TIME TO EVENT AND DISEASE PROGRESSION MODELLING IN ISCHEMIC STROKE USING PHARMACOMETRICS APPROACH

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by

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LIST OF ABBREVIATIONS

AF	Atrial Fibrillation
AIS	Acute Ischemic Stroke
AOR	Adjusted Odds Ratio
APTT	Activated Partial Thromboplastin Time
BG	Blood Glucose
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CKD	Chronic Kidney Diseases
CNS	Central Nervous System
DBP	Diastolic blood pressure
delayed HG	Delayed Hyperglycemia.
df	degree of freedom
DM	Diabetes Mellitus
DP	Disease Progression
FHOS	Family History of Stroke
GLP-1	Glucagon-Like Peptide-1
GOF	Goodness of Fit
HDL	High-Density Lipoprotein
HG	Hyperglycemia
HPLD	Hyperlipidemia
HR	Hazard Ratio
HSNZ	Hospital Sultanah Nur Zahirah
HT	Hemorrhagic Transformation
HTN	Hypertension

HU	Hyperuricemia
ICU	Intensive care unit
IHD	Ischemic Heart Disease
IS	Ischemic Stroke
IR	Insulin Resistance
IWRES	Individual Weighted Residuals
LDL	low-density lipoprotein
LPHG	Long Persistent Hyperglycemia
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
NLME	Non-Linear Mixed Effects
NNEUR	National Neurology Registry
NONMEM	Nonlinear Mixed Effects Modelling
OFV	Objective Function Value
OR	Odds Ratio
PT	Prothrombin Time
RSC	Recurrent Ischemic Stroke
RSE	Relative Standard Error
RUV	Residual Unexplained Variability
SAP	Stroke-Associated Pneumonia
SBP	Systolic Blood Pressure
SGLT2	Sodium-Glucose Transport Protein 2
SIR	Sampling Importance Resampling
SPHG	Short Persistent Hyperglycemia
TG	Triglyceride

TTE	Time to Event
VPC	Visual Predictive Checks

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‘TIME TO EVENT’ DAN PEMODELAN PERKEMBANGAN PENYAKIT DALAM STROK ISKEMIK MENGGUNAKAN PENDEKATAN FARMAKOMETRIK

ABSTRAK

Hyperglisemia (HG) semasa strok akut telah dikaitkan dengan hasil yang lebih teruk, termasuk hasil fungsi yang tidak dan radang paru-paru yang berkaitan dengan strok (SAP). Pemahaman dan kesedaran yang lebih baik mengenai corak HG dan faktor risiko berpotensi yang berkaitan dengan HG, peramal hasil yang buruk dalam kalangan pesakit yang mengalami HG semasa strok iskemik akut (AIS), akan dapat membantu membimbing pengurusan strok akut dan mencegah hasil yang buruk. Fasa I dalam tesis ini bertujuan untuk menilai peramal HG semasa AIS, SAP dalam kalangan pesakit-pesakit ini, dan peramal hasil fungsi yang tidak baik mengikut corak HG di kalangan pesakit yang mengalami HG semasa AIS. Manakala Fasa II dalam tesis ini bertujuan untuk mengukur kadar perubahan glukosa darah (BG) dalam tempoh 72 jam pertama AIS dalam kalangan pesakit yang mengalami HG dengan membangunkan model perkembangan penyakit menggunakan pendekatan parametrik. Dari keadaan akut strok iskemik (IS), kami mengarahkan kajian ke fasa kronik IS. Strok berulang adalah satu parameter hasil penting lain yang termasuk dalam matlamat pengurusan strok. Berbanding dengan strok pertama, gangguan neurologi yang disebabkan oleh pengulangan adalah lebih serius, lebih sukar untuk dirawat, dan mempunyai kematian yang lebih tinggi, terutamanya dalam kalangan pesakit IS dengan diabetes mellitus (DM). Walaupun terdapat korelasi yang diketahui antara faktor dan pengulangan IS, adakah risiko IS berulang akan berubah pada selang masa tertentu? Apakah risiko bagi IS berulang sekiranya tiada pengaruh peramal?

Bagaimana perbezaan risiko IS berulang antara mereka yang mempunyai DM dan tiada DM? Untuk menjawab kesemua soalan ini, tiga model 'time-to-event' (TTE) bagi IS berulang selepas IS indeks telah dibangunkan dalam Fasa III tesis ini. Data bagi Fasa I dan Fasa II telah diekstrak secara retrospektif daripada rekod perubatan pesakit. Data pesakit yang mengalami serangan AIS yang dimasukkan ke Hospital Sultanah Nur Zahirah (HSNZ), Kuala Terengganu, Malaysia, dari Januari 2017 hingga Disember 2020 telah digunakan dalam kedua-dua fasa ini. HG ditakrifkan sebagai tahap glukosa darah > 7.8 mmol /l. Pesakit yang mengalami HG semasa AIS dibahagikan lagi kepada tiga subkumpulan mengikut corak HG: (1) hiperglisemia berterusan pendek (SPHG) ditakrifkan sebagai HG pada masa kemasukan dan pada masa rawak dalam masa 24 jam selepas dimasukan ke hospital (2) hiperglisemia berterusan panjang (LPHG) ditakrifkan sebagai HG pada masa kemasukan ke hospital, dan sepanjang 72 jam selepas dimasukan ke hospital dan (3) kelewatan HG yang ditakrifkan sebagai HG yang berlaku 24 jam selepas kemasukan ke hospital. Pesakit yang mengalami SAP semasa AIS turut dilaporkan. Analisis regresi Cox dan survival Kaplan-Meier telah dijalankan bagi menentukan peramal hasil fungsi strok yang tidak baik, manakala analisis regresi logistik dijalankan untuk menilai peramal bagi HG dan SAP. Semua analisis telah dijalankan menggunakan perisian SPSS versi 22. Dalam Fasa II, corak HG telah diukur dengan lebih lanjut lagi melalui pembangunan model perkembangan penyakit (DP) HG dalam tempoh 72 jam pertama AIS. Model DP secara linear dan nonlinear telah diuji pada data menggunakan perisian NONMEM versi 7.5 melalui model garis dasar dan pembangunan model covariate. Model terbaik dipilih menggunakan anggaran kemungkinan maksimum, kebolehlaksanaan klinikal, 'goodness of fit' (GOF) dan pemeriksaan ramalan visual (VPC). Data bagi fasa III telah diekstrak daripada pangkalan data 'National

Neurology Registry of Malaysia'. Model bagi masa untuk berlakunya IS berulang telah dibangunkan menggunakan NONMEM versi 7.5. Tiga model risiko garis dasar; eksponential, Gompertz dan Weibull, disesuaikan keatas data. Data ini juga kemudiannya telah dibahagikan mengikut status DM, yang membawa kepada pembangunan dua model TTE iaitu dalam kalangan pesakit dengan DM (TTE model 2) dan bukan DM (model TTE 3). Pada Fasa I, seramai 412 pesakit dengan AIS telah terlibat dalam kajian ini. Daripada jumlah 412 tersebut, 169 pesakit mengalami normoglisemia, manakala 243 (58.98%) mempunyai HG dalam tempoh 72 jam selepas kemasukan ke hospital. DM, dan leukositosis dikaitkan dengan HG semasa AIS dengan nisbah kemungkinan yang diselaraskan (AOR) masing-masing sebanyak 22.94 (95%CI; 12.35-42.61) dan 2.71(1.47-4.97). LPHG adalah peramal penting untuk hasil fungsi strok yang tidak baik (HR = 1.89 (95%CI; 1.06-3.39), sementara berumur lebih daripada 60 tahun, leukositosis, dan NIHSS >14 semasa kemasukan ke hospital adalah peramal bagi SAP dengan masing-masing AOR 2.08 (95%CI;1.01-4.30), 2.83 (95%CI;1.41-5.67) dan 3.67 (95%CI;1.53-8.80). Keputusan daripada model DP yang dibangunkan menunjukkan BG garis dasar meningkat dengan ketara dalma kalangan pesakit DM iaitu sebanyak kira-kira 4 mmol/l berbanding dengan pesakit bukan DM. Manakala pesakit dengan DM yang menerima ubat antihiperlipid sebelum strok, BG garis dasar menurun sebanyak 2.25 mmol/l berbanding pesakit yang tidak menerima ubat antihiperlipid sebelum strok. Bagi mereka yang mempunyai hiperlipidaemia (HPLD) dan menerima ubatan beta-blockers sebelum IS, kadar perubahan BG semasa IS meningkat masing-masing sebanyak 0.052 mmol/l/ hari dan 0.049 mmol/l/ hari.

Dalam Fasa III, data daripada 7697 pesakit yang mempunyai sejarah serangan IS pertama dari tahun 2009 hingga 2016 telah diekstrak. Tiga ratus tiga puluh tiga (4.32%) pesakit mengalami sekurang-kurangnya satu IS berulang dalam tempoh

maksimum 7.37 tahun susulan. Model risiko Gompertz menggambarkan data dengan lebih baik. Risiko IS berulang diramalkan sebanyak 0.238 dalam tempoh enam bulan pertama selepas IS indeks dan risiko berkurang kepada 0.001 pada enam bulan selepas itu. Kehadiran faktor risiko seperti HPLD (nisbah bahaya (HR) 2.22 (95%CI: 1.81-2.72)), hipertensi (HR, 2.03 (95%CI: 1.52-2.71)), dan penyakit jantung iskemia (IHD) (HR,2.10 (95%CI: 1.64-2.69)) mempercepatkan risiko IS berulang. Manakala menerima antiplatelet (APLT) semasa strok menurunkan risiko IS berulang (HR,0.59 (95%CI: 0.79-0.44)) dalam keseluruhan populasi sebaliknya APLT gagal menunjukkan kesan pengurangan IS berulang yang signifikan dalam kalangan pesakit IS dengan DM. Kesimpulannya, DM sebelum strok adalah faktor ketara yang meningkatkan risiko mengalami HG semasa AIS, manakala LPHG didapati sebagai peramal utama hasil fungsi strok yang tidak baik selepas discaj dalam kalangan pesakit dengan HG semasa AIS. Peramal SAP dalam kalangan pesakit AIS dengan HG adalah berumur>60 tahun, leukositosis, dan NIHSS>14. BG garis dasar telah menurun dalam kalangan pesakit DM yang menerima ubat antihiperlipid sebelum strok. Manakala kehadiran HPLD dan menerima ubatan *beta blockers* sebelum IS meningkatkan kadar perubahan BG dari masa ke masa dalam kalangan pesakit DM yang mengalami HG semasa AIS. Risiko garis dasaar bagi IS berulang adalah yang tertinggi dalam tempoh enam bulan pertama selepas IS indeks. Ubat antiplatelet dan antihiperlipid tidak menurunkan risiko IS berulang secara signifikan dalam kalangan pesakit IS dengan DM. Ini menunjukan keperluan bagi strategi baru untuk pencegahan sekunder dalam kalangan pesakit-pesakit ini. Penemuan ini memberikan rasional bagi keperluan pemantauan yang lebih rapi untuk pesakit AIS dan pembangunan strategi baru untuk rawatan dan susulan dalam kalangan pesakit-pesakit ini, memberi penerangan tentang keperluan ‘personalized’ terapi dalam kalangan pesakit IS. Penemuan dalam Fasa III

tesis ini boleh membimbing doktor untuk memantau dengan lebih rapi, terutamanya dalam tempoh 6 bulan pertama selepas IS, dan mencadangkan keperluan untuk saringan pesakit yang lebih intensif serta strategi baru untuk pencegahan sekunder dalam kalangan pesakit IS dengan DM. Ini boleh membantu dalam strategi pencegahan masa depan mengikut anggaran risiko IS berulang bagi setiap pesakit.

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ABSTRACT

Hyperglycemia (HG) during acute stroke has been associated with worse outcomes, including unfavourable functional outcomes. A better understanding and awareness of HG patterns and the potential risk factors associated with HG, predictors of poor outcomes among patients with HG during an acute ischemic stroke (AIS), would help to guide acute stroke management and prevention of poor outcomes. Phase I in this thesis aimed to assess the predictors of HG during AIS, and predictors of unfavourable functional outcomes according to HG pattern among patients with HG during AIS. While phase II in this thesis aimed to quantify the rate of blood glucose (BG) changes over the first 72 hours of AIS among patients with HG by developing disease progression models using a pharmacometrics approach. From the acute state of ischemic stroke (IS), we are directing the study to the chronic phase of the IS. Recurrent stroke is another vital outcome parameter included in the goal of stroke management. Three time-to-event (TTE) models of recurrent IS after the index IS were developed in phase III to estimate the baseline hazard of recurrent IS during different time intervals. The data for phase I and phase II was extracted retrospectively from patients' medical records. Data of patients with AIS admitted to Hospital Sultanah Nur Zahirah (HSNZ), Kuala Terengganu, Malaysia, from January 2017 to December 2020 were included in these phases. HG was defined as a blood glucose level > 7.8 mmol/l. The patients with HG during the AIS were further divided into three subgroups according to HG pattern: (1) short persistent hyperglycemia (SPHG) is defined as HG at the time of admission and at a random time within 24 h after admission, (2) long

persistent hyperglycemia (LPHG) is defined as HG at the time of admission, and throughout the 72 hr of admission and (3) delayed HG defined as HG developed 24 h after admission. Cox regression and Kaplan-Meier survival analysis were performed to assess unfavourable functional outcomes predictors, while logistic regression analysis was performed to assess HG predictors. In phase II, the HG pattern was further quantified via the development of disease progression (DP) models of HG during the first 72 hours of AIS using NONMEM software version 7.5. The best model was selected using maximum likelihood estimation, clinical plausibility, the goodness of fit (GOF) and visual predictive checks (VPC). Data for phase III were extracted from the National Neurology Registry of Malaysia database. Time to recurrent IS models was developed using NONMEM version 7.5. The data was divided according to DM status, leading to two TTE models development; among patients with DM (TTE model 2) and non-DM (TTE model 3). In phase I, a total of 412 patients with AIS were included. Of 412, 169 patients had normoglycemia, while 243 (58.98%) had HG within 72 hours of admission. DM, and leukocytosis, were significantly associated with HG during AIS with an adjusted odds ratio (AOR) of 22.94 (95%CI; 12.35-42.61) and 2.71(1.47-4.97), respectively. The LPHG was the significant predictor for the unfavourable functional outcome (HR =1.89 (95%CI; 1.06-3.39). Results from the developed DP models demonstrated the baseline BG increased significantly among patients with DM by approximately 4 mmol/l compared with patients with non-DM. While patients with DM receiving antihyperlipidemic drugs prior to stroke decreased baseline BG by 2.25 mmol/l compared with peers who did not receive antihyperlipidemic drugs prior to the stroke. Having had hyperlipidemia (HPLD) and receiving beta-blockers prior to the IS increased the rate of BG changes over the acute state of IS by 0.052 mmol/l/day and 0.049 mmol/l/day, respectively. In phase III, data

from 7697 patients with a history of their first IS attack from the year 2009 to 2016 was extracted. Three hundred and thirty-three (4.32%) patients developed at least one recurrent IS within the maximum 7.37 years of follow-up. The hazard of recurrent IS was predicted to be 0.238 within the first six months after the index IS and reduced to 0.001 six months after the index attack. The presence of typical risk factors such as HPLD (hazard ratio (HR) 2.22 (95%CI: 1.81-2.72)), hypertension (HR, 2.03 (95%CI: 1.52-2.71)), and ischemic heart disease (IHD) (HR,2.10(95%CI: 1.64-2.69)) accelerated the hazard of recurrence IS. While receiving antiplatelet (APLT) upon stroke decreased this hazard (HR,0.59 (95%CI: 0.79-0.44)) among the whole population. In conclusion, prior stroke DM was a significant independent factor that increased the risk of HG during AIS, while LPHG was found as the main predictor of unfavourable functional outcomes after discharge among patients with HG during AIS. The baseline BG was decreased among patients with DM who were receiving antihyperlipidemic drugs prior to stroke. While the presence of HPLD and receiving beta-blockers prior IS increased the rate of BG changes over time among patients with HG during AIS who had DM prior to stroke attack. Baseline hazard of recurrent IS was the highest during first six months after index IS. Receiving antiplatelet and antihyperlipidemic medications failed to demonstrate significant association with reducing recurrence IS among IS patients with DM. These findings may provide a rationale for keeping close monitoring for AIS patients and develop new strategies for treatment and follow up among these patients, shed light on the need for personalized therapy among IS patients. The findings of phase III may guide the clinicians to keep close monitoring, especially during the first 6 months after IS, and suggest a need for more intensive patients screening and new strategies for secondary prevention among IS patients with DM.

CHAPTER 1

INTRODUCTION

1.1 Overview of Stroke

Stroke is the second most common cause of mortality and the third most common cause of disability worldwide (Lozano, Naghavi et al. 2012). Globally, 68% of all strokes are ischemic, and 32% are hemorrhagic (Lozano, Naghavi et al. 2012). Ischemic stroke (IS) occurs due to blockage of blood vessels, which limits the blood supply to the brain, whereas hemorrhagic stroke occurs due to rupture of blood vessels leading to blood spillage in the intracranial cavity (Caplan 2016).

1.2 Stroke Epidemiology

It was reported in 2016 that approximately 80.1 million stroke cases afflicted 39 million men and 41.1 million women (Johnson, Nguyen et al. 2019). In Malaysia, the epidemiological literature on stroke was scarce until the National Neurology Registry (NNEUR) of Malaysia was implanted in 2009 (Aziz, Sidek et al. , Kooi, Peng et al. 2016). In Malaysia, stroke cases are witnessed as the third most common cause of mortality and topped the nation's rate of disability (Ganasegeran, Ch'ng et al. 2020). In 2016 alone, stroke accounted for 11,284 cases, mostly affecting men (55%) and those aged 60 years or older (60%) (Aziz, Sidek et al.). Stroke has a high economic burden (Lee, Shafie et al. 2017) owing to significant functional disabilities and psychiatric morbidities burdening patients, caregivers, and healthcare systems (Kooi, Peng et al. 2016). Between 2012 and March 2019, there were 14,396 stroke cases reported across eleven states in Malaysia. Cases of stroke were higher in Northern Region (Pulau Pinang, Kedah and Perlis), the East Coast Region (Kelantan and

Terengganu), and the Southern Region (Negeri Sembilan). Nevertheless, the geographical distribution of stroke cases across states recorded a red alert for Terengganu as the highest stroke count in Malaysia (6,744 cases), while Selangor was the lowest (510 cases). Sarawak is considered the second city with the highest cases (2,340). At the same time, the numbers of cases in Pulau Pinang, Kelantan, Kedah, and Perlis were 1754, 1620, 623 and 554, respectively (Ganasegeran, Ch'ng et al. 2020).

While as for IS, the global incidence in 2017 was reported as 101.3 (91–113.6) per 100,000 population (Saini, Guada et al. 2021). In 2016, 2.7 million deaths worldwide were accounted for owing to IS (Johnson, Nguyen et al. 2019).

In Malaysia, the incidence of IS was reported as 96.2 per 100,00 population (Aziz, Lee et al. 2015) in 2014. There was a rising trend in Malaysia from 2008 to 2016 among the younger population. 1.9% to 2.6% of cases were reported for aged 35 to 39 years, 11.9% to 13.0% for 55 to 59 years, and 13.2% to 14.1% for 60 to 64 years (Hwong, Ang et al. 2021). Similarly, the incidence of IS is increasing globally among young adults (age <50 years) (Kissela, Khoury et al. 2012, Béjot, Delpont et al. 2016, Tibæk, Dehlendorff et al. 2016, Ekker, Verhoeven et al. 2019) which has risen by 40% in recent decades (Tang, Han et al. 2022), affecting over two million young patients with stroke every year (Béjot, Delpont et al. 2016, Tang, Han et al. 2022). Additionally, young patients with stroke have an extended life expectancy which may lead to heavy economic burdens on individuals and society (Feigin, Roth et al. 2016).

1.3 Ischemic Stroke Cascade

The clinical staging of IS (Cramer 2008, Rehme, Eickhoff et al. 2012, Zhao, Li et al. 2014) is generally defined as (i) acute stage: a condition at the first two weeks of

stroke attack; (ii) subacute stage: a condition at 3–11 weeks post-stroke; (iii) early chronic stage: a condition at 12–24 weeks post-stroke and (iv) chronic stage: a condition at ≥ 24 weeks post-stroke. Different cascades may have different impacts on the outcomes, requiring early classification of its predictors to assist in personalizing the management and treatment.

1.4 Complications during an acute ischemic stroke (AIS)

The most commonly reported events during the first days of AIS are elevated blood pressure (BP), hyperthermia, hyperglycemia (HG), stroke-associated pneumonia (SAP), and hemorrhagic transformation (HT).

BP elevation of >140/90 mmHg (Sharma 2016) during the AIS or elevated over the premorbid levels (BP levels before IS occurrence) are observed in approximately 60% of AIS patients during the first 24 h of symptom onset (Appiah, Minhas et al. 2018). Elevated poststroke BP upon admission is significantly associated with poor functional outcomes three months after stroke (Appleton, Sprigg et al. 2016). Hyperthermia (body temperature ⩾ 38°C) during the acute state occurs in up to 50% of IS patients (Ntaios, Dziedzic et al. 2015). Hyperthermia is significantly correlated to poor outcomes and increased deaths (Di Carlo, Lamassa et al. 2018).

Another common complication during the AIS is HG. HG is an elevated random blood sugar of > 7.8 mmol/l upon hospital admission (Reshi, Streib et al. 2017, Cerecedo-Lopez, Cantu-Aldana et al. 2020). This HG condition is associated with poor prognosis, including unfavourable functional outcomes, hemorrhagic transformation (HT), prolonged hospitalization, and increased disability and mortality (Reshi, Streib et al. 2017). Besides, SAP is the most frequent medical complication during acute

stroke, with incidence reported as 3%-44% (Papavasileiou, Milionis et al. 2015). It is thought that SAP is a part of stroke-induced immunosuppression. Higher mortality was reported among stroke patients with SAP during acute state at three months and one year after stroke compared to stroke patients without SAP. HT is also a common complication during the acute phase of IS. It occurs when the blood-brain barrier is highly disrupted to permit the transition of peripheral blood into the brain. Its occurrence is exacerbated by reperfusion with alteplase or endovascular therapy (Spronk, Sykes et al. 2021).

1.5 Hyperglycemia (HG) during AIS

Pathophysiology of HG during AIS

Central nervous system (CNS) constitutes 2% of total body weight but consumes 20% of cardiac output and 20% of total energy (Cunnane, Nugent et al. 2011). Almost all available energy is derived from glucose via aerobic metabolism (Cunnane, Nugent et al. 2011). As the brain does not store energy locally, cerebral tissue survival depends on a continuous supply of oxygen and glucose (Magistretti and Allaman 2013). As in AIS, reduced blood flow to the brain leads to reduced glucose and oxygen delivery. The inadequate amount of oxygen and glucose causes an inability to sustain neuronal integrity, leading to metabolic stress and the eventual death of neurons (Reshi, Streib et al. 2017). As a result, utilization of anaerobic metabolism to sustain the dying neuronal tissue may be an alternative developing pathway to maintain viability. The anaerobic metabolism may stimulate a physiologic response by increasing glucose production intended to deliver a higher glucose concentration to the energy-deprived penumbra (Reshi, Streib et al. 2017).

Impact of HG during AIS

HG increases inflammatory, thrombotic, and vasoconstrictive reactions (Martini and Kent 2007) and increases glutamate concentration, leading to mitochondrial injury and cell death associated with excessive calcium influx through ion channels. Through all these mechanisms, HG directly contributes to the exacerbation of neuronal injuries related to AIS (Clark, Payton et al. 2014).

Furthermore, HG has a role in accelerating ischemic injury through calcium overload, which induces arrhythmias and affects the blood-brain barrier, contributing to the hemorrhagic conversion of infarcts (Baird, Parsons et al. 2003). It also augments the ischemic injury through multiple potential mechanisms, such as endothelial dysfunction, increased oxidative stress, and impaired fibrinolysis (MacDougall and Muir 2011, Kaur, Kaur et al. 2018).

Increased BG levels for more than 7.8 mmol/l during the acute phase of stroke are potentially associated with adverse stroke outcomes (Johnston, Bruno et al. 2019). Several clinical and experimental studies have shown that HG during acute stroke is associated with poor outcomes, including greater infarct growth (Baird, Parsons et al. 2003, Shimoyama, Kimura et al. 2014), hemorrhagic infarct conversion (Ahmed, Davalos et al. 2010, Masrur, Cox et al. 2015), unfavourable functional outcomes (modified Rankin Scale (mRS) >2) (Zewde, Mengesha et al. 2019), and stroke recurrence (Zhu, Pan et al. 2019).

1.6 Stroke-associated pneumonia (SAP)

Definition and epidemiology

SAP is defined as pneumonia occurring within the first seven days after stroke onset in non-ventilated patients (Cugy and Sibon 2017). There is a considerable

variation in SAP's overall reported prevalence, ranging from 2.3% to 44% (Smith, Kishore et al. 2015, Cugy and Sibon 2017) in cases admitted to stroke units. This variation could be explained by the variation of recording sites of SAP in the hospital, i.e. stroke centers, wards, high dependency units, medical ICUs, neuro ICUs, etc. (Ahmad, Siddique et al. 2020)

Several studies have shown that HG is a risk factor for infection (Rodriguez-Buitrago, Basem et al. 2019, Chávez-Reyes, Escárcega-González et al. 2021). Pneumonia onset in stroke patients is highly associated with post-stroke body dysfunctions. The inflammation caused by infection is an essential factor in intensifying brain injury after stroke (Ruhnau, Schulze et al. 2017).

SAP Pathogenesis

The pathogenesis of SAP is highly related to the body dysfunction caused by stroke. Aspiration caused by the disturbance of consciousness and dysphagia after stroke, as well as stroke-induced immunosuppression, are considered as the most important pathogenesis of SAP (Zhang, Ji et al. 2017). A total of 40%-70% stroke patients manifested with decrease in consciousness, dysphagia, decline in protective reflex, lower esophageal sphincter dysfunction, decline in swallow-breathing coordination and decline in cough reflex. Thus, these may lead stroke patients to easily aspirate oropharynx and nasopharynx secretions, and stomach contents into the lungs and cause SAP (Pacheco-Castilho, Vanin et al. 2019, Ouyang, Boaden et al. 2020).

Another possible mechanism of SAP is due to immunosuppression induced by stroke. After an acute stroke, the immune system tries to prevent further inflammatory stimuli and protect brain tissue, but as a result, this prevention may lead to stroke-induced immunosuppression syndrome and infection. Brain injury due to stroke causes

the release of immunoregulatory mediators such as interleukins and tumour necrosis factors. These immunoregulatory mediators act on blood vessels, nerve endings, and adrenal glands and subsequently potentiate the release of norepinephrine, glucocorticoids, and acetylcholine. These three substances act on immune cell receptors and down-regulate these cells' immune function, weakening the immune function, and making stroke patients susceptible to infection (Shim and Wong 2016).

SAP Diagnostic criteria

SAP is diagnosed based on the criteria defined by the Centers for Disease Control and Prevention (Table 1.1) (Horan et al. 2008, Smith, Kishore et al. 2015).

Table 1.1 SAP diagnostic criteria by Centers for Disease Control and Prevention

SAP diagnostic criteria
At least meet one of the following criteria: (1) Fever without other clear cause (body temperature ≥ 38 °C). (2) Leukopenia (≤ $4\,000\times10^9$/L) or leukocytosis (≥$10\,000\times10^9$/L). (3) Age ≥ 70 years old, change in consciousness state without other clear cause.
AND at least meet two of the following criteria: (1) Newly emerged purulent sputum properties changes or respiratory secretion increases or needs for sputum suction increases within 24 hours. (2) Newly emerged or aggravated cough, dyspnea, or shortness of breath (respiratory rate > 25 times/minute). (3) Find rales or crackles or broncho respiratory sounds during lung auscultation. (4) Impaired gas exchange (such as hypoxemia (PaO_2/FiO_2≤300), increase in oxygen demand.
Chest imaging meet one of the following criteria: Newly emerged or progressing infiltrating shadow, solid shadow or ground glass shadow (For patients without underlying cardiopulmonary disease) A chest imaging test with any of the above imaging features is acceptable

Reproduced from SAP diagnostic criteria by Centers for Disease Control and Prevention (Horan et al. 2008, Smith, Kishore et al. 2015).

1.7 Stroke severity measures

1.7.1 National Institutes of Health Stroke Scale (NIHSS)

The National Institutes of Health Stroke Scale (NIHSS) is a tool healthcare providers use to objectively quantify the impairment caused by a stroke (Kwah and Diong 2014). The NIHSS is composed of 11 items, each of which scores a specific ability between 0 and 4. For each item, a score of 0 typically indicates a normal function in that specific ability, while a higher score indicates some level of impairment. Each item's individual scores are summed to calculate a patient's total NIHSS score. The maximum possible score is 42, with the minimum score being 0 (Kwah and Diong 2014). The Stroke severity may be stratified based on NIHSS scores as follows (Zhuo, Qu et al. 2021): Very Severe: >25, Severe: 15 – 24, Mild to Moderately Severe: 5 – 14, Mild: 1 – 5.

Table 1.2 National Institutes of Health Stroke Scale description (Kwah and Diong 2014)

Category	Score description
1a) level of consciousness (LOC)	0 Alert 1 Drowsy 2 Stuporous 3 Coma
1b) LOC questions (month, age)	0 Answers both correctly 1 Answers 1 correctly 2 Incorrect on both
1c) LOC commands (open and close eyes, grip and release nonparetic hand)	0 Obeys both correctly 1 Obeys one correctly 2 Incorrect on both
2) Best gaze (follow finger)	0 Normal 1 Partial gaze palsy 2 Forced deviation
3) Best visual (visual fields)	0 No visual loss 1 Partial hemianopia 2 Complete hemianopia 3 Bilateral hemianopia
4) Facial palsy (show teeth, raise brows, squeeze eyes shut)	0 Normal 1 Minor 2 Partial 3 Complete
5 a) Motor arm left (raise 90°, hold 10 seconds)	0 No drift 1 Drift 2 Cannot resist gravity 3 No effort against gravity 4 No movement
5 b) Motor arm right (raise 90°, hold 10 seconds)	0 No drift 1 Drift 2 Cannot resist gravity 3 No effort against gravity 4 No movement
6 a) Motor leg left (raise 30°, hold 5 seconds)	0 No drift 1 Drift 2 Cannot resist gravity 3 No effort against gravity 4 No movement

Table 1.2 (Continued)

Category	Score description
6 b) Motor leg right (raise 30°, hold 5 seconds)	0 No drift 1 Drift 2 Cannot resist gravity 3 No effort against gravity 4 No movement
7) Limb ataxia (finger-nose, heel-shin)	0 Absent 1 Present in 1 limb 2 Present in 2 limbs
8) Sensory (pinprick to face, arm, leg)	0 Normal 1 Partial loss 2 Severe loss
9) Extinction/neglect (double simultaneous testing)	0 No neglect 1 Partial neglect 2 Complete neglect
10) Dysarthria (speech clarity to “mama, baseball, huckleberry, tip-top, fifty-fifty”)	0 Normal articulation 1 Mild to moderate dysarthria 2 Near to unintelligible or worse
11) Best language (name items, describe pictures)	0 No aphasia 1 Mild to moderate aphasia 2 Severe aphasias 3 Mute
Total score	0-42

1.7.2 Modified Rankin Scale (mRS)

The modified Rankin Scale (mRS) has been widely used as a stroke outcome measure (Nunn, Bath et al. 2016, Saver, Goyal et al. 2016). The scale comprises seven levels, from 0 to 6 (Ganesh, Luengo-Fernandez et al. 2018), with higher scores indicating more significant disability and where 0-2 is generally considered a good outcome with individuals assuming complete functional independence. A modified Rankin Scale of 6 is often used to denote a deceased individual.

Table 1.3 Modified Rankin Scale description
(Ganesh, Luengo-Fernandez et al. 2018)

Scale	Modified Rankin Scale description
0	No symptoms/normal (physical, cognitive etc.)
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability: unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability: requiring some help, but able to walk without assistance from another individual (use of walking aids alone is not counted as assistance)
4	Moderately severe disability: unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent, and requiring constant nursing care and attention
6	Dead

Overall, the mRS offers a brief yet broad ranging assessment of function. As a global measure of functional recovery that captures clinically meaningful change, mRS is perhaps best suited as endpoint in large trials of potential stroke treatments (Taylor-Rowan, Wilson et al. 2018).

1.8 Recurrent ischemic stroke (IS)

The risk of recurrent stroke is high for the survivors of IS (Donnan and Fisher 2008, Varona 2011, Davis and Donnan 2012). Almost 33% of the IS Malaysian population had a recurrent stroke (Kooi, Peng et al. 2016). Compared with the first stroke, neurological impairment caused by recurrence is more serious, more difficult to treat, and has a higher mortality (Zhuo, Wu et al. 2020). Hankey et al. showed that patients who possessed recurrent stroke had 9.4 odds of becoming disabled or even dying at five years post-stroke (95% CI: 3.0, 30.0) (Hankey, Jamrozik et al. 2002). Therefore, secondary prevention after the first IS is of great significance in reducing the recurrence of IS (Zhuo, Wu et al. 2020). The reported risk factors of recurrent

stroke vary (Xu, Liu et al. 2007, Lee, Wu et al. 2016, Buenaflor 2017) in which hypertension (HTN), atrial fibrillation (AF), diabetes mellitus (DM), hyperlipidemia (HPLD), ischemic heart diseases (IHD), and smoking were the most common predictors of recurrent stroke (Modrego, Mainar et al. 2004, Leoo, Lindgren et al. 2008).

1.9 Primary and secondary prevention of ischemic stroke

Primary prevention aims to prevent disease or injury before it occurs by preventing or altering hazards exposure that causes disease or injury. In comparison, the secondary prevention goal is decreasing the impact of a disease or injury that has already occurred by treating the disease or injury and encouraging personal strategies to prevent reinjury or recurrence (Kisling and Das 2021).

According to American Heart Association/American Stroke Association guidelines, the significant decline in the incidence of stroke relates to vascular risk factors management, including control of hypertension (HTN), diabetes mellitus (DM), hyperlipidemia (HPLD), and smoking cessation (Kleindorfer, Towfighi et al. 2021). Therefore, addressing these risk factors for primary and secondary stroke prevention is crucial.

1.9.1 Primary prevention of ischemic stroke

Lifestyle modification

Lifestyle modifications are recommended, including weight loss, a healthy diet, smoking cessation, and regular physical activity (Piepoli and Villani 2017).

Optimal control of blood pressure.

Reducing blood pressure in persons with HTN is highly effective in preventing IS. A previous study showed that every 10-mm Hg reduction in systolic blood pressure (SBP) and 5-mm Hg reduction in diastolic blood pressure (DBP) reduces the risk of stroke by 41% among patients with HTN (Law, Morris et al. 2009). SBP should be lowered in patients with DM to <130/80 mm Hg (Williams, Mancia et al. 2018), while it should be lowered carefully to <140/90 mm Hg in nondiabetics (Williams, Mancia et al. 2018, Diener and Hankey 2020). Most antihypertensive drugs exhibited therapeutic benefits in reducing IS, except alpha-blockers (Lai, Kuo et al. 2016).

Optimal control of lipid level

Among the statins, rosuvastatin and atorvastatin are the most effective in lowering CV events (Yebyo, Aschmann et al. 2019). The risk of a first stroke is lowered by about 21% for every 1-mmol/l reduction in LDL cholesterol concentration with therapy by statin (Diener and Hankey 2020). Non-statin therapies reduce LDL cholesterol through the upregulation of LDL receptor expression, and they are associated with a similar risk reduction percentage of major vascular events per decrease in LDL cholesterol as statin therapies (Diener and Hankey 2020).

Optimal control of high blood glucose

Diabetes mellitus (DM) increases the hazard of IS (Elhefnawy, Ghadzi et al. 2022). Moreover, IS patients with DM also have a poor prognosis, a high mortality rate (Chen, Ovbiagele et al. 2016) and a high risk of recurrent stroke compared to those without DM (Anwar, Jahan et al. 2017). In Malaysia, patients with DM represent 27.4% to 55.2% of IS population (Kooi, Peng et al. 2016). At least one drug in each of the three glucose-lowering medications could be effective in the primary prevention of IS in patients with DM: thiazolidinediones, glucagon-like protein 1 (GLP-1)

receptor agonist, and sodium-glucose cotransporter two inhibitors (Arnott, Li et al. 2020).

Antithrombotic therapy

Aspirin use in people with no history of CV disease is associated with a smaller risk of IS than control subjects but with an increased risk of bleeding (Zheng and Roddick 2019).

1.9.2 Secondary stroke prevention after ischemic stroke

Optimal control of blood pressure

The blood pressure-lowering effect for secondary stroke prevention is consistent, regardless of previous HTN and most subtypes of stroke (Diener and Hankey 2020). Reducing blood pressure as secondary prevention lowers the risk of recurrent stroke (Kitagawa, Yamamoto et al. 2019). It was observed that antihypertensive treatment lowers the hazard of recurrent stroke by about one-quarter (Xie, Atkins et al. 2016). The optimal blood pressure target for secondary stroke prevention is <130/80 mm Hg and might be 120- to 128-mm Hg systolic and 65- to 70-mm Hg diastolic (Kitagawa, Yamamoto et al. 2019). All antihypertensive drugs are most likely effective in secondary stroke prevention. Beta-blockers may be least preferred due to increased variability in blood pressure (Rashid, Leonardi-Bee et al. 2003, Katsanos, Filippatou et al. 2017). Moreover, beta-blockers can cause troublesome symptoms such as insomnia, fatigue, and exercise intolerance, as well as life-threatening symptoms such as bradyarrhythmia and hypotension (Floyd 2014). Most IS patients need a combination of antihypertensive medications and lifestyle

modification as secondary prevention to prevent recurrent IS (Diener and Hankey 2020).

Optimal control of lipid level

IS patients should be treated with a statin regardless of the initial LDL cholesterol level. The target range for LDL cholesterol levels is 70 to 100 mg/dl. Patients with IS due to atherosclerosis and LDL cholesterol levels between 100 and 190 mg/dl should be considered for treatment with 80mg atorvastatin (Yaghi and Elkind 2015). According to the American Stroke Association and American Heart Association guidelines, for achieving a goal of LDL cholesterol < 70 mg/dl in IS patients, lipid-lowering therapy with a statin and ezetimibe are recommended to reduce the risk of major cardiovascular events. In case of statin and ezetimibe therapy are failed to reduce LDL-C to <70 mg/dL, it is recommended to use proprotein convertase subtilisin/kexin type inhibitor therapy to prevent atherosclerotic cardiovascular disease events (Kleindorfer, Towfighi et al. 2021).

Optimal control of high blood glucose

IS patients with DM also have a higher risk of recurrent stroke than those without DM (Anwar, Jahan et al. 2017). Antihyperglycemic drugs with demonstrated benefits on cardiovascular consequences, such as Glucagon-like peptide-1 (GLP-1) receptor agonists or Sodium-Glucose Transport Protein 2 (SGLT2) inhibitors, should be considered in IS patients with type 2 diabetes (Das, Everett et al. 2020). GLP-1 and SGLT2 inhibitors exhibited protective effects on cardiovascular events among patients with established cardiovascular disease (Dong, Chang et al. 2022). Moreover, Zhou et

al. reported that SGLT2 inhibitors were associated with a 50% decrease in stroke risk (Gerstein, Colhoun et al. 2019).

Antithrombotic therapy

IS patients should be treated with aspirin, clopidogrel, or a combination of aspirin plus extended-release dipyridamole. The combination of clopidogrel plus aspirin is not superior to either aspirin or clopidogrel alone and increases the risk of bleeding (Shah, Liu et al. 2022). Dual antiplatelet therapy (aspirin plus clopidogrel) is recommended only for the short term (21 days) in patients with TIA and a high risk of IS recurrence (Kleindorfer, Towfighi et al. 2021).

1.10 Pharmacometrics

FDA defines Pharmacometrics as an emerging science that quantifies drug, disease, and trial information to support drug development and/or regulatory decisions (Williams and Ette 2007). Pharmacometrics is considered a collection of model-based approaches used to organize our understanding of a system's behavior concisely using mathematics as a language to allow simulation of the system's output. These models can be divided into three broad classes (van der Graaf 2012): (1) exposure-response models that focus on the link between the drug dose, concentration in blood (or another matrix), disease exposure and clinical response such as drug effectiveness and undesirable effects; (2) disease models to describe the status of disease over time (disease progression modelling); (3) clinical trial models that describe patient characteristics, adherence, rate of dropout cases and so on.

Pharmacometrics analysis involves data collected from experimental data in individuals and groups (populations) of biological preparations, animals, or human subjects. This thesis focuses on population pharmacometrics modelling involving data from the population of IS patients.

1.11 Population modelling

Population modelling identifies and describes relationships between a population's physiologic characteristics and observed drug exposure or response (Mould and Upton 2012). As illustrated in Figure 1.1 population consists of different categories of patients such as geriatrics, patients with different comorbidities, those overweight, and pregnant women.

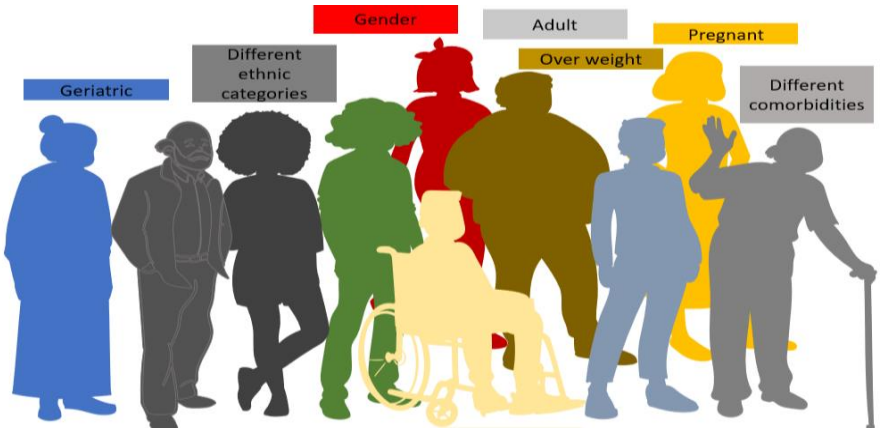

Figure 1.1 Demonstrated figure showing different categories of patients in population

Generally, due to the differences within the population, there are variabilities in response between individuals within the population. Figure 1.2 shows examples of variabilities in BG rate reduction among individuals in the population after one hour of receiving syrup containing 75 grams of glucose at the same time seen from blood sampling (left side) and how these variabilities appeared during population analysis (right side).

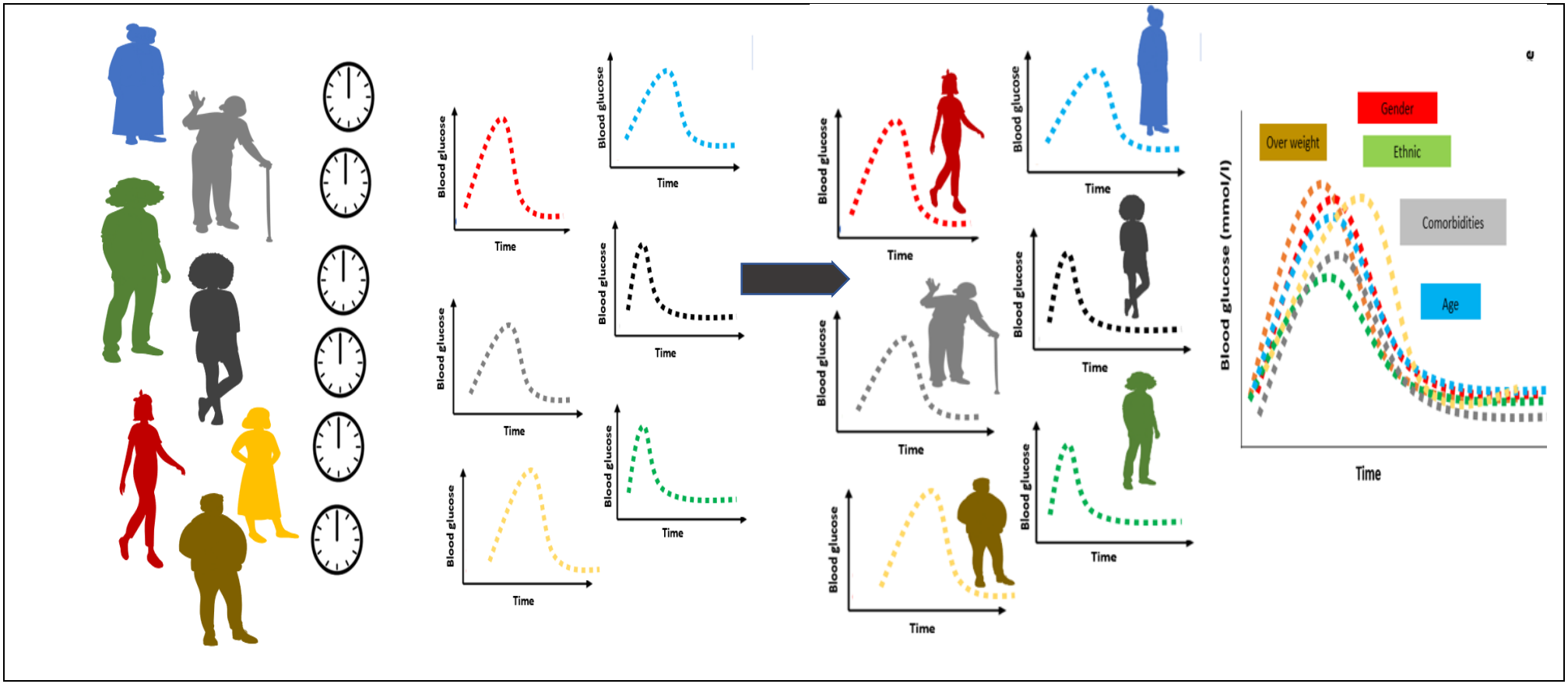

Figure 1.2 Examples of variabilities (e.g., blood glucose) among individuals in a population that could be seen from blood sampling (left side) and how these variabilities appeared during population analysis (right side).

Conventionally, population model parameters are assessed either by the naïve pooled approach, which fits the combined data from all the individuals while ignoring individual differences or via a two-stage approach by fitting individual data separately and combining individual parameter estimates to generate mean (population) parameters. Both methods may cause bias in parameter estimates especially involving missing samples and other data errors (KuKanich, Huff et al. 2007).

In order to minimize the limitation of naïve pooled and two-stage approach, the non-linear mixed effects (NLME) approach was introduced by Sheiner et al. (Sheiner and Beal 1981). In addition, NLME allowed the pooling of sparse data from many subjects (Figure 1.3) to estimate the population mean parameters between subjects' variability (BSV) which describes how much deviation of the value of an individual's parameter (e.g. drug's clearance or rate of blood glucose reduction over time) from the mean of the population, and the covariate effects that quantitate and explain variability in response (Ibrahim, Nordgren et al. 2019).

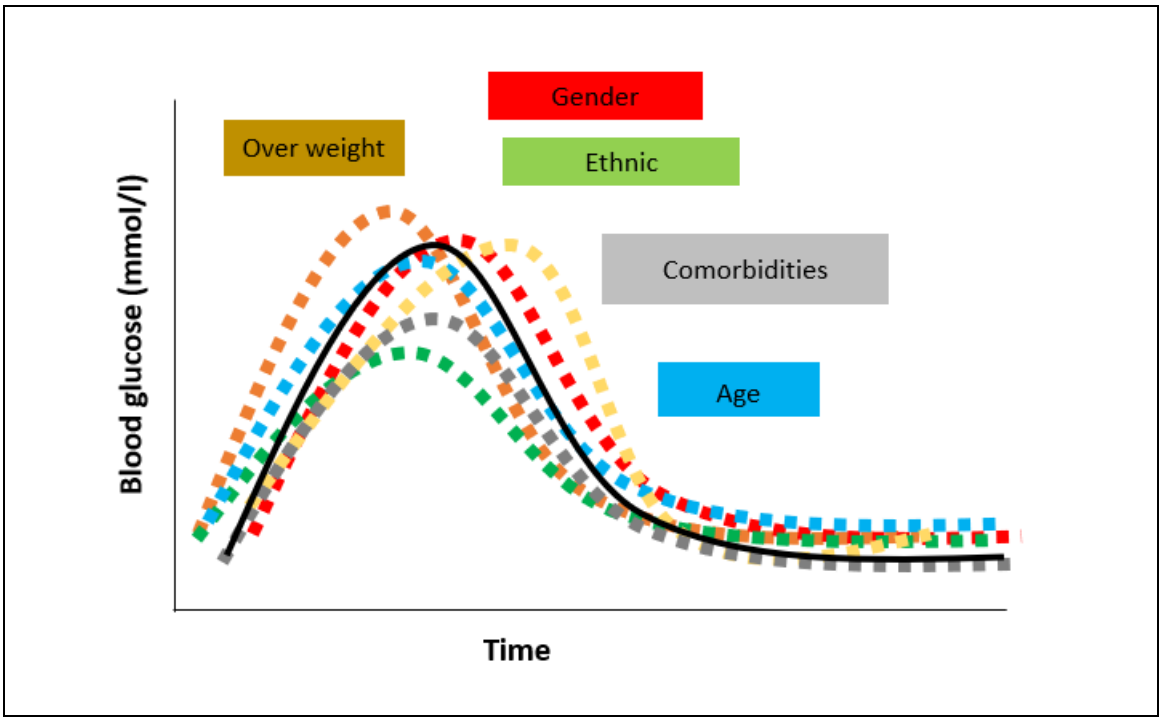

Figure 1.3 Demonstrated figure showing the idea of population analysis among patients with different characteristics like age, comorbidities, and gender to show how differences within individuals influence the population data. Black line represents mean of population value.

Pharmacometrics commonly uses this NLME approach as an analysis tool. These models contain a mathematical equation for system description, with a structural component describing the typical behavior called fixed effects and a stochastic component describing the variability of the behavior, called random effects (Owen and Fiedler-Kelly 2014). This combination of fixed and random effects contributes to the "mixed effects" term. The advantage of using NLME is that the importance of the individual in population models is highlighted by the description of variability (Figure 1.4), with data from each individual contributing to the identification of general trends such as changes in BG levels with changing weight or age, and the consequent estimation of the population characteristics (Ibrahim, Nordgren et al. 2019).

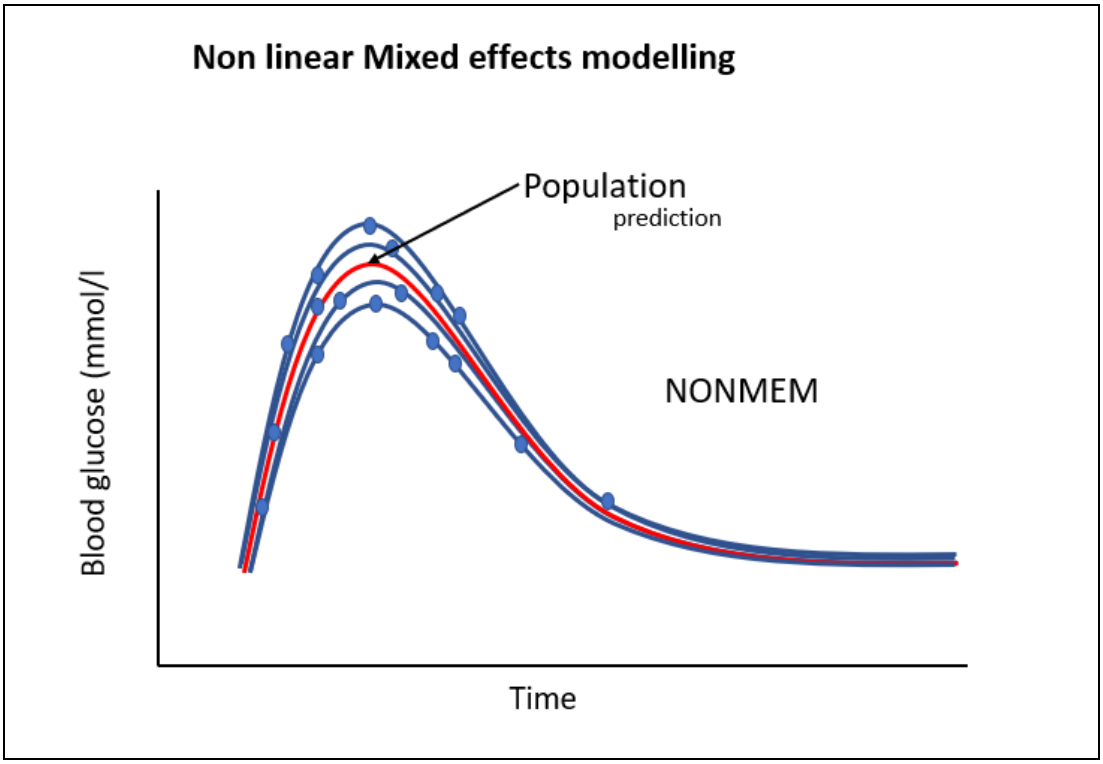

Figure 1.4 Demonstrated figure of nonlinear mixed effect modelling showing how NONMEM incorporate data from individuals to develop population prediction model

Pharmacometrics models consist of several components: structural models, stochastic models, and covariate models. Structural models are functions that describe the time course of a measured response and can be represented as algebraic or differential equations. Stochastic models describe the variability or random effects in the observed data, and covariate models describe the influence of factors such as demographics or disease on the individual time course of the response. Thus, pharmacometrics model building commonly follows a basic algorithm in which the base model is developed first by determining the structural and stochastic model and followed by covariate model building, linking influential factors or covariates to model parameters (Figure 1.5) (Byon, Smith et al. 2013).

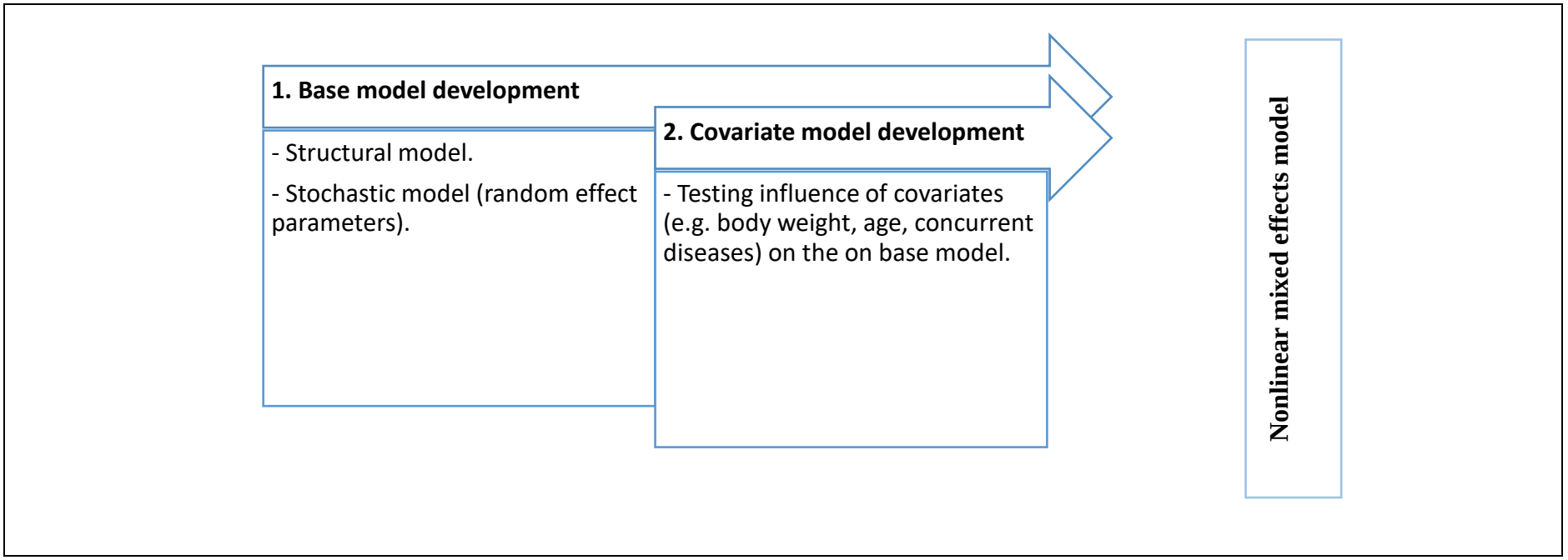

Figure 1.5 Basic algorithm of building population pharmacometrics model (nonlinear mixed effect model).

1.12 Estimated parameters in pharmacometrics.

Population models usually have fixed effect as well as random-effect parameters (including BSV and residual unexplained variability (RUV)) and are therefore called “mixed-effect” models (Byon, Smith et al. 2013). Fixed effects are represented by parameters “THETA” that have the same value for every subject. THETA is typically estimated from the data. BSV is represented by ETA, which indicates the value of the difference between an individual’s parameter and the population. While RUV is defined by a quantity (EPS) reflecting the difference between the observed data for an individual and the model’s prediction (the residual) (Figure 1.6).

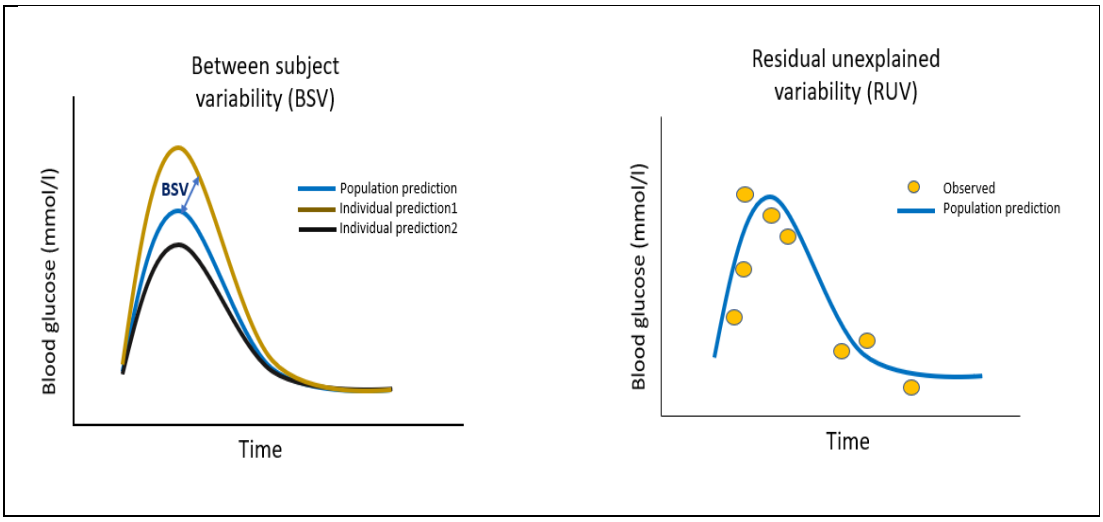

Figure 1.6 Random effect parameters (BSV and RUV) in population prediction models where BSV refers to the difference between individual and population prediction while RUV refers to the difference between observed data from individual and population prediction.

ETA is assumed to be normally or log-normally distributed across the population being evaluated. It is centered around zero and summarized by its variance (or SD), often called OMEGA. OMEGA describes the distribution of BSV for the parameter across the population (Figure 1.7).