The Correlation of Model-Based Insulin Sensitivity and Respiratory P/F Score

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Abstract. Insulin resistance and impaired respiratory function have been associated together and have been suggested to be potential predictors for organ failures in ICU. Insulin resistance is however difficult to measure in real time especially in the case of critically-ill patients. ICING models enable the estimation of insulin sensitivity (SI) as a reflection of the resistance. Knowing their levels and of impaired lung function level could be useful first and foremost to determine potential respiratory organ failure. The relationship between them was studied using a retrospective data of 20 patients ((mean ± SD) age: 62.5 ± 12.2) admitted to the Universiti Malaya Medical Centre ICU, Kuala Lumpur. Data on gender, age, race, admission diagnosis and morbidities were collected in each patient. Correlation of per-patient SI to P/F (PO2/PiO2) score was determined using Pearson correlation score. In this single-centre study, results indicated that the generated SI can potentially replace insulin resistance measurement. Correlation scores were negatively high for 4 patients (<-8.0), but the data from respiratory side were small and unbalanced to generate any general pattern. In conclusion, the estimated SI can be used for further studies with more data to link and predict the decline of respiratory failure in the ICU.

Keywords: Insulin resistance · Insulin sensitivity · Lung failure · Respiratory failure · Organ failure

1 Introduction

Intensive care units (ICUs) treat critically-ill patients with multiple complications, and the common goal is the prevention of further organ dysfunction, the management of established organ failures and avoidance of mortality [1–3]. These patients with and without history of diabetes are however exposed to stress hyperglycaemia with associated mechanism such as insulin resistance, effect of medications and impaired glucose deficiency [4, 5]. In non-intensive care setting, several published studies suggested the association between reduced lung function, insulin resistance, Diabetes Mellitus, and cardiovascular disease development [6, 7]. Diabetes Mellitus is considered amongst the risk factors for the progress of obstructive lung disease [8]. The information on co-existence of impaired respiratory function, insulin resistance and Diabetes Mellitus has

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been considered to improve treatment decision making as well as optimizing the clinical resources of both respiratory and glycaemic based failures [8]. In the same direction, current studies are initiated for ICU context.

Insulin resistance and glycaemic variation can be evaluated as a function of insulin sensitivity (SI) [9], a physiological parameter that describes the metabolic variation based on insulin concentration and glucose clearance. Insulin sensitivity is an inverse representation of insulin resistance. However in contrary to SI, there is no method yet to determine the resistance in real-time, and especially in the context of ICU [10]. ICING physiological model uses frequent available data such as blood glucose (BG) level, insulin deliverance and provided nutrition. It has the ability to estimate SI continuously. However based on current operation, input data are normally obtained hourly, thus allowing only hourly estimations of SI. ICING has been validated clinically and has been used extensively in different applications ranging from automated and personalized glycaemic control [11–15] to early detection of sepsis in ICU [16]. No prior study has been done on the association of the ICING-based insulin sensitivity and lung function health in critically-ill patients.

One of the most common score in the ICU used to diagnose the severity of lung function is the P/F ratio of partial pressure of oxygen PO2 (P) from the arterial blood gas test to the FiO2 (F), the fraction of inspired oxygen that a patient receives. The PO2 rises with increasing FiO2. Inadequate or decreased oxygen exchange decreases the ratio. It is one of the four criteria applied to define respiratory failure. The objective of the study is to determine if estimated insulin sensitivity using ICING model plays an associative role towards P/F score in patients admitted to Intensive Care Unit from Malaysia.

2 Methods

2.1 ICING Insulin Sensitivity Estimation

The model used to estimate SI is the clinically validated Intensive Care Insulin-Nutrition-Glucose (ICING) model. This model is built upon 7 equations which can be referred to in previous publications on SI model developments [17–19]. The equations describe the interaction between several physiological systems as shown in Fig. 1. Clinical inputs needed to compute each SI are; i) the BG level (in mmol/L); ii) administered insulin (in mU/L); and iii) provided nutrition to be translated into dextrose intake (in mmol/minute). Whilst the inputs are not provided every hour, SI (L.min/mU) can still be fitted hourly using integral-based fitting method [20]. SI estimation accuracy can be measured through BG fitting error. Each measured BG is compared with the estimated BG that produces hourly SI. ICING model SI estimation using integral-based fitting is guaranteed with less than 1% of fitting error.

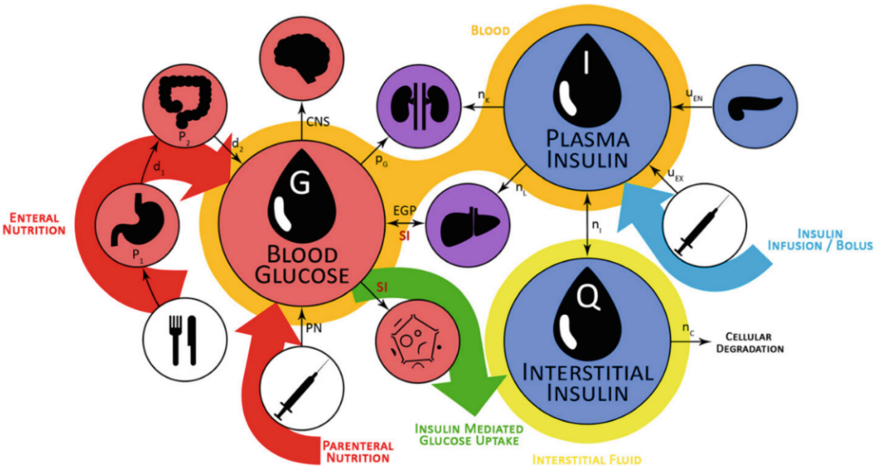

Fig. 1. The compartment representation of the physiological ICING model showing several functions; inputs and outputs linked to pancreas, intestine, stomach, central nervous system, liver and kidney [21].

2.2 Respiratory P/F Score

P/F score is commonly used measurement, in acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) [22–24]. ALI describes the pulmonary response to a broad range of injuries occurring either directly to the lung or as a consequence of injury or inflammation at other sites of the body. ARDS represents the more severe end of this condition. P/F ratio of <300 defines ALI or mild ARDS, <200 to moderate ARDS and <100 alarms for severe ARDS. In the same way, the score is also adopted in Sequential Organ Failure Assessment (SOFA) [25] to track and to determine the extent of a person's organ function or rate of failure to six organs, including respiratory. The scores range from 0 to $+4$, going from fine to worst. A detection of change in daily SOFA score of ≥ 2 indicates that a patient is suffering from lung failure.

In the ICU, PO2 and FiO2 are measured and recorded separately according to clinical needs. For this study, P/F scores were collected whenever pO2 and FIO2 were available in the same record hour. Each patient's hourly SI was then compared with computed P/F score using Pearson correlation which measures the linear correlation between the two variables. It takes a range of values from $+1$ to -1. A value 0 quantifies no association between the two variables. A positive value indicates that as the value of one variable increases, so does the other, in positive association.

2.3 Patients Data and Correlation Study

20 patients' data were extracted for this study. Criteria of inclusion include, i) ICU stay between 24 h to 120 h and ii) Patients with minimal five P/F score. Patients detail can be referred to in Table 1. A total of 1297 h of SI estimations and 265 P/F scores were used in the study. 14 out of 20 patients were diagnosed with Diabetes Mellitus. Amongst the 14 patients, 11 patients had hypertension and 8 patients had dyslipidemia.

Table 1. Clinical details of all 20 patients.

Patient ID	Age	Sex	Race*	Admission condition	Comorbidity**	ICU stay (Day- hours)	Available P/F score	APACHE II Score
UM03	69	M	C	Post saucerization of right shoulder carbuncle with CAP	DM	3–67	16	8
UM09	64	M	M	Post drainage of ludwig's angina with severe metabolic acidosis, acute on CKD and sepsis	DM, HPT, Dyslipidemia, CKD	3–56	13	13
UM12	77	M	M	Post left nephrectomy for bosniak 3 renal cyst complicated by intraoperative presumed sepsis	DM, HPT, Dyslipidemia	2–33	6	24
UM19	44	M	M	Bilateral necrotizing pneumonia tro pulmonary tuberculosis	DM	5–108	22	23
UM20	48	M	C	OHF with CO2 narcosis, cover for pneumonia	OSA, CCF	2–39	10	10
UM23	39	M	M	Polytrauma with severe traumatic brain injury	None	4–74	15	17
UM29	74	F	C	Polytrauma secondary to motor vehicle accident	None	3–49	8	16
UM30	69	M	M	Septic shock secondary to right thigh abscess	DM, HPT, CKD	3–58	5	17
UM35	58	M	I	Atypical pneumonia with fluid overload, acute on CKD	DM, HPT, Dyslipidemia	5–110	22	20
UM37	68	F	C	Cardiogenic and septic shock (e.coli bacteremia)	DM, HPT, Ischaemic Heart Disease, End stage renal failure	4–74	6	27
UM43	78	M	C	Acute on chronic subdural hemorrhage with acute hydrocephalus, AKI and uncontrolled DM	DM, Dyslipidemia, Previous Ischaemic stroke	3–41	6	28
UM44	59	F	I	Dengue fever in critical phase with warning signs (lethargy, confusion, transaminitis)	DM, HPT, Dyslipidemia	4–87	29	11

(*continued*)

Table 1. (*continued*)

Patient ID	Age	Sex	Race*	Admission condition	Comorbidity**	ICU stay (Day- hours)	Available P/F score	APACHE II Score
UM45	71	F	M	Post exploratory laparotomy for caecal mass with intestinal obstruction	Severe primary hypothyroidism, Hypocortisolism	3–45	8	15
UM46	54	F	I	Dengue fever with transaminitis and uncontrolled DM	DM, HPT	4–93	44	14
UM48	69	F	I	Post right hemiglossectomy + right modified radical neck dissection, right hemithyroidectomy with right floor of mouth flap for right tongue squamous cell carcinoma	None	3–52	7	10
UM54	39	F	I	CAP	DM, HPT	4–87	17	17
UM56	73	F	M	Left lower limb necrotizing fasciitis post wound debridement and fasciotomy	DM, HPT, Dyslipidemia	4–57	7	7
UM58	73	F	M	Post laparotomy for obstructed splenic flexure tumour with bowel ischaemia complicated with metabolic acidosis	None	4–65	9	
UM60	64	M	M	Sepsis secondary to infected diabetic foot ulcer with severe metabolic acidosis and hyperlactataemia	DM, HPT, Dyslipidemia, IHD	2–35	10	
UM61	60	M	C	Recurrent stroke, cover for pneumonia	DM, HPT, Dyslipidemia, stroke	3–67	5	

*M: Malay, I: Indian and C: Chinese
**AKI: Acute Kidney Injury, DM: Diabetes Mellitus, CAP: Community Acquired Pneumonia, CCF: Congestive Cardiac Failure, CKD: Chronic Kidney Disease, HPT: Hypertension, IHD: Ischemic Heart Disease, and OSA: Obstructive Sleep Apnea,

3 Results

Figure 2 shows the scatter plot of all 167 estimated SI values with associated P/F scores. The majority of patients with existing P/F score had lower than 0.001 mmol/min SI. This group's median and IQR SI are 15.16 [4.43–39.09]10^{-5} L.min/mU. Low SI indicates higher insulin resistance, found in this cohort. In particular, 236 had zero SI which

indicated SI in the order of 10^{-7}. The percentage of P/F score in each range; <100 to >400 are displayed on the right hand of the graph, highlighting a slightly skewed distribution towards better respiratory condition of patients.

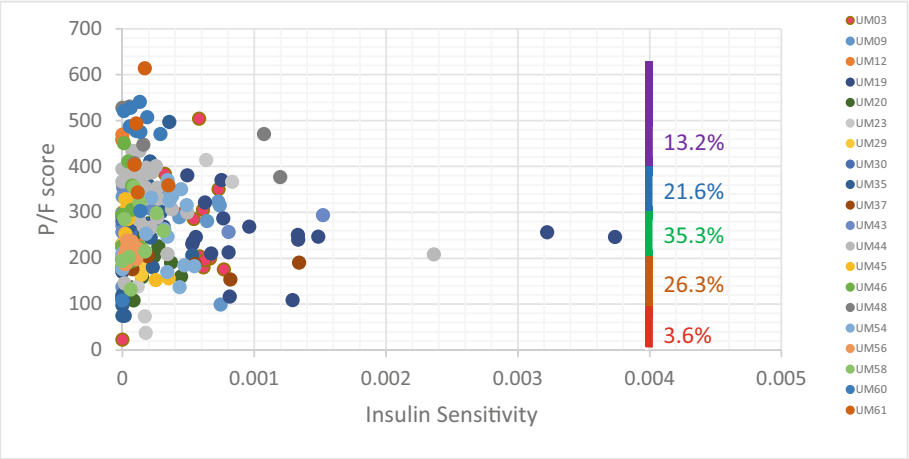

Fig. 2. The scatter plot of insulin sensitivity vs. P/F score. The P/F score distribution (%) can be referred to on the right side of the graph.

Figure 3 illustrates the correlation score between SI and P/F score for all patients. The graph distinguishes the diabetic from the non-diabetic patients using red bars. According to this, 11 have negative values. Most had more than −0.2 correlation, and patient UM30 had a perfect negative correlation. Those with positive values have lower than +0.4 correlation.

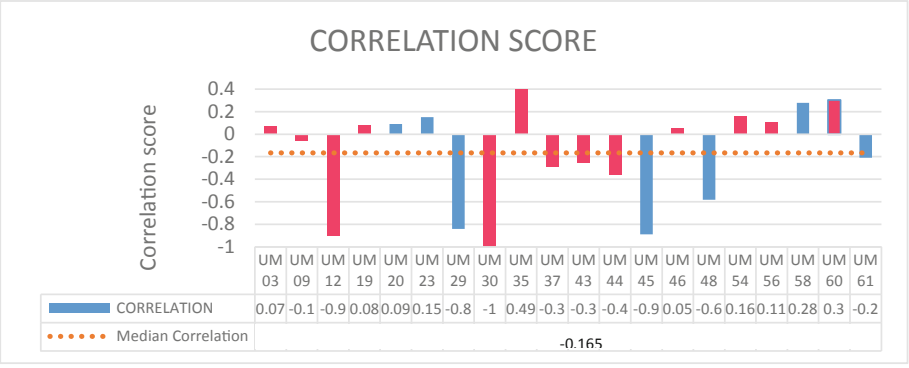

Fig. 3. The correlation score for all patients. The diabetic patients are distinguished from the non-diabetics using red bars.

4 Discussion

Our findings revealed that in particular, at times where PO2 and FiO2 record existed in the same hour, the associated estimated SI were very low, indicating the existence of high insulin resistance for most of studied patients. The median SI was 15.16 [4.43–39.09] 10^{-5} L.min/mU. In this cohort, 3.6% of the P/F scores were below 100, which is the lower limit of severe ARDS and were affecting 3 patients (UM03, UM23 and UM35). These three patients had positive P/F score correlation with their SI variation. 61.6% were in the mild and moderate ARDS limit. The finding confirms not only the link between high insulin resistance and impaired lung function, but also the usability of the estimated SIs to complement clinical measurement of insulin resistance.

Some patients showed very high negative correlation between SI and the P/F score whilst many stays within ± 0.4 correlation which is important but not significant. Studies on their demographic, admission diagnosis, severity APACHE II score and comorbidities showed no clear pattern. The 4 highest negative correlations nevertheless share some common characteristics such as older than 69 years old and have less than 60 h stay. The pattern either doesn't exist, or it could be attributed to the low ratio of available SI over P/F scores (1297:265). We believe better correlation scores can be obtained if we interpolate the P/F score to match the number of hourly SI. With the availability of the interpolated data, more studies on time series development can equally be performed.

Two studies using limited and irregular data showed a close association between Diabetes Mellitus and hypertension towards estimated SI-based glycaemic control results, using Bayesian Network [26, 27]. Bayesian Network is an approach that use correlation weight to develop probabilistical causal or risk models. Another perspective from these studies is to use Bayesian Network to model the co-relationship between the various elements existing in current data.

5 Conclusion

Insulin resistance should be considered amongst the risk factors for deterioration in lung function. However, their usage is clinically limited in decision making as the measurement is difficult to obtain, especially in the ICU. This suggests exploring the usage of model-based generated insulin sensitivity which is a parameter that is the inverse of insulin resistance. Current intention however must be supported with more generated data from the respiratory side. Subsequent studies with bigger and sufficient data will include the SI role to predict lung failure in advance based on time series model. SI-based prediction may lead to effective interventions targeting respective organ failure prevention.

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