentor, and I would like to express my gratitude for her cooperation and enterprising spirit during my involvement in the clinical trials. Also, thanks to staff members of Clinical Governance Unit who were extraordinarily welcoming while I had my office at the Lodge. Thank you, Louise & Allan Evans, for being a great support all this while, for those delicious cupcakes, and for your generosity in introducing me to some of the finest restaurants, and tourist spots in Newcastle. You both are undoubtedly great ambassadors of what Newcastle stands for.

Big thanks go to my family, parents in particular, without whom I will not be here where I am placed today. Mum and Dad. I am forever indebted for your selfless love, tenacity, unflinching support, and faith in me. You both have been a pivotal anchor to my life. I would also like to thank my other-half for her continued love, motivation, and patience. My five-year-old daughter has been a blessing all this while. I love you so much, my angel, and I promise to spend more time with you in future. I could not have embarked on an endeavour like this without their support. They have kept me going despite the odds of being far away from them. At my heart, they are with me always. Last, but not the least, I would like to remember my late grandfather who used to enthuse me to pursue medicine and delve into clinical research. He continues to be my greatest inspiration. On the closing note, thank you G-d for your blessings to me, and my family; for the strength, you bestow every passing day and for all the beautiful people and surprises that you bring our way! Baruch Hashem.☺

Thank you!

Sonu Bhaskar
25/01/2017
Newcastle, Australia
“Every man, if he so desires, becomes the sculptor of his own brain.”

- Santiago Ramón y Cajal, Noble Prize in Medicine, 1906
The photo of the sculpture, located in front of the Hunter Building at the University of Newcastle (Callaghan), depicts time-compass with an engraved adage “use time to make better world” (top), and an equation of time (bottom).

_Dated 8th of August 2016._
PEER REVIEWED PUBLICATIONS INCLUDED IN THIS THESIS

PUBLICATION I:


PUBLICATION II:


PUBLICATION III:


PUBLICATION IV:

CONFERENCE PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS THESIS

I. Bhaskar S, Bivard A, Parsons M, Nilsson M, Attia JR, Stanwell P, Levi C. Delayed cortical vein filling is associated with poor baseline collateral status in acute ischemic stroke. Tenth FENS Forum of Neuroscience; Copenhagen (Denmark); 4 July 2016; (Poster).

II. Bhaskar S, Bivard A, Parsons M, Nilsson M, Attia JR, Stanwell P, Levi C. Delay of Late-Venous Phase Cortical Vein filling in Acute Ischemic Stroke patients. Third European Congress of NeuroRehabilitation; Vienna (Austria); 1-4 December 2015; (Oral).

III. Bhaskar S, Bivard A, Parsons M, Attia JR, Stanwell P, Levi C. Favourable collateral status is associated with post-ischemic perilesional hyperperfusion at 24 hours: an arterial spin labelling (ASL) study. NEUROVASCON 2015, Fifth Annual Conference of the Cerebrovascular Society of India; Ludhiana (India); 18-20 September 2015; (Oral).

IV. Bhaskar S, Bivard A, Parsons M, Attia JR, Stanwell P, Levi C. Role of lesion topography in predicting 24 hours perilesional hyperperfusion. Brain Ischemia Conference; Rome (Italy); December 10-12, 2014; (Oral).


VI. Bhaskar S. Frontiers in Stroke Imaging: Applications to Diagnostics, Thrombolysis and Treatment. Department of Radiology, Kaunas University Hospital, Kaunas (Lithuania); January 15, 2015; (Oral).

VII. Bhaskar S. Neuroimaging in Stroke: Clinical and Neuroradiological Perspectives. Clinical Grand Rounds, Manning Base Hospital, Taree (Australia); October 16th, 2014; (Oral).
AWARDS, SCHOLARSHIPS AND GRANTS (2013-16)

I. **Grant in Aids (4000 AUD) award (2016-17)**, Faculty of Health & Medicine, University of Newcastle.

II. Nominated for “**Young Investigator Awards oral paper category**” at Brain Ischemia Conference, **Rome, Italy** (2014).

III. Hunter Medical Research Institute (HMRI) & Centre for Translational Neuroscience & Mental Health (CTNMH) **Top-Up Scholarship (15000 AUD)**.

IV. **Doctoral Scholarship, University of Newcastle (2013-2016)**.

V. Travel Grant (1200 AUD), Hunter New England (HNE) Health, Newcastle.

VI. HMRI **small project** infrastructure grant (5000 AUD).

EXTRA-CURRICULAR

1. Clinical research associate for **TnT and T3** stroke clinical trials (conjointly with Australian Catholic University, John Hunter Hospital, HMRI, and University of Newcastle).

2. Conjoint Lecturer, University of Newcastle.

3. Leadership role as **iLEAD Executive** for the Faculty of Health & Medicine, University of Newcastle. Organised seminars and talks at the faculty including one guest lecture by the Sydney nodal officer of **Médecins Sans Frontières (Doctors without Borders)** to encourage medical volunteering initiatives among young doctors.

4. Certificate course in ‘**Concept Development Workshop for Trials and Translational Research Studies**’ held on 31st October 2014 at the Clinical Trials Centre, the University of Sydney.

5. Memberships to **Stroke Society of Australasia**, **Australian Neuroscience Society**, and **Australasian Cognitive Neuroscience Society**.

6. Medical Volunteer during **Special Olympics (2013)** held in Newcastle.
“I slept and dreamt that life was joy. I awoke and saw that life was service. I acted and behold, service was joy.”

- Rabindranath Tagore, Noble Prize in Literature, 1913
PREFACE

The author, **Dr Sonu Bhaskar**, was working as a doctoral researcher/clinical research fellow jointly at Department of Neurology, John Hunter Hospital, and Schools of Public Health & Medicine, and School of Health Sciences, at the Faculty of Health & Medicine, the University of Newcastle during doctoral research. The topic of the doctoral research was “**Individual patient profiling using clinical and neuroradiological biomarkers in acute ischemic stroke: application of advanced multimodal neuroimaging**”. The scientific research on this thesis was undertaken at the Department of Neurology and Hunter Medical Research Institute (HMRI), John Hunter Hospital from 2013 to 2016 during the author’s engagement as a clinical research associate/fellow at the Department of Neurology, John Hunter Hospital.

A/Prof Peter Stanwell, Prof Christopher Levi, Prof Michael Nilsson, and Dr Andrew Bivard at the Department of Neurology (John Hunter Hospital), Stroke Research Team (HMRI), School of Public Health & Medicine, and School of Health Sciences (University of Newcastle) supervised the project. This project has received funding from the University of Newcastle, HMRI and Hunter New England (HNE) Health.

<table>
<thead>
<tr>
<th>A/Prof Peter Stanwell</th>
<th>Prof Christopher Levi</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Signed</strong></td>
<td><strong>Signed</strong></td>
</tr>
<tr>
<td>17.02.2017</td>
<td>13.02.2017</td>
</tr>
<tr>
<td><strong>Date</strong></td>
<td><strong>Date</strong></td>
</tr>
</tbody>
</table>
“God is the light shining in the midst of darkness, not to deny that there is darkness in the world but to reassure us that we do not have to be afraid of the darkness because darkness will always yield to light. As theologian David Griffin puts in, God is all-powerful, His power enables people to deal with events beyond their control, and He gives us the strength to do those things because He is with us.”

Harold S. Kushner
# TABLE OF CONTENTS

THESIS TOPIC: INDIVIDUAL PATIENT PROFILING USING CLINICAL AND NEURORADIOLOGICAL BIOMARKERS IN ACUTE ISCHEMIC STROKE: APPLICATION OF ADVANCED MULTIMODAL NEUROIMAGING

| DECLARATIONS | 4 |
| ACKNOWLEDGEMENTS | 6 |
| PEER REVIEWED PUBLICATIONS INCLUDED IN THE THESIS | 10 |
| CONFERENCES PUBLICATIONS AND PRESENTATIONS | 11 |
| AWARDS, SCHOLARSHIPS AND GRANTS | 12 |
| PREFACE | 14 |
| LIST OF ABBREVIATIONS | 19 |
| SYNOPSIS | 22 |
| OVERVIEW OF THE THESIS | 24 |

## CHAPTER 1
BACKGROUND - PATHOPHYSIOLOGY OF STROKE AND NEUROIMAGING APPROACHES TO DIAGNOSTICS AND TREATMENT OF ACUTE ISCHEMIC STROKE

### SECTION 1. STROKE PATHOPHYSIOLOGY
1.1. Background .............................................. 32
1.1.1. Introduction to Stroke .................................. 32
1.1.2. Prevalence & Burden of Stroke .......................... 33
1.1.3. Stroke Aetiology ......................................... 34
1.1.4. Hemorrhage .............................................. 35
1.1.4.1. Pathophysiology of Intracerebral haemorrhage (ICH) .............................................. 35
1.1.4.2. Pathophysiology of Subarachnoid haemorrhage (SAH) .............................................. 38
1.1.5. Pathophysiology of Ischemic Stroke ....................... 38
1.1.5.1. Thrombosis .............................................. 40
1.1.5.2. Embolism .............................................. 40
1.1.5.3. Systemic Hypoperfusion ................................ 41
1.1.6. Focal Ischemia ............................................ 41
1.1.6.1. Mechanism of neuronal injury in focal ischemia .............................................. 42
1.1.6.2. Oedema formation ....................................... 43

### SECTION 2. STROKE DIAGNOSIS
1.2. Stroke diagnosis ........................................... 45
1.2.1. Stroke assessment scales .................................. 45
1.2.2. Stroke subtype classification system ....................... 47

### SECTION 3. NEUROIMAGING IN ACUTE STROKE
1.3. Neuroimaging in acute stroke ................................ 49
1.3.1. Goals of neuroimaging in stroke .......................... 49
1.3.2. Neuroimaging techniques for stroke diagnostics and treatment .............................................. 50
1.3.3. Computed Tomography in Acute stroke imaging ............... 54
1.3.3.1. Non-contrast CT (NCCT) .................................. 54
1.3.3.2. CT Perfusion .............................................. 57
1.3.3.3. CT Angiography ........................................... 59
1.3.4. MRI in Stroke Imaging .................................................. 63
1.3.4.1. Magnetic Resonance Angiography ............................ 64
1.3.4.2. Diffusion-Weighted Imaging (DWI) ....................... 65
1.3.4.3. Perfusion-weighted imaging (PWI) and the mismatch concept .......................... 66
1.3.4.3.1. Arterial Spin Labelling (ASL) ................................. 68
1.3.4.3.2. Dynamic susceptibility contrast-enhanced perfusion-weighted imaging (DSC-PWI) .................................................. 71
1.3.5. MR vs. CT in stroke .................................................. 73

1.4. Conclusion ................................................................. 73

CHAPTER 2
INDIVIDUAL PATIENT PROFILING FOR THROMBOLYTIC THERAPY IN ACUTE ISCHEMIC STROKE

2. Abstract .............................................................................. 78
2.1. Introduction ................................................................. 79
2.2. Time-based vs. individual patient profiling approach ........... 80
2.3. Evolution of reperfusion therapy ....................................... 82
2.3.1. Intravenous thrombolysis ........................................... 84
2.3.2. Endovascular treatment .............................................. 87
2.3.2.1. Intra-arterial thrombolysis ..................................... 87
2.3.2.2. Mechanical thrombectomy ..................................... 89
2.3.2.2.1. Clinical trials with first generation devices .......... 91
2.3.2.2.2. Clinical trials with second-generation devices .......... 92
2.3.2.2.3. Phase three clinical trials with second-generation devices .................................................. 92
2.3.3. Combined intravenous and endovascular therapy: a multimodal reperfusion therapy (MMRT) approach .................................................. 97
2.3.4. The role of collaterals in penumbral sustenance and recanalization .... 98
2.4. Patient profiling using neuroimaging-based approaches ........ 100
2.5. Prognostic Neuroimaging and Clinical Scales ...................... 102
2.5. Limitations and Unresolved Questions of Endovascular Reperfusion Therapy .................................................. 104
2.6. Conclusions, Discussions, and Future Recommendations .......... 107

CHAPTER 3
PROGNOSTICATION OF ACUTE ISCHEMIC STROKE USING BASELINE STROKE SEVERITY

3. Chapter .............................................................................. 147
3.1. Contributions ................................................................. 148
3.2. Publication ................................................................. 151

CHAPTER 4
LESION TOPOGRAPHY AND PERI-LESIONAL HYPERPERFUSION IN ISCHEMIC STROKE

4. Chapter .............................................................................. 173
4.1. Introduction ................................................................. 174
4.2. Contributions ................................................................. 177
4.3. Publication ................................................................. 179
4.4. Supplementary Information ........................................... 194
CHAPTER 5
DELAY OF LATE-VENOUS PHASE CORTICAL VEIN FILLING IN ACUTE ISCHEMIC STROKE PATIENTS: A NOVEL NEURORADIOLOGICAL BIOMARKER

5. Chapter........................................................................................................ 197
5.1. Introduction............................................................................................. 198
5.2. Contributions ......................................................................................... 200
5.3. Publication .............................................................................................. 202
5.4. Supplementary Information................................................................. 214

CHAPTER 6
ASSOCIATION OF CORTICAL VEIN FILLING WITH CLOT LOCATION AND CLINICAL OUTCOMES IN ACUTE ISCHEMIC STROKE PATIENTS

6. Chapter........................................................................................................ 221
6.1. Introduction............................................................................................. 222
6.2. Contributions ......................................................................................... 224
6.3. Publication .............................................................................................. 226
6.4. Supplementary Information................................................................. 238

CHAPTER 7
CONCLUSION AND FUTURE DISCUSSIONS

7. Chapter........................................................................................................ 245
7.1. Conclusion............................................................................................. 246
7.1.1. Profiling based on stroke severity: Is baseline stroke severity an essential covariate in any analysis of stroke outcome?.......................... 246
7.1.2. Perilesional hyperperfusion (PLH) on arterial spin labelling (ASL) perfusion MRI: Is PLH marker of good tissue outcome? Are good collaterals associated with PLH at 24 hours?...................................................... 247
7.1.3. Delayed-cortical venous filling on dCTA: A novel prognostic biomarker for AIS?......................................................................................... 248
7.1.4. Delayed-LCVF: a surrogate measure of collateral flow?...................... 249
7.1.5. Does the location of clot influence delayed-LCVF?............................... 250
7.1.6. Does delayed-LCVF associate with clinical outcome in acute ischemic stroke?.................................................................................... 250
7.1.7. ASL and dCTA can be used to identify surrogate imaging markers which may be of prognostic value......................................................... 251
7.2. Future works and discussions............................................................... 253

REFERENCES............................................................................................... 254
APPENDICES................................................................................................. 322
**LIST OF SYMBOLS/ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Abbreviation and Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADC</td>
<td>Apparent diffusion coefficient</td>
</tr>
<tr>
<td>AIS</td>
<td>Acute Ischemic Stroke</td>
</tr>
<tr>
<td>ASL</td>
<td>Arterial spin labelling</td>
</tr>
<tr>
<td>ASITN/SIR</td>
<td>American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology</td>
</tr>
<tr>
<td>ASPECTS</td>
<td>Alberta Stroke Program Early Computed Tomography Score</td>
</tr>
<tr>
<td>ATLANTIS</td>
<td>The Alteplase ThromboLysis for Acute Noninterventional Therapy in Ischemic Stroke</td>
</tr>
<tr>
<td>BAO</td>
<td>Basilar artery occlusion</td>
</tr>
<tr>
<td>BASICS</td>
<td>Basilar Artery International Cooperation Study</td>
</tr>
<tr>
<td>BASIS</td>
<td>Boston Acute Stroke Imaging Scale</td>
</tr>
<tr>
<td>BI</td>
<td>Barthel Index</td>
</tr>
<tr>
<td>BOLD</td>
<td>Blood-oxygen-level dependent</td>
</tr>
<tr>
<td>CASES</td>
<td>Canadian Alteplase for Stroke Effectiveness Study</td>
</tr>
<tr>
<td>CBF</td>
<td>Cerebral blood flow</td>
</tr>
<tr>
<td>CBV</td>
<td>Cerebral blood volume</td>
</tr>
<tr>
<td>CC</td>
<td>Correlation coefficient</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
</tr>
<tr>
<td>CTA</td>
<td>Computed tomography angiography</td>
</tr>
<tr>
<td>CTA-SI</td>
<td>Computed tomography angiographic source image</td>
</tr>
<tr>
<td>CTP</td>
<td>Computer tomography perfusion</td>
</tr>
<tr>
<td>CCT</td>
<td>Cranial computed tomography</td>
</tr>
<tr>
<td>DEDAS</td>
<td>Dose Escalation of Desmoteplase for Acute Ischemic Stroke</td>
</tr>
<tr>
<td>DEFUSE</td>
<td>Diffusion and perfusion imaging Evaluation For Understanding Stroke Evolution</td>
</tr>
<tr>
<td>DIAS</td>
<td>Desmoteplase in Acute Ischemic Stroke</td>
</tr>
<tr>
<td>DSC–PWI</td>
<td>Dynamic susceptibility contrast-enhanced perfusion-weighted imaging</td>
</tr>
<tr>
<td>DWI</td>
<td>Diffusion-weighted imaging</td>
</tr>
<tr>
<td>ECASS</td>
<td>European Cooperative Acute Stroke Study</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>EPI</td>
<td>Echo planar imaging</td>
</tr>
<tr>
<td>EPITHET</td>
<td>Echoplanar Imaging Thrombolysis Evaluation Trial</td>
</tr>
<tr>
<td>ERIC</td>
<td>Embolus Retriever with Interlinked Cage</td>
</tr>
<tr>
<td>ESC</td>
<td>Endovascular stroke centre</td>
</tr>
<tr>
<td>ESCAPE</td>
<td>Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times</td>
</tr>
<tr>
<td>ET</td>
<td>Endovascular thrombectomy</td>
</tr>
<tr>
<td>EXTEND-IA</td>
<td>Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial</td>
</tr>
<tr>
<td>FA</td>
<td>Flip angle</td>
</tr>
<tr>
<td>FLAIR</td>
<td>Fluid-attenuated inversion recovery</td>
</tr>
<tr>
<td>FWHM</td>
<td>Full width at half maximal</td>
</tr>
<tr>
<td>GOLIATH</td>
<td>General or Local Anaesthesia in Intra-arterial Therapy</td>
</tr>
<tr>
<td>IPC</td>
<td>Inferior parietal cortex</td>
</tr>
<tr>
<td>ICA</td>
<td>Internal carotid artery</td>
</tr>
</tbody>
</table>
ICH  Intracerebral haemorrhage
IST-3  Third international stroke trial
IQR  Interquartile range
IV/IA  Intravenous/Intra-arterial
LFF  Low-frequency fluctuations
LVO  Large vessel occlusion
M1/M2  Proximal portion/insular portion of the MCA
MCA  Middle cerebral artery
MCI  Mild cognitive impairment
MNI  Montreal Neurological Institute
MOST  Multi-Arm Optimisation of Stroke Thrombolysis
MPC  Maximal peak concentration
MPFC  Medial prefrontal cortex
MRA  Magnetic resonance angiography
MRA-SI  Magnetic resonance angiography-source imaging
MR CLEAN  Multicenter Randomised Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands
MR  Recanalization of Stroke Clots Using Embolectomy
RESCUE  Magnetic resonance imaging
mRS  Modified Rankin score
MT  Mechanical thrombectomy
mTICI  Modified Thrombolysis in Cerebral Infarction
MTT  Mean transit time
NCCT  Non-contrast computed tomography
NIHSS  National Institutes of Health Stroke Scale
NIINDS  National Institute of Neurological Disorders and Stroke
NNT  Number needed to treat
PCA  Posterior cerebral artery
PCC  Posterior cingulate cortex
PET  Positron emission tomography
PROACT  Prolyse in Acute Cerebral Thromboembolism
PWI  Perfusion-weighted imaging
RACE  Rapid Arterial occlusion Evaluation
REVASCAT  Randomised Trial of Revascularization with Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation LVO Presenting within Eight Hours of Symptom Onset
ROC  Receiver-operating characteristics
ROI  Region-of-interest
ROSIE  ReoPro Retavase Reperfusion of Stroke Safety Study
rtPA  Recombinant Tissue Plasminogen Activator
SAH  Subarachnoid Haemorrhage
SI  Source imaging
sICH  Symptomatic intracerebral haemorrhage
SIESTA  Sedation vs. Intubation for Endovascular Stroke Treatment
SITS  Safe Implementation of Thrombolysis in Stroke
SK  Streptokinase
SNR  Signal-to-noise ratio
SOFIA  Soft Torqueable Catheter Optimized For Intracranial Access
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPECT</td>
<td>Single-photon emission computed tomography</td>
</tr>
<tr>
<td>SPM</td>
<td>Statistical parametric mapping</td>
</tr>
<tr>
<td>START</td>
<td>Imaging Guided Patient Selection for Interventional Revascularization Therapy</td>
</tr>
<tr>
<td>SWIFT- PRIME</td>
<td>Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment</td>
</tr>
<tr>
<td>TE</td>
<td>Echo time</td>
</tr>
<tr>
<td>TESPI</td>
<td>Thrombolysis in Elderly Stroke Patients in Italy</td>
</tr>
<tr>
<td>THRACE</td>
<td>Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke</td>
</tr>
<tr>
<td>TIA</td>
<td>Transient ischemic attack</td>
</tr>
<tr>
<td>TICA</td>
<td>Terminal internal carotid artery</td>
</tr>
<tr>
<td>TIMI</td>
<td>Thrombolysis in Myocardial Infarction</td>
</tr>
<tr>
<td>TR</td>
<td>Repetition time</td>
</tr>
<tr>
<td>TSA</td>
<td>Time-shift analysis</td>
</tr>
<tr>
<td>TTP</td>
<td>Time to peak</td>
</tr>
<tr>
<td>UK</td>
<td>Urokinase</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
SYNOPSIS

THESIS TITLE: INDIVIDUAL PATIENT PROFILING USING CLINICAL AND NEURORADIOLOGICAL BIOMARKERS IN ACUTE ISCHEMIC STROKE: APPLICATION OF ADVANCED MULTIMODAL NEUROIMAGING

ABSTRACT

The aim of the thesis is to study clinical and neuroradiological biomarkers towards individual patient profiling in acute ischaemic stroke (AIS). There is existing evidence that individual patient profiling using a combination of initial stroke severity, infarct topography and surrogate neuroimaging markers provide clinicians with prognostically relevant information that can guide the selection of patients for acute interventions and/or planning and conduct of rehabilitation. Perilesional brain perfusion neuroimaging and cortical venous drain angiography may be additional measures of prognostic relevance. Combinations of these prognostic variables could potentially allow the development of more sophisticated approaches to selection of post-stroke patients for recovery assistance interventions and AIS patients for thrombolytic and/or endovascular treatments. The overall goal of the thesis is to examine specific subgroups of AIS patients and assess functional outcome, where subgroups are defined by, (a) clinically in terms of stroke severity profile (measured using National Institute of Health Stroke Severity (NIHSS) scale), and (b) neuroradiologically depending upon: lesion topography, presence or absence of peri-lesional hyperperfusion, and presence or absence of delayed late venous phase cortical vein filling (delayed-LCVF). Advanced neuroimaging such as arterial spin labelling (ASL) magnetic resonance imaging (MRI) and dynamic computed tomography angiography (dCTA) can be effectively used to discern surrogate imaging biomarkers, investigate underlying post-ischemic pathophysiological mechanisms, identify stroke subtype, and predict the clinical course of AIS patients receiving reperfusion therapy.
“Gam zu l'tova. This too is for the good.”

- Nachum Ish Gamzu, *Talmud, Taanit, 21a*
OVERVIEW OF THE THESIS

Intravenous thrombolysis, in conjunction with the endovascular intra-arterial thrombolysis, is the only approved treatment for acute ischemic stroke (AIS). The advent of thrombolysis has revolutionised how a subgroup of stroke patients is managed in clinical settings and are evaluated using neuroimaging techniques; so that the effective treatment can be tailored to achieve maximum clinical benefit in the interest of the patients. The identification of precise stroke-subtype using advanced multimodal neuroimaging can guide clinicians to choose and prescribe optimal therapy to the stroke patients. The patient selection or individual profiling for thrombolytic trials can be improved by applying a combined approach where both clinical and imaging metrics could be factored in the prognostic models. Furthermore, the PhD thesis will also enhance our knowledge on the use of clinical (baseline stroke severity), and advanced neuroimaging (arterial spin labelling (ASL)-magnetic resonance imaging (MRI) and computed tomographic angiography (CTA) in particular) prognostic markers in selecting patients who will benefit from the thrombolytic therapy even beyond the therapeutic time-window. We believe that the findings of our study may be incorporated in future thrombolytic trials so that efficient selection of a group of patients will provide synergistic treatment benefits to those who will receive the therapy and those who are currently disqualified due to the time-window restrictions.

Outline of the PhD thesis

The goal of the thesis is to pursue an individual patient profiling based approach towards diagnosis, treatment and recovery of stroke patients. The underlying mechanism of recovery following stroke remains intriguing and poses a challenge for clinicians interested in vascular neurology. Clinically, depending on the location/site of lesion, stroke comes as an interesting and challenging construct owing to its specific pathogenesis, distinct neuropsychological features and reasonable prognosis. To study the underlying mechanisms of stroke recovery, selection of patients based on aetiology, imaging parameters is essential for the efficient and comprehensive design of the clinical trials to assess the efficacy of drugs/intervention in stroke. In the first part of the thesis, we will give an overview of stroke epidemiology, pathophysiology and role of neuroimaging in diagnosis, patient selection for thrombolytic trials, and
follow-up treatment (Chapter 1), followed by the review on thrombolysis and patient profiling based approach in AIS (Chapter 2). Subsequently, in the following chapter (Chapter 3) [1], we investigated putative (and degree of) impact of stroke severity in predicting the overall functional outcome, in-hospital placement and death at 90 days, in comparison with age, admission to the stroke unit and thrombolytic treatment. Prediction models for short-term and long-term mortality are important in determining a prognostic prescription for the patients.

In chapter 4, the recovery profiles of ischemic stroke patients with middle cerebral artery occlusion using the topographical characterization of ischemic lesions and neuroradiological study of peri-lesional hyperperfusion on ASL-MRI were investigated [2]. The analysis included a review of CT (non-contrast CT (NCCT)/ perfusion computed tomography (CTP)/CTA) and MRI (diffusion-weighted imaging (DWI)/perfusion weighted imaging (PWI)/ASL) imaging datasets. The classification of patients based on the topography of the lesion; and studying its impact on the recovery profile of the patients may give us insights into the haemodynamic basis. Also, the role of patency of collateral status was also investigated to study its causative association with peri-lesional hyperperfusion. In Chapter 5, we report the incidence of delayed-cortical vein filling in late venous phase in AIS patients as a potential biomarker [3]. We also investigated its association with collateral status. Subsequently, in Chapter 6, follow-up studies were conducted to determine the association of delayed-cortical vein filling with clinical outcomes in AIS patients [4]. Furthermore, the prognostic link of delayed cortical vein filling with early angiographic reperfusion, 90 days functional outcome, and site of occlusion were also studied.

The thesis is based on four original research papers [1-4]. These studies were carried out on a cohort of AIS patients admitted to a comprehensive stroke centre, Department of Neurology, John Hunter Hospital.

**Paper I: Stroke Severity profiling study [1]:** In Chapter 3 [1], we explore the prognostic role of initial stroke severity in AIS. Epidemiological studies on the extent of the interaction and/or influence of stroke severity on clinical outcomes are necessary. Initial severity of stroke and age are both recognised to be important influences on the likelihood of death following AIS - however, the extent of the interaction is uncertain. AIS patients treated with IV-rtPA have only a 4–16% chance...
of good outcome at one year with baseline stroke severity of NIHSS > 20, assessed using National Institute of Health Stroke Scale (NIHSS), and for patients with NIHSS<10 the chance increases to 60–70% [5, 6]. The findings were recently reconfirmed [7]. These results suggest that NIHSS is a significant covariate in the selection of patients for an appropriate thrombolytic therapy, or for the assessment of stroke outcome. Individual profiling based on pre-defined NIHSS thresholds will potentially achieve the desired outcome for the patient with improved treatment efficacy. However, these findings need further validation. The aim of the present study was to investigate the putative (and degree of) impact of initial stroke severity in predicting the overall functional outcome, in-hospital placement and mortality in AIS, in comparison with age, admission to the stroke unit and thrombolytic treatment. We looked at the independent effects of the baseline stroke severity measured using the NIHSS scores as compared with age and other covariates. By strength of significance, we meant to quantify the independent effect of stroke severity in predicting mortality using receiver-operating characteristics (ROC) area and odds ratio (OR). We hypothesised that NIHSS would be the dominant clinical determinant of stroke prognosis.

**Paper 2: Peri-lesional hyperperfusion in acute ischemic stroke: An arterial spin labelling (ASL) study [2]:** In Chapter 4, we used ASL in the pathophysiological investigation of perilesional hyperperfusion (PLH). Focal hyperperfusion after AIS could be of prognostic value depending upon its spatial localisation and temporal dynamics. A recent study using ASL MRI has shown that a select group of patients with ischemic stroke show focal regions of PLH on ASL at 24 hours and that these patients have better clinical recovery from their initial stroke [8]. Factors associated with late-stage (12-24 hours) PLH, identified using ASL, are poorly defined. Leptomeningeal collaterals are relatively dense in and around the cortical superior, middle cerebral vascular territory. Therefore, arterial collaterals supplying the perilesional areas around the infarct topographies involving superior cortical MCA, and lenticulostriate (feeding the striatocapsular region) arterial territories may have a role in focal PLH patterns observed on ASL. To this end, a study of the association of baseline collateral status and the topography of infarcts with late-stage (12-24 hours) PLH may be useful in understanding the underlying pathophysiological mechanism. In this prospective study, we sought to examine clinical and neuroradiological correlates...
of late-stage (12-24 hours) post-ischaemic focal PLH in a group of AIS patients using ASL mapping of brain perfusion. The specific aims of the study were:

(1) To investigate the association of PLH at 24 hours with baseline collateral status.
(2) To identify infarct topographies that associate with PLH at 24 hours (identified using MRI ASL blood flow measurement).
(3) To investigate the factors associated with early PLH in these infarct topographies.

Our underlying hypotheses were: (a) that better collateral flow grades will be associated with PLH, (b) that there will be variation in the degree of PLH seen depending on the topography of the ischaemic lesion, and (c) that the infarction in the superior cortical MCA and deep MCA territories such as in striatocapsular region (as per Marchal et al. [9]) would more commonly show evidence of PLH than other infarct topographies.

**Paper 3: Delay of late venous phase cortical vein filling in acute ischemic stroke patients: a novel neuroradiological biomarker [3].** In Chapter 5[3], we reported a novel phenomenon, delayed late venous phase cortical vein filling (LCVF), observed on four-dimensional (4D) dynamic computed tomography angiography (dCTA) obtained using 320-detector row 640-slice multidetector CT (MDCT) scanner, in AIS patients. Delayed late venous phase cortical vein filling (delayed-LCVF) is characterised by late venous phase opacification of cortical veins despite contrast clearance from contralateral cortical veins on dCTA [3]. The aim of this study was to examine the frequency of delayed-LCVF and assess its association to baseline collateral status. Neuroradiological assessment of the venous system may be beneficial in stroke prognostication and patient selection for acute intervention strategies. MDCT scanners allow for whole-brain, sub-second, and volumetric acquisition of four-dimensional (4D) dynamic time-resolved dCTA studies of the brain, in particular, visualisation of changes in perfusion [10, 11]. In addition to obtaining three-dimensional (3D) evaluation of intracranial vasculature, time-resolved dCTA allows visualisation of contrast flow from its arterial to venous phases and has demonstrated superior diagnostic accuracy in comparison to the single-phase conventional CT-angiography [11, 12]. Currently, clinical-neuroradiological assessments using CTA focus primarily on the cerebral arterial circulation. Information
on the haemodynamics and the drainage topography of the cerebral venous circulation may be useful for prognostication in stroke.

**Paper 4: Association of cortical vein filling with clot location and clinical outcomes in acute ischaemic stroke patients [4].** In Chapter 6 [4], we examined the association of late stage cortical vein drainage in a prospective cohort of AIS patients treated with IVT, with tissue at risk, clot location, and clinical outcome. The background to this work was our previous study (Chapter 5) where we reported delayed-LCVF as a novel dCTA finding in AIS patients [3]. The specific objectives of the study were:

(1) To examine the association of delayed-LCVF with ischemic infarct core and tissue at risk.

(2) To study the association of delayed-LCVF with clot location.

(3) To investigate if delayed-LCVF is associated with clinical outcomes including reperfusion status at 24 hours and 90-day functional outcome.

There are limited studies on the role of cortical veins in stroke pathophysiology, and their associations with thrombus location and clinical outcome [13-18].

Finally, in Chapter 7, we will revisit the overall findings of our studies reported in first six chapters, and provide further insights on the use of advanced neuroimaging in individualised patient profiling for prognostication and to guide acute and long-term intervention strategies in AIS.