A STUDY OF BIOMARKERS FOR DIAGNOSIS, OUTCOME PREDICTION AND ANTIBIOTIC THERAPY GUIDANCE IN SEPSIS

BY

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ABSTRACT

Sepsis is common in the ICU worldwide and contributes to high mortality. However, timely diagnosis, outcome prediction and antibiotic monitoring in sepsis remains challenging. In Chapter Three, the diagnostic value of model-based insulin sensitivity (SI) for sepsis was studied in 38 non-diabetics on their ICU admission in a cross-sectional study. The findings indicated that baseline SI was significantly lower in sepsis (n = 18) versus non-sepsis (n = 20) (0.996 ± 1.269 versus $5.012 \pm 4.930 \times 10^{-4}$ L/mU/min, $P = 0.002$), with clinically valid diagnostic performance (AUC 0.814). In Chapter Four, similar methodology was applied to a mixed cohort of 86 diabetic and non-diabetic patients newly admitted to ICU. Although baseline SI was significantly lower in sepsis (n = 41) versus non-sepsis (n = 45) (0.560 ± 0.676 versus $1.097 \pm 1.473 \times 10^{-4}$ L/mU/min, $P = 0.037$), the biomarker failed to diagnose sepsis in this cohort. Hence, model-based SI may be a useful diagnostic test of sepsis when specifically applied to the non-diabetic ICU patients. In Chapter Five, the prognostic value of a combination of biomarkers in sepsis was explored in a prospective cohort study of 159 ICU patients. It was found that a prediction equation utilizing baseline total leukocytes count, procalcitonin, interleukin-6 and arylesterase activity of paraoxonase-1 predicted 30-day mortality with a remarkable performance (AUC 0.814). Therefore, a multi-marker approach using these biomarkers may be a useful predictor of mortality in sepsis. In Chapter Six, the utility of point-of-care procalcitonin (POCT) to guide duration of antibiotic in the ICU was examined in a randomized-controlled trial. Eighty patients were allocated to either the POCT-guided arm (n = 40) or control arm (n = 40). The mean duration of antibiotic was 6.3 ± 2.1 days in the POCT-guided arm versus 9.1 ± 4.7 days in control arm ($P = 0.001$), while there was no significant difference in 30-day mortality. Thus, POCT guidance reduced antibiotic duration without compromising mortality in our patients.

خلاصة البحث

يعتبر إنتان شائع في وحدة العناية المركزة في جميع أنحاء العالم ويساهم في ارتفاع معدل الوفيات. ومع ذلك، لا يزال التشخيص في الوقت المناسب والتنبؤ بالنتائج ورصد المضادات الحيوية في التسمم يمثل تحديًا. وفي الباب الثالث، تمت دراسة القيمة التشخيصية لحساسية الأنسولين (ايس.اي) المستندة إلى النموذج للإنتان في 38 مريض غير مصاب بالسكري عند قبولهم في وحدة العناية المركزة في دراسة مقطعية. وأشارت النتائج إلى أن خط الأساس SI كان أقل بشكل ملحوظ في الإنتان (ن = 18) مقابل غير الإنتان (ن = 20) (0.996 ± 1.269 مقابل 5.012 ± 4.930 × 10^{-4} L/mU/min، $P = 0.002$) ، مع أداء تشخيصي صالح سريريًا (AUC 0.814). وفي الباب الرابع، تم تطبيق منهجية مماثلة على مجموعة مختلطة من 86 مريضا بالسكري وغير المصابين بالبول السكري تم قبولهم حديثًا في وحدة العناية المركزة. على الرغم من أن الخط الأساسي (ايس.اي) كان أقل بشكل ملحوظ في التسمم (ن = 41) مقابل التسمم (ن = 45) (0.560 ± 0.676 مقابل 1.097 ± 1.473 × 10^{-4} L/mU/min، $P = 0.037$) لتشخيص الإنتان في هذه المجموعة. وبالتالي، قد يكون SI المستندة إلى نموذج اختبار تشخيصي مفيد من تعفن الدم عند تطبيقها على وجه التحديد لمرضى ICU غير المصابين بالسكري. وفي الباب الخامس، تم استكشاف قيمة النذير لمجموعة من المؤشرات الحيوية في الإنتان في دراسة الأتراب المحتملين من 159 مريضا وحدة العناية المركزة. وقد وجد أن معادلة التنبؤ باستخدام عدد خلايا الدم البيضاء وبروكالسيتونين وإنترلوكين 6 وارليستسراس نشاط من المتوقع للوفوروكسوناز 1 وتوقع وفاة 30 يوما مع أداء ملحوظ (AUC 0.814). ولذلك، قد يكون اتباع نهج متعدد العلامات باستخدام هذه المؤشرات الحيوية مؤشرا مفيدا للوفيات في الإنتان. وفي الباب السادس، تم فحص فائدة بروكالسيتونين نقطة الرعاية (بي.او.سي.تي) لتوجيه مدة المضادات الحيوية في وحدة العناية المركزة في تجربة عشوائية محكومة. وتم تخصيص ثمانين مريضا إما إلى الذراع الموجهة (بي.او.سي.تي) (ن = 40) أو ذراع التحكم (ن = 40). وكان متوسط مدة المضادات الحيوية 6.3 ± 2.1 يوم في الذراع الموجهة (بي.او.سي.تي) مقابل 9.1 ± 4.7 أيام في ذراع التحكم ($P = 0.001$)، في حين لم يكن هناك فرق كبير في وفيات لمدة 30 يوما. وبالتالي، خفضت التوجيه (بي.او.سي.تي) مدة المضادات الحيوية دون المساس الوفيات في المرضى.

APPROVAL PAGE

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DECLARATION

I hereby declare that this thesis is the result of my own investigations, except where otherwise stated. I also declare that it has not been previously or concurrently submitted as a whole for any other degrees at IIUM or other institutions.

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TABLE OF CONTENTS

Abstract ii
Abstract in Arabic iii
Approval page iv
Declaration v
Copyright Page vi
Acknowledgements vii
Table of Contents viii
List of Tables xii
List of Figures xiii
List of Abbreviations xv

CHAPTER ONE: INTRODUCTION 1
1.1 Background 1
1.2 Problem Statement 2
1.3 Aims 4
1.4 Significance of the Study 4

CHAPTER TWO: LITERATURE REVIEW 6
2.1 Sepsis Definitions 6
2.1.1 Sepsis-1 Definitions 7
2.1.2 Limitations of Sepsis-1 Definitions 7
2.1.3 Sepsis-2 Definitions 9
2.1.4 Limitations of Sepsis-2 Definitions 10
2.1.5 Sepsis-3 Definitions 10
2.2 Pathophysiology of Sepsis 12
2.2.1 Inflammation and Immune System 12
2.2.2 Endothelium and Coagulation System 13
2.3 Biomarkers In Sepsis 14
2.3.1 Definitions of Biomarkers 14
2.3.2 Rationale of Using Biomarkers 14
2.3.3 Types of Sepsis Biomarkers 14
2.3.4 Limitations of Biomarkers 16
2.4 Statistical Principles To Evaluate Biomarkers 16
2.4.1 Likelihood Ratios 20
2.4.2 Risk Stratification Analysis 21
2.5 Insulin Sensitivity 22
2.5.1 Measurement of Insulin Sensitivity 23
2.5.2 Model-based Insulin Sensitivity for Diagnosis of Sepsis 30
2.6 Procalcitonin 31
2.6.1 Procalcitonin to Guide Antibiotic Therapy 31
2.6.2 Procalcitonin for Outcome Prediction in Sepsis 35
2.7 Interleukin-6 37
2.7.1 Interleukin-6 for Outcome Prediction in Sepsis 37
2.8 Paraoxonase-1 38
2.8.1 Paraoxonase-1 for Outcome Prediction in Sepsis 39

2.9 Total Leukocytes Count....39
2.9.1 Total Leukocytes Count for Diagnosis of Sepsis....40
2.9.2 Total Leukocytes Count for Outcome Prediction in Sepsis....40
2.10 Multi-Marker Panels In Sepsis....41
2.10.1 Clinical Examples....41
2.11 Conceptual Frameworks....44
2.11.1 Model-Based Insulin Sensitivity for Diagnosis of Sepsis....44
2.11.2 Multi-Marker Approach for Outcome Prediction in Sepsis....47
2.11.3 POCT for Antibiotic Therapy Guidance in Sepsis....50

CHAPTER THREE: MODEL-BASED INSULIN SENSITIVITY FOR DIAGNOSIS OF SEPSIS IN THE NON-DIABETIC CRITICALLY ILL PATIENTS....52
3.1 Introduction....52
3.2 Objectives and Hypotheses....54
3.3 Materials and Methods....54
3.3.1 Study Design and Participants....54
3.3.2 Data Collection....55
3.3.3 Insulin Sensitivity Assessment....55
3.3.4 Patients' Selection....56
3.3.5 Definitions....57
3.3.6 Statistical Analysis....58
3.3.7 Sample Size Calculation....58
3.4 Results....59
3.4.1 Clinical-Demographic Profiles....59
3.4.2 Blood Glucose Profiles....61
3.4.3 Insulin Sensitivity Profiles....62
3.4.4 Diagnostic Value of Model-Based Insulin Sensitivity....63
3.5 Discussion....68
3.5.1 Baseline Characteristics....68
3.5.2 Blood Glucose Profiles....68
3.5.3 Insulin Sensitivity Profiles....69
3.5.4 Diagnostic Value of Model-Based Insulin Sensitivity....70
3.5.5 Strengths and Limitations....72
3.6 Conclusion....73

CHAPTER FOUR: MODEL-BASED INSULIN SENSITIVITY FOR DIAGNOSIS OF SEPSIS IN THE DIABETIC AND NON-DIABETIC CRITICALLY ILL PATIENTS....75
4.1 Materials and Methods....75
4.1.1 Study Design and Participants....75
4.1.2 Data Collection....76
4.1.3 Insulin Sensitivity Assessment....76
4.1.4 Patients' Selection....76
4.1.5 Definitions....77
4.1.6 Statistical Analysis....77
4.1.7 Sample Size Calculation....78
4.2 Results....78
4.2.1 Clinical-Demographic Profiles....78

4.2.2 Insulin Sensitivity Levels....80
4.2.3 Diagnostic Value of Model-Based Insulin Sensitivity....80
4.3 Discussion....83
4.3.1 Clinical-Demographic Profiles....83
4.3.2 Levels and Diagnostic Value of Model-Based Insulin Sensitivity....84
4.3.3 Strengths and Limitations....85
4.4 Conclusion....85

CHAPTER FIVE: MULTI-MARKER APPROACH FOR OUTCOME PREDICTION IN SEPSIS....86
5.1 Introduction....86
5.2 Objectives and Hypotheses....87
5.3 Materials and Methods....88
5.3.1 Study Design and Participants....88
5.3.2 Data Collection....89
5.3.3 Sample Collection and Processing....89
5.3.4 Biomarkers Assays....90
5.3.5 Patients' Selection....91
5.3.6 Statistical Analysis....91
5.3.7 Sample Size Calculation....92
5.4 Results....92
5.4.1 Clinical-Demographic Profiles....92
5.4.2 Biomarker Profiles....94
5.4.3 Development of Sepsis Mortality Score....96
5.4.4 Predictive Performance of Sepsis Mortality Score....98
5.4.5 Construction of a Final Model Incorporating the 'Sepsis Mortality Score'....101
5.4.6 Risk Stratification Analysis....102
5.4.7 Predictive Ability of Sepsis Mortality Score for Other Outcome....104
5.5 Discussion....105
5.5.1 Principal Findings....105
5.5.2 Merits of Our Multi-Marker Panel....106
5.5.3 Sequential Organ Failure Assessment Score versus Multi-Marker Panels....109
5.5.4 Strengths and Limitations....109
5.6 Conclusion....110

CHAPTER SIX: POINT-OF-CARE PROCALCITONIN TO GUIDE ANTIBIOTIC DURATION IN THE INTENSIVE CARE UNIT....112
6.1 Introduction....112
6.2 Objectives and Hypotheses....115
6.3 Materials and Methods....115
6.3.1 Study Design....115
6.3.2 Participants....116
6.3.3 Randomisation, Allocation Concealment and Blinding....117
6.3.4 Procedures....118
6.3.5 Procalcitonin Measurement....119

6.3.6 Data Collection 120
6.3.7 Outcome Measures and Definitions 121
6.3.8 Statistical Analysis 122
6.3.9 Sample Size Calculation 122
6.4 Results 122
6.4.1 Clinical-Demographic Profiles 122
6.4.2 Primary Outcome 124
6.4.3 Secondary Outcomes 126
6.4.4 Adherence to the Study Protocol 127
6.5 Discussion 127
6.5.1 Principal Findings 127
6.5.2 Relations to Previous Studies 128
6.5.3 Strengths and Limitations 129
6.6 Conclusion 132

CHAPTER SEVEN: GENERAL CONCLUSION 133
7.1 Overview of Aims and Hypotheses 133
7.2 Summary and Overall Conclusion 134
7.3 Suggested Further Studies 138
7.3.1 Model-based Insulin Sensitivity for Diagnosis of Sepsis 138
7.3.2 Multi-marker Approach for Outcome Prediction in Sepsis 138
7.3.3 Point-of-care Procalcitonin for Guidance of Antibiotic Therapy in Sepsis 138

REFERENCES 139

APPENDIX A: PUBLISHED MANUSCRIPT OF FINDINGS OF CHAPTER THREE 153
APPENDIX B: ETHICAL APPROVAL LETTER FOR CONDUCT OF STUDY OF CHAPTER THREE 159
APPENDIX C: BLOOD GLUCOSE MANAGEMENT PROTOCOL BY MALAYSIAN SOCIETY OF INTENSIVE CARE 160
APPENDIX D: ETHICAL APPROVAL LETTER FOR CONDUCT OF STUDY OF CHAPTER FOUR 163
APPENDIX E: PUBLISHED MANUSCIPT OF FINDINGS OF CHAPTER FIVE 164
APPENDIX F: ETHICAL APPROVAL LETTER FOR CONDUCT OF STUDY OF CHAPTER FIVE 170
APPENDIX G: PUBLISHED MANUSCRIPT OF THE SECONDARY ANALYSIS OF FINDINGS OF CHAPTER FIVE 171
APPENDIX H: ACCEPTANCE LETTER FOR PUBLICATION OF MANUSCRIPT OF FINDINGS OF CHAPTER SIX 178
APPENDIX I: ETHICAL APPROVAL LETTER FOR CONDUCT OF STUDY OF CHAPTER SIX IN IIUM 180
APPENDIX J: ETHICAL APPROVAL LETTER FOR CONDUCT OF STUDY OF CHAPTER SIX IN USM 181
APPENDIX K: PUBLICATIONS ARISING 182
APPENDIX L: AWARDS 184

LIST OF TABLES

Table 1.1 Notable information about sepsis 2

Table 2.1 Definitions and diagnostic criteria for sepsis 8

Table 2.2 The Sequential Organ Failure Assessment score (Vincent et al., 1996) 11

Table 2.3 Rule of thumb: Correspondence between positive (PLR) and negative (NLR) likelihood ratios and area under the curve (AUC) and the diagnostic value of a biomarker 21

Table 2.4 The different models of glucose-insulin system 25

Table 2.5 Nomenclatures of the the Intensive Control of Insulin-Nutrition-Glucose model 29

Table 2.6 Previous studies on procalcitonin-guided antibiotic therapy 32

Table 3.1 Baseline clinical-demographic profiles 60

Table 3.2 Insulin sensitivity profiles (in $\times 10^{-4}$ L/mu/min) in the first 24 hours of ICU admission of non-sepsis and sepsis 62

Table 3.3 Diagnostic performance of model-based SI for sepsis in the non-diabetic critically ill patients 64

Table 3.4 Multivariate logistic regression analysis 65

Table 3.5 Diagnostic performances of model-based SI and routine clinical markers for sepsis 66

Table 4.1 Baseline clinical-demographic profiles 79

Table 4.2 Multivariate logistic regression analysis 82

Table 5.1 Baseline clinical-demographic profiles 93

Table 5.2 Total leukocytes count, procalcitonin, interleukin-6, paraoxonase and arylesterase activities in the survivors and non-survivors and their predictive performance for 30-day mortality 95

Table 5.3 Results of multivariate logistic regression and derivation of the Sepsis Mortality Score 97

Table 6.1 Baseline clinical-demographic profiles 123

Table 6.2 Primary and secondary outcome measures 125

LIST OF FIGURES

Figure 2.1 Types of sepsis biomarkers classified according to pathophysiology of sepsis and organ dysfunction. *Reproduced from Reinhart et al*. (Reinhart, Bauer, Riedemann, & Hartog, 2012) 15

Figure 2.2 Statistical basics to evaluate biomarkers 17

Figure 2.3 Calculation of sensitivity and specificity 18

Figure 2.4 Receiver operating characteristic curve 19

Figure 2.5 Calculation of positive and negative predictive values 20

Figure 2.6 Schematic representation of the glucose-insulin system model. *Reproduced from Uyttendaele, Dickson, Shaw, Desaive, & Chase (2017)* 27

Figure 2.7 Conceptual framework on the cross-sectional studies of model-based insulin sensitivity for diagnosis of sepsis 46

Figure 2.8 Conceptual framework on the prospective cohort study of multi-marker approach for mortality prediction in sepsis 49

Figure 2.9 Conceptual framework on the randomised-controlled trial of POCT-versus standard-of-care-guided antibiotic therapy in the ICU 51

Figure 3.1 Flowchart of patients' selection 57

Figure 3.2 The blood glucose profiles (in mmol/L) in the first 24 hours of ICU admission of non-sepsis and sepsis 61

Figure 3.3 Insulin sensitivity profiles (in $\times 10^{-4}$ L/mu/min) in the first 24 hours of ICU admission of non-sepsis and sepsis 63

Figure 3.4 Receiver operating characteristic curves of Sequential Organ Failure Assessment score with and without insulin sensitivity 67

Figure 4.1 Flowchart of patients' selection 77

Figure 4.2 Baseline insulin sensitivity levels among sepsis and non-sepsis in a mixed cohort of diabetic and non-diabetic critically ill patients 80

Figure 4.3 Receiver operating characteristic curve of baseline insulin sensitivity for discrimination of sepsis in a mixed cohort of diabetic and non-diabetic critically ill patients 81

Figure 4.4 Baseline SI levels among sepsis and non-sepsis in the non-diabetic critically ill patients 82

Figure 5.1 The predictive performance of the Sepsis Mortality Score 98

Figure 5.2 Receiver operating characteristics curves of the Sepsis Mortality Score compared to its constituent individual biomarkers for their mortality predictive performance 99

Figure 5.3 Receiver operating characteristics curves of the Sequential Organ Failure Assessment score, Sepsis Mortality Score and combination of the two scores for their mortality predictive performance 100

Figure 5.4 Kaplan-Meier plot showing survival according to increased Sepsis Mortality Score (>30.4) in the entire cohort 101

Figure 5.5 Accuracy of mortality prediction based on a clinical model with and without Sepsis Mortality Score 102

Figure 5.6 Risk assessment plot 103

Figure 5.7 Receiver operating characteristics curves of the Sepsis Mortality Score for prediction of A) High-degree organ failure and B) Septic shock 105

Figure 6.1 Trial profile 117

Figure 6.2 Guidelines for stopping of antibiotic according to procalcitonin concentrations (Bouadma et al., 2010) 119

Figure 6.3 Finecare™ PCT Rapid Test along with Finecare™ FIA Meter (CIGA Healthcare Ltd, Ballymena, UK) 120

LIST OF ABBREVIATIONS

ACCP	American College of Chest Physicians
AMR	Antimicrobial resistance
APACHE II	Acute Physiology and Chronic Health Evaluation II Score
AUC	Area under the curve
ARE	Arylesterase
BG	Blood glucose
cfNRI	Category-free net reclassification improvement
CI	Confidence interval
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
CV	Coefficient of variation
DM	Diabetes mellitus
ED	Emergency Department
EG	Endothelial glycocalyx
HTAA	Hospital Tengku Ampuan Afzan
HUSM	Hospital Universiti Sains Malaysia
ICING	Intensive Control of Insulin-Nutrition-Glucose
ICU	Intensive care unit
IDI	Integrated discrimination improvement
IIUMMC	International Islamic University of Malaysia Medical Centre
IL	Interleukin
IP	1-specificty

IS	Integrated sensitivity
IREC	International Islamic University of Malaysia Research Ethics Committee
LMIC	Low- and middle-income countries
MDR	Multi-drug resistant
MYR	Malaysian Ringgit
NLR	Negative likelihood ratio
NMRR	National Medical Research Registry
NPV	Negative predictive value
NRI	Net reclassification improvement
OR	Odd ratio
POC	Point-of-care
POCT	Point-of-care procalcitonin
PON-1	Paraoxonase-1
PCT	Procalcitonin
PLR	Positive likelihood ratio
PPV	Positive predictive value
PRR	Pattern Recognition Receptor
RCT	Randomized-controlled trial
ROC	Receiver operating characteristics curve
RRT	Renal replacement therapy
SAPS II	Simplified Acute Physiology Score
SCCM	Society of Critical Care Medicine
SI	Insulin sensitivity

SD	Standard deviation
SIRS	Systemic Inflammatory Response Syndrome
SOFA	Sequential Organ Failure Assessment
SS	Sepsis Score
STAR	Stochastic Targeted Glycaemic Control
sTREM	soluble triggering receptor expressed on myeloid cells
TLC	Total leukocytes count
TLR	Toll-like receptor
TNF	Tumour necrosis factor
VIF	Variation inflation factor
v-SUPAR	soluble urokinase-type plasminogen activator receptor

CHAPTER ONE

INTRODUCTION

1.1 BACKGROUND

Sepsis, a condition characterized by a dysregulated host response to infection, afflicts millions of people worldwide each year (Fleischmann et al., 2016). Multiple studies suggest that the incidence of sepsis is alarmingly increasing (Álvaro-Meca et al., 2018; Meyer et al., 2018). Furthermore, patients diagnosed with sepsis are estimated to have in-hospital mortality rate more than 10%, while in its most severe form i.e. septic shock, the mortality rate can reach more than 40% (Singer et al., 2016). Adverse outcome of sepsis is not limited to increase mortality risk. A recent study suggests that sepsis may worsen or result in new chronic diseases and leads to development of persistent cognitive and functional impairments among the survivors (Calsavara, Nobre, Barichello, & Teixeira, 2018). Not only sepsis is common and lethal, it is the single most expensive condition treated in hospitals (Paoli, Reynolds, Sinha, Gitlin, & Crouser, 2018). Additionally, sepsis is one of the most common reasons for intensive care unit (ICU) admission throughout the world and was the most common cause of death among critically ill patients in non-coronary ICUs (Perner et al., 2016). The burden of sepsis in low- and middle-income countries (LMICs) is even higher (Kwizera et al., 2018). In Malaysia, a country considered as upper middle-income, sepsis is among the leading cause of admission to the Ministry of Health ICUs. According to Malaysian Registry of Intensive Care, sepsis was the first leading cause of admission to the Ministry of Health ICUs in 2017, with mortality rate of 41.6% (Tai, Lim, Mohd Nor, Ismail & Wan Ismail, 2017). The magnitude of the problems of sepsis are summarized in Table 1.1.

Table 1.1 Notable information about sepsis

Notable information	Details
High incidence	An estimated of 31.5 million people are treated each year for sepsis (Fleischmann et al., 2016). The incidence is even higher in low- and middle-income countries.
High mortality	More than 10% for sepsis, and more than 40% for septic shock (Singer et al., 2016).
High morbidity	May worsen or result in new chronic diseases, and lead to development of persistent cognitive and functional impairments among the survivors (Calsavara et al., 2018).
High cost to treat	The most expensive condition treated in the United States (Paoli et al., 2018).
Sepsis in ICU	One of the most common reasons for ICU admission throughout the world and the most common cause of death among critically ill patients in non-coronary ICUs (Perner et al., 2016).

Note. ICU, intensive care unit

1.2 PROBLEM STATEMENT

Considering the magnitude of its problem, immediate treatment of sepsis is required, which first necessitates its timely and accurate diagnosis. Nevertheless, prompt diagnosis of sepsis in critical care has many challenges. Blood culture results are considered the most accepted tool to clinically diagnose infection, but this takes at least 24 to 48 hours to process (Lambregts, Bernards, van der Beek, Visser, & de Boer, 2019). Biomarker tests have been developed to facilitate early diagnosis of sepsis, but they still suffer some disadvantages. There are many sepsis biomarkers, but none has sufficient specificity or sensitivity to be routinely employed in clinical practice (Larsen & Petersen, 2017). Furthermore, a minimum lag time of typically two to three hours is still present (van Engelen, Wiersinga, Scicluna, & van der Poll, 2018), and biomarkers are generally expensive. Therefore, other markers must be

investigated to assist in making the timeliest, accurate, and cost-effective diagnosis of sepsis. Sepsis is known to have a negative effect on insulin sensitivity (SI). The SI profiles of a patient can be generated using a mathematical glucose-insulin system model i.e. model-based SI. However, to our knowledge, the performance of model-based SI as a diagnostic biomarker of sepsis has been under-explored.

The other mainstay in the management of sepsis is early recognition of which patients who are least likely to survive and thus benefit from aggressive treatment approaches. This outcome prediction in sepsis is currently done mostly via clinical scoring systems, such as the Sequential Organ Failure Assessment (SOFA) score (Vincent et al., 1996). However, clinical scoring systems were generated to assess severity of illness of general ICU patients and not primarily for sepsis patients. Concerning this limitation, biomarkers were proposed as useful tools for the prognostication of sepsis. A singular ideal biomarker has not yet been identified; an alternative approach is to shift research focus to a combination of several biomarkers to assess risk in sepsis. Nevertheless, the optimal multi-marker approach for outcome prediction in sepsis is yet to be determined.

Timely, appropriate and adequate antibiotic therapy is of paramount importance in sepsis. However, overly long course is undesirable because of side effects and increasing antimicrobial resistance (AMR) (Lomazzi, Moore, Johnson, Balasegaram, & Borisch, 2019). Therefore, specific biomarkers for resolution of sepsis might assist the ICU physicians in making decisions on antibiotic therapy on an individual basis. Several studies have shown that biomarker guidance using procalcitonin (PCT) can reduce the duration of antibiotic treatment, without compromising the safety outcome (Deliberato et al., 2013; Hohn et al., 2013; de Jong, 2016; Svoboda, Kantorová, Scheer, Radvanova, & Radvan, 2007). However, majority

of the studies were conducted in the setting of Western population. More importantly, all the studies utilised the standard laboratory method, which can be logistically and economically challenging with several hours or more of turnaround time. Point-of-care PCT (POCT) may overcome some of the problems related to the current existing technologies. To our knowledge, POCT detection as a tool to guide antibiotic discontinuation in the critically ill patients has not yet been evaluated in any clinical trials.

1.3 AIMS

The current thesis is divided into four sub-studies. The aim of the first study was to determine the capability of model-based SI to become a new biomarker for diagnosis of sepsis in the non-diabetic critically ill patients (Chapter Three). The second study was to assess the performance of the same biomarker but in an extended cohort of critically ill patients that included both the diabetic and non-diabetic patients (Chapter Four). The third study intended to investigate the prognostic value of a multi-marker approach for mortality prediction in critically ill patients with sepsis (Chapter Five). Finally, the last study was to evaluate the usefulness of POCT to guide the duration of antibiotic therapy in our local ICU (Chapter Six).

1.4 SIGNIFICANCE OF THE STUDY

The unmet clinical need of a reliable tool to rapidly identify sepsis could potentially be improved with evaluation of a new biomarker such as SI. This will have implications for clinicians in terms of timely diagnosis and potentially starting appropriate treatments. Early identification and treatment of sepsis with appropriate antibiotic has been shown to significantly reduce sepsis-related mortality (Liu et al.,

2017). The effective and early treatment of serious infections prevents progression to organ dysfunction or even septic shock and allows care to be provided at lower cost (Bochud, Bonten, Marchetti, & Calandra, 2004).

The difficulties in predicting the outcome of sepsis using the currently available tool can be aided by evaluation of a multi-marker panel. Outcome prediction tools in sepsis aim to assess the severity of the illness; and assign patients into different risk categories. This is of particular importance because patients at high risk may benefit from earlier clinical intervention, while low-risk patients may benefit from not undergoing unnecessary procedures. Thus, knowing where the patients reside on the spectrum of sepsis may lead to improved outcome.

Evaluation of POCT-guided antibiotic therapy will have implications for clinicians in terms of decision for antibiotic duration. Reduced duration of antibiotic administration has several advantages. First, it might contain the emergence of AMR in the ICU. Furthermore, reduced exposure to antibiotic therapy has been associated with a significant decrease in 28-day mortality, possibly the result of fewer side effects of antibiotic use (de Jong et al., 2016). Additionally, saving of antibiotic cost has been demonstrated in several studies (Deliberato et al., 2013; Schroeder et al., 2009). A lower medical cost is desirable to both hospital systems and the patients.

CHAPTER TWO

LITERATURE REVIEW

In Chapter One, it is apparent that managing sepsis in the ICU continues to pose challenges for the clinicians. The search for novel biomarkers that might better inform clinicians treating such patients are therefore sorely needed. This has been of great interest for research in sepsis and is also the focus of this thesis. Difficulty in identifying such markers is in part due to the complex heterogeneity of sepsis, resulting from the broad and vague definition of this condition based on numerous possible clinical signs and symptoms as well as an incomplete understanding of the underlying pathophysiology of this complex condition (Biron, Ayala, & Lomas-Neira, 2015). This chapter will begin by examining the definitions and pathophysiology of sepsis, then move to seeing the attempts that have been made so far in identifying biomarkers utility for sepsis management.

2.1 SEPSIS DEFINITIONS

The definition of sepsis has shifted over time. Prior to 1991, the physiological derangement characteristic of sepsis was referred by a variety of terms that were often used interchangeably, including “sepsis”, “septicaemia” and “septic syndrome”. In 1991, a conference was held by the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) to address the lack of consensus regarding the definition of sepsis and the difficulties this created in studies and treatment. This conference and its outcome are now referred to as Sepsis-1 (Bone et al., 1992). This was followed by Sepsis-2 (Levy et al., 2003) in 2001 and Sepsis-3 (Singer et al., 2016) in 2016.

2.1.1 Sepsis-1 Definitions

The ACCP and the SCCM convened in Chicago in 1991 and highlighted that sepsis was an ‘ongoing process’ (Bone et al., 1992). Systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, septic shock and multiple organ dysfunction syndrome began to be used in clinical practice. Sepsis was defined as the documentation of two or more SIRS criteria, in addition to known or suspected infection, while severe sepsis was defined as clinical sepsis accompanied by organ dysfunction, hypo-perfusion or hypotension. Septic shock is defined as a clinical display in which fluid-resistant hypotension is observed (Table 2.1).

2.1.2 Limitations of Sepsis-1 Definitions

Although the Sepsis-1 definitions consider the combination of infection and SIRS response as sepsis, a sepsis-like clinical picture may be observed without infection. The current significance of inflammation is non-specific and may manifest in many conditions. A good example of the sepsis-like statement is the hyperkinetic state after cardiac surgery without any infection which displays a very different prognosis and therapeutic approach from those of real sepsis. Moreover, sepsis is a complex interplay of pro- and anti-inflammatory responses and now evolves into two phases: hyper-inflammation and hypo-inflammation (Hotchkiss, Guillaume, & Didier, 2013). Therefore, the inflammation itself carries little meaning, because inflammation is a very non-specific response to any insult from minor trauma to complicated autoimmune disease.