INTERLEUKIN-6-TO-ALBUMIN RATIO FOR MORTALITY PREDICTION IN CRITICALLY ILL ELDERLY PATIENTS

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by

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LIST OF ABBREVATIONS AND SYMBOLS

%	Percentage
g/L	gram per litre
pg/mL	picogram per millilitre
APACHE II	Acute Physiological Assessment and Chronic Health Evaluation II
BMI	Body mass index
AUC	Area under curve
CI	Confidence interval
CRP	C-reactive protein
HUSM	Hospital Universiti Sains Malaysia
ICU	Intensive care unit
IIUMMC	International Islamic University of Malaysia Medical Centre
IL-6	Interleukin-6
IREC	International Islamic University of Malaysia Research Ethics Committee
IQR	Interquartile range
OR	Odds ratio
ROC	Receiver operating characteristics curve
SD	Standard deviation
SOFA	Sequential Organ Failure Assessment

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NISBAH INTERLEUKIN-6 KEPADA ALBUMIN UNTUK MERAMAL KEMATIAN DALAM PESAKIT TUA YANG SAKIT KRITIKAL

ABSTRAK

Hubungan antara interleukin-6 (IL-6) dan albumin serum dengan kematian dalam pesakit tua yang sakit kritikal, ditafsirkan secara bersama sebagai nisbah, hampir tidak dilaporkan. Tesis ini bertujuan untuk menyiasat nilai prognostik nisbah IL-6-kepada-albumin dalam populasi istimewa ini. Ia adalah sebuah kajian keratan rentas yang dijalankan di Unit Rawatan Intensif (ICU) yang bertempat di dua hospital universiti di Malaysia. Pesakit warga emas (berumur ≥60 tahun) yang dimasukkan ke ICU tersebut yang menjalani pengukuran serentak plasma IL-6 dan albumin serum telah direkrut. Nilai prognostik nisbah IL-6-kepada-albumin telah dinilai menggunakan analisis oleh lengkung "receiver-operating characteristic (ROC)". Seramai 112 pesakit tua yang sakit kritikal telah direkrut. Peratus kematian di kalangan pesakit ini ialah 22.3%. Nisbah IL-6-kepada-albumin didapati adalah lebih tinggi dengan ketara di kalangan pesakit tua yang meninggal berbanding pesakit tua yang terselamat (14.1 [IQR, 6.5-26.7] berbanding 2.5 [IQR, 0.6-9.2] pg/mL, P <0.001]. Kawasan di bawah lengkung ROC nisbah IL-6-kepada-albumin untuk meramalkan kematian di ICU ialah 0.766 (95% CI, 0.667- 0.865, P <0.001), iaitu lebih tinggi sedikit daripada IL-6 dan albumin sahaja, tetapi nilai ini tidak signifikan secara statistik. Selepas diselaraskan dengan keterukan penyakit, nisbah IL-6-kepada-albumin kekal sebagai peramal bebas kematian ICU dengan nisbah sebanyak 3.278 (95% CI, 1.382-7.770, P = 0.007). Perbandingan nisbah IL-6-kepada-albumin dengan skor APACHE II atau SOFA tidak menunjukkan superioriti. Selain itu, penambahan nisbah ini kepada skor APACHE II atau SOFA tidak meningkatkan keupayaan prognostik skor

tersebut dengan ketara. Kesimpulannya, nisbah IL-6-kepada-albumin yang tinggi dikaitkan secara bebas dengan kematian di ICU dalam pesakit tua yang sakit kritikal, tetapi penemuan kami tidak menunjukkan bahawa ia lebih baik daripada IL-6, APACHE II, atau SOFA sahaja.

INTERLEUKIN-6-TO-ALBUMIN RATIO FOR MORTALITY PREDICTION IN CRITICALLY ILL ELDERLY PATIENTS

ABSTRACT

The association between interleukin-6 (IL-6) and serum albumin with mortality in critically ill elderly patients, jointly interpreted as a ratio, has been scarcely reported. This thesis aimed to investigate the prognostic value of IL-6- to-albumin ratio in this special population. This was a cross-sectional study conducted in the mixed ICU of two university-affiliated hospitals in Malaysia. Consecutive elderly patients (aged ≥60 years) admitted to the ICU who underwent simultaneous measurement of plasma IL-6 and serum albumin were recruited. The prognostic value of IL-6-to-albumin ratio was assessed by analysis of the receiver-operating characteristic curve. A total of 112 critically ill elderly patients were recruited. The outcome of all-cause ICU mortality was 22.3%. The calculated IL-6-to-albumin ratio was significantly higher in the non-survivors compared to the survivors (14.1 [IQR, 6.5-26.7] versus 2.5[IQR, 0.6-9.2] pg/mL, P <0.001]. The area under the curve of IL- 6-to-albumin ratio for discrimination of ICU-mortality was 0.766 (95% CI, 0.667- 0.865, P <0.001) which was slightly higher than that of IL-6 and albumin alone, but statistically insignificant. After adjusting for severity of illness, the IL-6-to-albumin ratio remained as an independent predictor of ICU-mortality with adjusted odd ratio of 3.278 (95% CI, 1.382-7.770, *P* = 0.007). Comparison of the ratio with the APACHE II or SOFA score did not show its superiority. Also, additions of the ratio to the APACHE II or SOFA score did not significantly improve the prognostic ability of the scores. In conclusion,

a high IL-6-to-albumin ratio is independently associated with ICU-mortality in critically ill elderly patients, but our findings did not suggest that it is superior to the standalone IL-6, APACHE II, or SOFA score.

CHAPTER 1

INTRODUCTION

1.1 Background

As the proportion of the elderly in the general population grows, the number of elderly patients requiring Intensive Care Unit (ICU) admission is also increasing (Abuhasira *et al.*, 2022; Fuchs *et al.*, 2014). The median age of ICU patients is above 65 years in many countries, and the proportion of elderly patients being admitted to the ICU is increasing faster than any other age group. In one recent study, it is estimated that elderly patients will contribute as the biggest group of patients being admitted to the ICU, up to 30 to 40%, in the near future (Flaatten *et al.*, 2021).

Following ICU admission, elderly patients are more likely than younger patients to experience adverse outcome, including mortality (Miniksar & Özdemir, 2021). Mortality in the ICU is usually higher in elderly patients due to a lower physiological reserve and the presence of comorbidities, but also to a lower intensity of treatment compared to that received by younger patients. The patient's discharge from the ICU is not the end of the story; a higher mortality related to the lack of rehabilitation and long-term follow-up contributes to the fact that few elderly patients can recover their functionality after ICU discharge.

The healthcare-related cost in elderly ICU patients is also significantly higher than that in younger ICU patients. (Haas *et al.*, 2018). As it is widely known, ICU care is one of the most expensive, intensive, and intrusive endeavors in healthcare, even for the general populations. At the same time, ICU remains as a limited resource in many countries. Furthermore, ICU care can be futile for elderly patients. While old age should not be a contraindication for ICU admission, elderly patients often have reduced

physiological reserves, making them at risk for complications including ventilator-induced lung injury, hospital-acquired infections, haemodynamic instability, autonomic dysfunction, and neurologic complications which increase the mortality rate.

Given the magnitude of problems, the ability to predict mortality of critically ill elderly patients is therefore essential. This is to help the ICU physicians to determine the direction and intensity of treatment for this special population, while balancing with judicious utilisation of the limited and high-cost resources.

1.2 Problem Statement

The traditional method to prognosticate the critically ill patients is to use the clinical risk prediction models, such as the Acute Physiology and Chronic Health Evaluation (APACHE) II score and the Sequential Organ Failure Assessment (SOFA) score. However, such models were constructed for general use in heterogenous ICU populations and have only been validated in a few small studies of elderly patients (Khouli *et al.*, 2011; Merz *et al.*, 2007). Therefore, other methods must be investigated to assist in making a more accurate prognostication of the critically ill elderly patients. In this regard, the use of biomarkers has been proposed as a useful tool to aid in the prognostication of critically ill elderly patients. (Malézieux-Picard, Astrid et al., 2021). This is because biomarkers may represent certain pathophysiologic processes that are not necessarily reflected by established clinical risk factors.

Review of the current literature reveals that there are many biomarkers that have been assessed as tools to aid in the prognostication of critically ill elderly patients. Examples of such biomarkers are serum interleukin-6 (IL-6) and serum albumin, with IL-6 being the major regulator of acute phase protein synthesis while albumin is itself a negative acute-phase protein. High IL-6 and low albumin circulating concentrations are associated with worse outcomes in various conditions. However, available studies have mostly interpreted these biomarkers separately. By searching the keywords “interleukin-6” and “albumin” and “mortality” in PubMed, 175 results appeared but none of the studies have investigated the combination of the two biomarkers in the specific cohort of critically ill elderly patients.

Emerging evidence suggests that positive acute-phase protein, when used in combination with albumin, a negative acute-phase protein, may enhance the predictive capacity of the former. The use of a ratio between positive acute-phase protein and albumin was first reported by Fairclough et al (2009), using combination of C-reactive

protein (CRP) and albumin. The authors hypothesized and proved that such a ratio would provide a variable capable of merging the information provided by CRP and albumin into an index that correlated positively with the outcome, i.e., a higher ratio indicates worse outcome. Since then, several studies have also applied the ratio of IL-6 to albumin and demonstrated a positive correlation of such a ratio with worse outcome albeit in different conditions of acute non-cardioembolic ischemic stroke (An et al, 2018) and end-stage kidney disease (Li e al, 2023).

The current study aimed to address the knowledge gap regarding the usefulness of this ratio as a predictor of mortality in the specific group of critically ill elderly patients. Other than the reason of such a ratio being more representative of the ongoing pathophysiological process of critical illness, the combined use of IL-6 with albumin may not add significant additional cost compared to IL-6 used alone, considering albumin is a routine investigation used in ICU. If such a ratio did provide a superior predictive performance than either biomarker used alone, as we hypothesized, any extra cost incurred might be justified.

1.3 Study Objectives

The general objective of this study was to determine the capability of IL-6, serum albumin and the ratio of IL-6 to serum albumin to become a new prognostic tool to predict mortality in critically ill elderly patients. The specific objectives of this study were:

1. To study the association between IL-6, serum albumin and the IL-6-to-albumin ratio with ICU-mortality in critically ill elderly patients.
2. To determine the prognostic accuracy of IL-6, serum albumin and IL-6-to-albumin ratio for predicting ICU-mortality in critically ill elderly patients.
3. To evaluate the independent value of the IL-6-to-albumin ratio for predicting ICU-mortality in critically ill elderly patients.
4. To compare the prognostic accuracy of the IL-6-to-albumin ratio with APACHE II score and SOFA score in predicting ICU-mortality in critically ill elderly patients
5. To assess whether addition of the IL-6-to-albumin ratio would improve the prognostic accuracy of APACHE II score and SOFA score in predicting ICU-mortality in critically ill elderly patients.

1.4 Study Hypotheses

The hypotheses of this study were:

1. There is a significant association between IL-6, serum albumin and the IL-6-to-albumin ratio with ICU-mortality in critically ill elderly patients.
2. The prognostic accuracy of IL-6, serum albumin and the IL-6-to-albumin ratio for predicting ICU-mortality in critically ill elderly patients is good.
3. The IL-6-to-albumin ratio in an independent predictor of ICU-mortality in critically ill elderly patients.
4. The prognostic accuracy of the IL-6-to-albumin ratio is superior to that of APACHE II score and of SOFA score in predicting ICU-mortality in critically ill elderly patients.
5. The prognostic accuracy of APACHE II score and of SOFA score in predicting ICU-mortality in critically ill elderly patients would be improved by addition of the IL-6-to-albumin ratio.

1.5 Study Significance

Prognostication of the elderly patients being admitted to the ICU remains difficult with the widely used clinical scoring systems that were originally developed for the heterogenous critically ill patients. Combination of biomarkers that reflect certain pathophysiologic processes in ageing and critical illness, such as by serum albumin and IL-6, may aid in the prognostication of critically elderly patients but has not been well-studied. This research project will help to improve the prediction of outcome of elderly patients who require ICU admission. The findings of this study will benefit ICU physicians who often face conundrum in deciding the direction and magnitude of ICU therapy for the elderly population given the difficulty in predicting their outcome. The IL-6-to-albumin ratio proposed may be incorporated with the physician's decision-making at the bedside, especially considering that serum albumin is a routinely measured biomarker while IL-6 can be determined at the with a point-of-care analyser. Indirectly, this may translate to a better utilisation of limited and costly ICU resources.

1.6 Conceptual Framework

Figure 1.1 below outlines the conceptual framework of this study. This study intended to correlate the levels of IL-6 and serum albumin, the independent variables, with ICU-mortality as the dependent variable. Review of the literature indicated that there are many confounding variables that can contribute to mortality in the critically ill elderly patients.

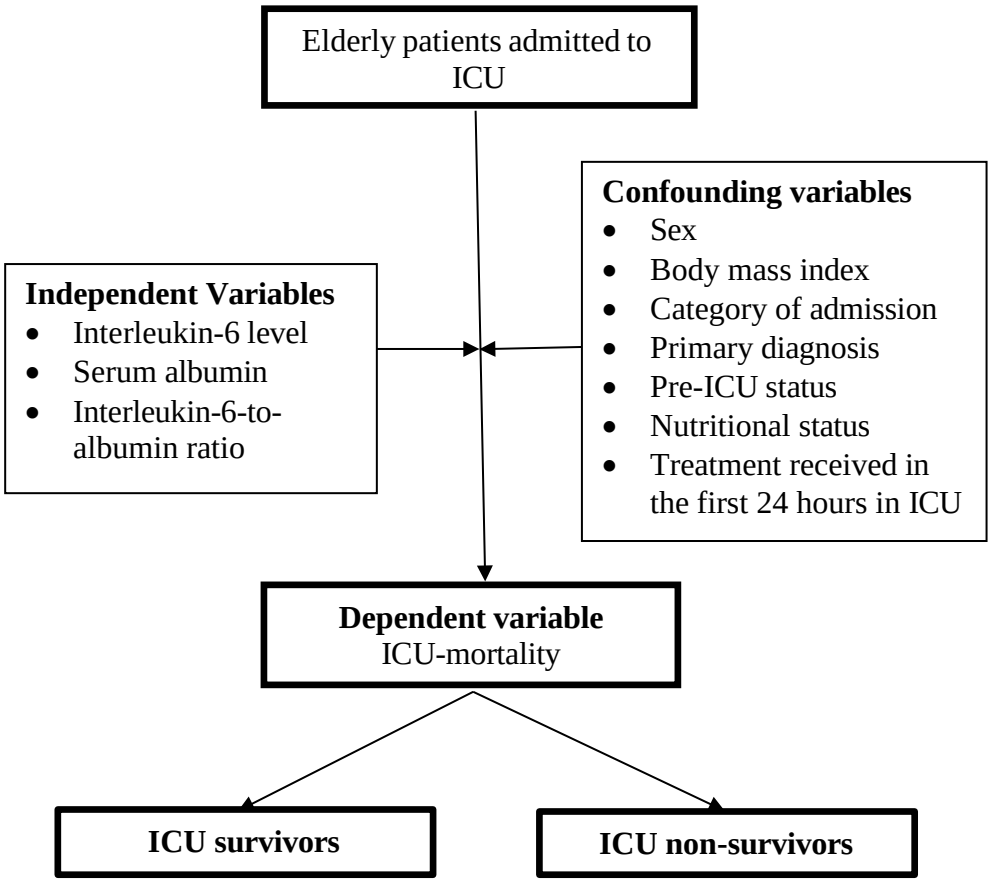

Figure 1.1: Conceptual framework of this study.

The influence of gender on outcomes if critical care treatment has been described in few small cohorts (Hollinger *et al.*, 2019; Todorov *et al.*, 2021). One of the studies illustrated the male gender was independently associated with hospital-mortality as well as among in critically elderly patients, the inflammatory response seems to be exaggerated in males compared with females because of the hormonal status (M. K. Angele *et al.*, 2012). Sex hormones play a functional role in regulating the immune responses and organ function, studies have indicated that female hormones are protective role in immune system while male sex hormones are deleterious (M. K. Angele *et al*, 2000). Another large ICU study in Beijing showed the male gender was associated with larger consumption of ICU resources

such as receiving more mechanical ventilation was strongly associated with ICU mortality (Ma *et al.*, 2022).

Obesity is a major health disorder that causes high morbidity and mortality (Akinnusi *et al.*, 2008). Body fat which can be translated by body mass index (BMI) is a simple division of body weight (kilogram) and height (meter^2). Based on the World Health Organisation classification, BMI of more than 25 is overweight while BMI over 30 is obese. Obesity is a major contributor to the progression of numerous disorders such as hypertension, diabetes mellitus and dyslipidaemia (Sanaie *et al.*, 2020). An ICU study in Iran illustrated the obesity class II (BMI of 35-40) was associated with highest mortality, this study was supported with a cohort study in United Kingdom, the study concluded severe obesity is an independent cause of death in critically ill patients (Aldawood *et al.*, 2006; Tremblay & Bandi, 2003).

Stratification of admission category in intensive care unit such as medical admission and surgical admission can have different prognosis of ICU outcomes. Nielsson et al reported that absolute mortality was higher in medical and acute surgical patients (27.7% and 26.7%) as compared to elective surgical patients (4.6%) (Nielsson *et al.*, 2014b). Medical patients are more ill as they suffered from more decompensation of underlying chronic disease thus having poorer survival outcomes (de Rooij *et al.*, 2006b; Williams *et al.*, 2005). Furthermore, the primary diagnosis can influence the ICU mortality outcomes, study has shown presence of cardiovascular and central nervous system failure are the major risk factors for death in ICU (Mayr *et al.*, 2006). Impaired organ perfusion or shock which can be seen in most of the ICU patients in sepsis are proved to have strong prognostic impact in critically ill patients

(J.-L. Vincent & De, 2001). Besides, acute renal failure had a high significant impact on ICU mortality outcomes in few previous studies and Viktoria D Mayr et al reported that acute renal failure that required renal replacement therapy will have increased the risk of death of critically ill patients in ICU (Mayr *et al.*, 2006).

Most of the critically ill patients will be given treatment of inotropes or vasopressors, renal replacement therapy and mechanical ventilation in ICU setting. These treatments have been proven to associate with the ICU prognostic outcomes. Inotropic and vasopressors agents are the most common used therapies in intensive care setting for the management of hemodynamically instability. The use of inotropic and vasopressors agents has been shown to be an independent factor of early mortality and call for close monitoring of critically ill patients (Motiejunaite *et al.*, 2022). Several mechanisms may explain the increased ICU mortality observed in patient exposed to inotropes or vasopressors. Usage of inotropes has been associated with immunosuppression, bacterial growth, and biofilm formation which while vasopressor may cause excessive vasoconstriction leading to impaired microcirculation and tissue hypoxia which may contribute to poor outcomes in intensive care settings (Bracht *et al.*, 2012; Lyte *et al.*, 2003).

Next, a study conducted by Serpa Neto *et al.* (2018) showed that critically ill patients who received mechanical ventilation within 48 hours is independently associated with higher in-hospital mortality (Serpa Neto *et al.*, 2018). Mechanical ventilation is used to stabilize and homogenize patient in acute phase of disease but does not modify the severity of disease and underlying comorbidities, and by comparing elderly and younger age group, it is still proven that usage of mechanical

ventilation in elderly group has higher ICU mortality than younger age group (Santa Cruz *et al.*, 2019).

Frailty is defined as clinically recognisable state of increased vulnerability resulting from ageing reducing multiple physiological reserves and functions such that the ability to adapt the acute phase of disease is compromised. Among elderly, frailty may be the most useful concept of severe disease requiring for critical care. Clinical Frailty Score (CFS) is a widely acknowledged tool for frailty assessment for the past decades (Church *et al.*, 2020). The presence of frailty which can be described by CFS score greater or equal to 5 has association with increased morbidity in older patients. The most likely explanation is that frail elderly patients ultimately will reach a point of exhaustion of their physiological and functional reserves even though they can survive through the acute phase of critical illness (Fronczek *et al.*, 2021).

Comorbidity is an important determinant of ICU outcome and may improve prognostic predictions for critically ill patients. Charlson Comorbidity Index (CCI) is a widely used clinical scoring system to assess prognosis based on patient's underlying comorbidities. Not only CCI has been used as a successful predictor of mortality in medical conditions such as cardiovascular, rheumatological and infectious disease but also in conditions that required surgical interventions (Christensen *et al.*, 2011). A study in Australia including 11000 critical care patients has reported the comorbidity, as measured by CCI is one of the most important determinants of the prognosis in the predictor model (Talib *et al.*, 2017).

To our knowledge, malnutrition is highly prevalence in critically ill elderly patients, and it is associated with poor outcomes including all-cause mortality. Heyland *et al.* (2011) introduced this nutritional assessment tool, NUTRIC score to benefit the critically ill patients that have marked catabolic stress state by providing aggressive nutritional support during ICU stay, thereby to attenuate the metabolic response to stress and reduce mortality rate (Heyland *et al.*, 2011). NUTRIC score combines few parameters such as acute starvation which is based on the duration of hospital stay before ICU admission, acute inflammation which is assessed by IL-6 value, chronic inflammatory parameters which is based on the number of comorbidities, and the severity of illness assessed by APACHE II and SOFA score. Total 10 points can be calculated, the score ≥6 is categorised as high score which is

associated with higher 28-day mortality.

CHAPTER 2

LITERATURE REVIEW

Aging is a complex transition, characterised by progressive and widely predictable changes that are associated with physiological and cognitive vulnerability, making individuals more susceptible to diseases, diminishing physiological reserves, and the endpoint of the process is death.

2.1 Definition of Elderly

The definition of elderly differs across articles, with no exact definition being entrenched to date (Okada *et al.*, 2017). Cut-off points of 60 and 65 years old are the ages that have been regularly used as the beginning of elderly age. Physiologically, the beginning of 60 years old has been associated with aging in all solid organ systems. The United Nations World Assembly on Ageing held in Vienna in 1982 defined elderly as individuals aged 60 years old and above. As a result, the policy maker of Malaysia has accepted this demarcation and is officially used in planning for senior citizens. Elderly adults can be classified into 3 age groups: the young-old (60-69 years), old-old (70-79 years) and oldest-old (80 years or more) (Alterovitz & Mendelsohn, 2013; Heo *et al.*, 2017).

2.2 Prevalence of Elderly Patients Admitted to ICU

The proportion of the elderly patients out of total ICU admission in various countries has been reportedly between 11.2 and 57.5% (Table 2.1). However, the majority of the epidemiological studies of the elderly admitted to the ICU are single-centre, which may result in selection bias, limiting our ability to understand the broad picture of the number of elderly patients admitted to the ICU. Adding to this problem

is that the definition used to define the cut-off point of elderly age is not unanimous.

Table 2.1: Summary of literature regarding prevalence of elderly patients admitted to ICU.

Country	Study Duration	Total ICU admission	Percentage of Elderly	Definition of Elderly
Netherlands	2005-2014	671029	232898 (34.7%)	≥ 80 years old
United States	2011-2018	19510	7265 (37.2%)	≥ 65 years old
Australia and New Zealand	2000-2015	120123	45466 (37.8%)	≥ 65 years old
Sub-Saharan	2011-2015	2116	237 (11.2%)	≥65 years old
Belgium	2002-2006	13964	8030 (57.5%)	≥65 years old

2.3 Mortality Outcome of Elderly Patients Admitted to ICU

During the past 20 years, the main primary outcome used in epidemiological studies of elderly patients admitted to the ICU was ICU- or hospital-mortality. Nielsson *et al.* performed a cohort study of 47, 596 patients in Northern Denmark from 2005 to 2011 that found the mortality rate of elderly patients is outrageous when it is compared with the younger patients. In the study, the mortality rate of patients aged 65-79 years old was 31%, 8% for patients 50-64 years old and 2.7% for patients between 15 to 49 years old. Besides, the study illustrated that the mortality rate of elderly patients in medical and acute surgical cases was higher than the elective surgical cases, being 43.7%, 39.6%, and 11.6%, respectively (Nielsson *et al.*, 2014a). These results are very similar to what Rooji *et al.* found in the Netherlands that advanced age is increasing the risk of death in the ICU, especially in patients with severe medical illness and worsening renal function during ICU stay (de Rooij

et al., 2005, 2006a). Moreover, the outcome of 233 elderly patients in Yalgado Hospital, Sub-Saharan, demonstrated overall mortality of 73% which was caused by the limitation due to poverty in ICU, lack of equipment, and human resources (Lankoandé *et al.*, 2018).

2.4 Factors Influencing Mortality Outcome of Elderly Patients Admitted to ICU

These statistics raise the curiosity of why mortality seems to be more prevalent among elderly patients than younger patients. In a recent systematic review, severity score, diagnosis at admission, and use of mechanical ventilation were the independent factors most frequently associated with ICU-mortality in elderly patients admitted to ICU (Vallet, H *et al*., 2021). On the other hand, age, comorbidities, functional status, and severity score at admission were the independent factors most frequently associated with 3 to 6- and 12-months-mortality (Vallet, H *et al*., 2021). However, substantial variation exists in the prognostic factors evaluated across different studies, limiting our ability to understand the broad picture of factors associated with mortality in elderly patients admitted to ICU.

2.5 Mortality Scoring Systems

As noted earlier, having an accurate tool to predict the outcome of elderly patients admitted to ICU is imperative to allow for patient-centred decision making. This is traditionally done using the APACHE II score and the SOFA score.

The APACHE score has been widely used in the ICU for years. It has the ability to predict the severity of illness and aftermath of multisystem organ failure. The APACHE scoring system consists of three parts which are subdivided into acute physiological score (APS), age adjustment and chronic health evaluation (Figure 2.1). APS is the largest component of APACHE which is derived by twelve physiological parameters that are obtained in the first 24 hours of admissions, only the worst values will be used. However, the flaw of this APS is measurement can be altered or corrected by therapeutic intervention such as catecholamines

or vasopressor administration and ventilatory management. The second component is the age adjustment, patients ≥ 65years old will be assigned five points, this may cause overestimation of the severity of illness. The third component is the chronic health evaluation but there is no score for coronary bypass grafting. Although there is evolution of the APACHE scoring system with a greater number of variables and more statistically accurate, but the mean time to introduce APACHE IV in a patient is 37.3 minutes which is very time consuming. Thus, APACHE II score is still used in clinical practice, and it has been the gold standard to predict mortality in ICU.

	Physiologic variable[b]	Point score								
		+4	+3	+2	+1	0	+1	+2	+3	+4
1	Temperature	⩾41°	39–40.9°	–	38.5–38.9°	36–38.4°	34–35.9°	32–33.9°	30–31.9°	⩽29.9°
2	Mean arterial pressure (mm Hg)	⩾160	130–159	110–129	–	70–109	–	50–69	–	⩽49
3	Heart rate	⩾180	140–179	110–139	–	70-109	–	55–69	40–54	⩽39
4	Respiratory rate(non-ventilated or ventilated)	⩾50	35–49	–	25–34	12–24	10–11	6-9	–	⩽5
5	Oxygenation:									
	a) FiO_2 ⩾ 0.5: use A-aDO_2	⩾500	350–499	200–349	–	<200	–	–	–	–
	b) FiO_2 < 0.5: use PaO_2 (mm Hg)	–	–	–	–	>70	61–70	–	55–60	<55
6	Arterial pH	⩾7.7	7.6–7.69	–	7.5–7.59	7.33–7.49	–	7.25–7.32	7.15–7.24	<7.15
7	Serum Na (mMol/L)	⩾180	160–179	155–159	150–154	130–149	–	120–129	111–119	⩽110
8	Serum K (mMol/L)	⩾7	6–6.9	–	5.5–5.9	3.5–5.4	3–3.4	2.5–2.9	–	<2.5
9	Serum creatinine (mg/dL): double point score for acute renal failure	⩾++++3.5	2–3.4	1.5–1.9	–	0.6–1.4	–	<0.6	–	––
10	Hct (%)	⩾60	–	50–59.9	46–49.9	30–45.9	–	20–29.9	–	<20
11	WBC (in 1000s)	⩾40	–	20–39.9	15–19.9	3–14.9	–	1–2.9	–	<1
12	Glasgow coma score (GCS)	Score = 15 minus actual GCS								
Acute physiology score is the sum of the 12 individual variable points										
Add 0 points for the age <44.2 points. 45–54 years: three points. 55–64 years: five points. 65–74 years: six points ⩾75 years										
APACHE II score = acute physiology score + age points + chronic health points. Minimum score = 0; maximum score = 71. Increasing score is associated with increasinf = g risk of hospital death										
Add chronic health ststus points: two points if elective postoperative patient with immunocompromise or history of severe organ insufficiency: five points for nonoperative patient or emergency postperative patient with immunocompromise or severe organ insufficiency[c]										
13[d]	Serum HCO_3(venous-mMol/L) use only if no ABGs52	⩾52	41–51.9	–	32–40.9	22–31.9	–	18–21.9	15–17.9	<15

Adapted from Knaus WA. Draper EA. Wagner DP. Zimmermam JB: APACHE II: A severity of disease classification system. *Critial care medicine* 13: 818–829. 1985.
Interpretation of APACHE II scores (predicted mortality rate).
0–4 = ~4% death rate 10–14 = ~15% death rate 20–24 = ~40% death rate 30–34 = ~75% death rate.
5–9 = ~8% death rate 15–19 = ~25% death rate 25–29 = ~55% death rate Over 34 = ~85% death rate.
[a] APACHE II Score = acute physiology score + age points + chronic health points. Minimum score = 0; maximum score = 71. Increasing score is associated with increasing risk of hospital death.
[b] Choose worst value in the past 24 h.
[c] Chronic health status: Organ sufficiency (e.g. hepatic, cardiovascular, renal, pulmonary) or immuno-compromised state must have preceded current admission.
[d] Optional variable: use only if no ABGs.

Figure 2.1: APACHE II Scoring System

The SOFA score was initially developed as a prognostic tool for management in sepsis. Later, it was realised that it has equal application for non-septic patients (Minne *et al.*, 2008). There are few terminologies used for SOFA score, one of them is Admission SOFA. For Admission SOFA, the worst parameters are used within 24 hours of admission. SOFA score can describe the degree of organ dysfunction and to evaluate mortality. Organ dysfunction or failure is highly correlated with mortality of patients in ICU. SOFA scoring system assigns points to six organ systems: respiratory, cardiovascular, renal, haematological, hepatic, and central nervous system (CNS) (Figure 2.2). It has a total 24 points, if the score is between 0 to 6, the predicted mortality is less than 10%; for score of 13-14, mortality is expected for 50% and score above 15, mortality of 90% should be expected. However, this scoring system has limitation, the CNS component has the least accuracy with most errors as there is no reliable assessment of Glasgow Coma Scale (GCS) in intubated or sedated patient, and often the normal GCS (15/15) will be used if no prior recorded value (Lambden *et al.*, 2019).

System	Score				
	0	1	2	3	4
Respiration					
PaO_2/FIO_2, mmHg (kPa)	⩾400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3\ \mu L^{-1}$	⩾150	<150	<100	<50	<20
Liver					
Bilirubin, mg dL^{-1} (μmol L^{-1})	<1.2 (20)	1.2–1.9 (20–32)	2.0–5.9 (33–101)	6.0–11.9 (102–204)	>12.0 (204)
Cardiovascular	MAP ⩾ 70 mmHg	MAP < 70 mmHg	Dopamine < 5 or dobutamine (any dose)[a]	Dopamine 5.1–15 or epinephrine ⩽ 0.1 or norepinephrine ⩽ 0.1[a]	Dopamine > 15 or epinephrine > 0.1 or norepinephrine > 0.1[a]
Central Nervous System (CNS)					
Glasgow Coma Scale score[b]	15	13–14	10–12	6–9	<6
Renal					
Creatinine, mg dL^{-1} (μmol L^{-1})	<1.2 (110)	1.2–1.9 (110–170)	2.0–3.4 (171–299)	3.5–4.9 (300–440)	>5.0 (440)
Urine output, mL per day				<500	<200

FIO_2: fraction of inspired oxygen; MAP: mean arterial pressure; PaO_2: partial pressure of oxygen.
[a]Catecholamine doses are given as $\mu g\,kg^{-1}\,min^{-1}$ for at least 1 h.
[b]Glasgow Coma Scale scores range from 3 to 15; higher score indicates better neurological function.

Figure 2.2: SOFA Scoring System

Review of the literature reveals that only few studies have attempted to validate the APACHE II score and SOFA score in the critically ill elderly population (Romo Gonzales *et al.*, 2015). In the first study, the ability of these scoring systems to predict mortality was validated in 95 elderly patients (age at least 80 years) being admitted to ICU. The predictive ability of these scoring systems is considered good with area under the curve (AUC) of 0.76 for APACHE II score and 0.75 for SOFA score. The limitation of this study is the retrospective and the single-centre nature of the study design and involved a small number of subjects. In another study, performances of the APACHE II score and the SOFA score were assessed in predicting mortality outcome in 106 ICU patients age at least 65 years. The AUC was 0.76 for the APACHE II score and 0.74 for the initial SOFA score. Overall, the APACHE II score and the SOFA score can be said to have a good ability to discriminate critically ill elderly patients who are going to die or not during the ICU stay.

2.6 Prognostic Biomarkers for Mortality in Critically Ill Elderly Patients

Given that the ability to accurately predict the outcome of critically ill elderly patients is difficult with the currently available scoring systems, there is a need to search for additional objective tests. Biomarker tests can fulfil this role. Biomarkers is defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" by the National Institutes of Health Biomarkers Definitions Working Group.

2.6.1 Interleukin-6

Interleukin-6 (IL-6) is a multifunctional cytokine with a wide range of biological activities that plays both anti-inflammatory and pro-inflammatory roles (Tanaka *et al.*, 2014). It is produced in a local lesion of the inflammation site, mainly by monocytes and endothelial cells. Then, it moves to the liver by haematogenous route and induces acute phase protein such as C-reactive protein and serum amyloid A. The serum amyloid A produced by IL-6 is the major culprit, it will complicate the chronic inflammatory state by causing rapid multiorgan failure if it persists for a long duration. The normal plasma level of IL-6 is less than 5 pg/mL. Persistently elevated IL-6 levels especially when the levels are more than 500 pg/mL were found in patients with multiorgan failure.

Looking back into 1993, William Ershler deduced the association of plasma level of IL-6 in aging and chronic morbidity and this hypothesis turned out to be predictive (Bioscience & Ershler, 1993). Most recent attention has focused on the IL-6 may be used as a prognostic factor for outcomes in critically ill patients. Harris et al

found out that higher plasma level of IL-6 doubles the risk of death in elderly patients (Harris *et al.*, 1999). Besides, Pallas et al noted critically ill patients who died had a significantly higher plasma level of IL-6 than those who had survived (Miguel-Bayarri *et al.*, 2012). In a recent study, IL-6 is suggested to be useful as an early biomarker for mortality in newly admitted critically ill patients, where patients with plasma levels of IL-6 of greater than 124.14 pg/mL on the third day of ICU admission were 6.1 times more likely to die than those with lower levels (Pallás Beneyto, Luis Alberto et al., 2016). As a conclusion, plasma level of IL-6 can be utilised as a prognostic factor for outcome in critically ill patients, and possibly for elderly patients in ICU, which is the hypothesis of this thesis.

2.6.2 Serum Albumin

Albumin is the most plentiful plasma protein, representing 50% of plasma protein, with a concentration ranging from 35 to 55 g/L (Gounden, 2021). It plays a crucial role to maintain the plasma colloid osmotic pressure to pervert extravasation of fluid from vascular compartments. Additionally, it has significant anti- inflammatory and antioxidative properties. Studies have shown that serum albumin can be used as a nutritional marker in critically ill patients, and it has significant correlation to the Mini Nutrition Assessment in hospitalized elderly patients (Shuhada *et al.*, 2017). Low serum albumin or hypoalbuminemia is defined as serum albumin less than 35 g/L. The prevalence of hypoalbuminemia in critically ill elderly patients is greater than 70% and it has been reported to be associated with increased patient morbidity and mortality as evidenced by more severe infection and poorer nutritional status (Brock *et al.*, 2016).

The mechanism of hypoalbuminemia in critically ill patients is because of the alteration of the serum albumin distribution between intravascular and extravascular compartments which consequently affects its synthesis, clearance, and degradation. Acute inflammation state will lead to cytokine activation. Simultaneously, albumin synthesis will decrease, in effect of acting as negative acute phase reactant. Low albumin reflects cytokine activation and ongoing interleukin- 6 mediated inflammation, hence as a secondary marker of a single underlying process. As the serum albumin level has reduced, it may lead to capillary leakage following the intravascular redistribution. Besides, serum albumin has an antioxidative effect with endothelial cells protection. Thus, ischemia and oxidative stress can occur in patients with low serum albumin.

2.7 Statistical Analysis on How to Use Biomarkers

There are four statistical steps to evaluate a new biomarker (Figure 2.3) (Gerlach & Toussaint, 2011). The first step is to determine the significance of the biomarker in relation to the condition being studied. This can be done by designing two cohorts, for example, survivors versus non-survivors, and the new marker is specifically measured at a time point. Then, the data of biomarker is compared between the two cohorts with independent t-test or Mann-Whitney u-test.

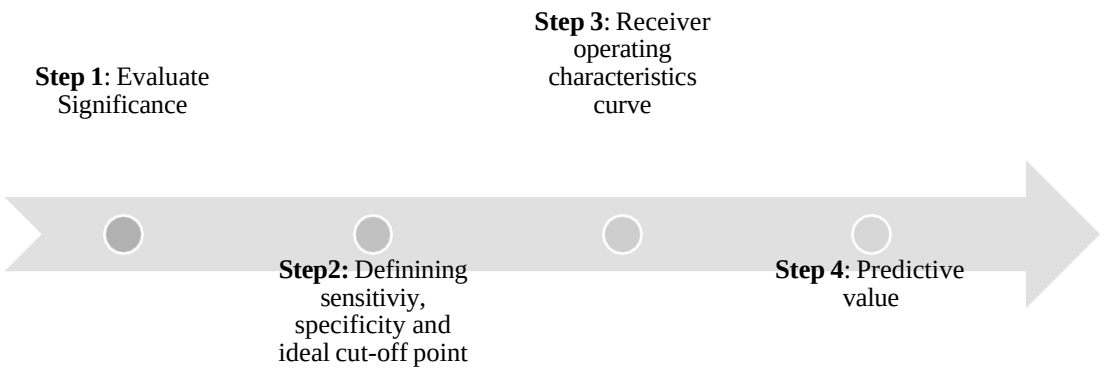

Figure 2.3: Statistical basics to evaluate a new biomarker.

Secondly, the sensitivity, specificity and the ideal cut off point of the biomarker should be determined. The quality of a biomarker depends on its sensitivity and specificity. Sensitivity is a measurement of how well a test can identify true positive while specificity is a measurement of how well a test can identify true negative. Next, ideal cut-off point plays an important role as the ideal cut-off point is set at the maximum point of the sensitivity and specificity. However, the data for sensitivity and the specificity vary with the adjustment of the cut-off point. The higher the cut-off, the more the sensitivity decreases, whereas specificity increases. Thus, the definition of ideal cut off pint remains unpredictable.

As indicated earlier, the significance of a biomarker is not sufficient for accepting it as a useful tool, and the definition of sensitivity and specificity has high association with the cut-off. The more objective method is to use the receiver operating characteristics (ROC) for the further analysis. ROC curve illustrates the association between sensitivity and specificity depending on the different cut off points and transfers it into a graph. The more the knee of the curve at the upper left corner of graph, the better the biomarker is. There is no certain value to define good or bad biomarkers, but a minimum area under curve (AUC) of 0.7 is required, and values more than 0.8 are good.

Lastly, determination of the biomarker's predictive value is needed to complete this evaluation. To determine its predictive value, the subgroups of positive and negative tests are separately analysed. The positive predictive value (PPV) is defined as the subjects with positive results truly have the risk while negative predictive value (NPV) is the probability that subjects with negative results do not have the risk.

Although sensitivity and specificity are not markedly influenced by the prevalence of the disease, PPV and NPV are affected by prevalence (Ray, Manach, Riou, & Houle, 2010). Likelihood ratios (LR) are another way of describing the diagnostic or prognostic value of a biomarker, which are not dependant on disease prevalence. Thus, LR is considered as a robust global measure of the diagnostic properties of a test. LR corresponds to the ratios of the likelihood of the observed test result in the diseased versus non-diseased populations. Two dimensions of accuracy must be considered, the LR for a positive test (PLR) and the LR for a negative test (NLR).