USING RED CELL DISTRIBUTION WIDTH (RDW) TO IMPROVE PROGNOSTIC PERFORMANCE OF CRB 65 AND TO COMPARE ITS ACCURACY WITH CURB 65 IN PREDICTING 30 - DAY MORTALITY IN ADULT PATIENTS HOSPITALIZED FOR COMMUNITY ACQUIRED PNEUMONIA (CAP) FROM EMERGENCY DEPARTMENT OF HOSPITAL UNIVERSITI SAINS MALAYSIA (USM): A RETROSPECTIVE OBSERVATIONAL STUDY

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LIST OF ABBREVIATIONS

1	RDW	Red Cell Distribution Width
2	CRB 65	Confusion, Respiratory rate, Blood Pressure, Age ≥ 65
3	CURB 65	Confusion, Urea, Respiratory rate , Blood Pressure , Age ≥ 65
4	CAP	Community Acquired Pneumonia
5	USM	Universiti Sains Malaysia
6	ED	Emergency Department
7	ROC	Receiver Operating Characteristic Curve
8	CI	Confidence Interval
9	AUC	Area Under Curve
10	ICU	Intensive Care Unit
11	PSI	Pneumonia Severity Index
12	CBC	Complete Blood Count
13	RBC	Red Blood Cell
14	STEMI	ST Elevatation Myocardial Infarction
15	qSOFA	Quick Sequential Organ Failure Assessment
16	hB	Hemoglobin
17	SPSS	Statistical Package for the Social Sciences
18	PPV	Positive Predictive Value
19	NPV	Negative Predictive Value
20	SD	Standard Deviation
21	IQR	Inter Quartile Range
22	ARDS	Acute Respiratory Distress Syndrome

ABSTRAK

Pengenalan:

Kisaran ukuran sel darah merah (RDW) dan kadar kematian seringkali dikaji dalam pelbagai penyakit. Walau bagaimanapun, hubungan antara RDW dan kadar kematian dalam penyakit radang paru-paru yang diperolehi oleh komuniti (CAP) masih tidak diketahui. Kami berhasrat untuk menggunakan RDW untuk meningkatkan nilai prognostik kriteria pemarkahan Confusion , Respiratory rate , Blood Pressure dan umur melebihi 65 tahun (CRB 65) dan membandingkan ketepatannya dengan kriteria pemarkahan Confusion ,Urea , Respiratory rate , Blood Pressure dan umur melebihi 65 tahun (CURB 65) dalam meramalkan kadar kematian dalam 30 hari di kalangan pesakit radang paru – paru komuniti.

Tatacara:

Analisis kohort retrospektif pesakit yang dimasukkan ke hospital untuk penyakit radang paru – paru komuniti dijalankan. CRB 65 dan CURB 65 dinilai untuk setiap pesakit. Skor ketiga dinilai dengan menambahkan RDW ke dalam kriteria pemarkahan CRB 65 yang sedia ada. Hasil utama adalah untuk mengenal pasti kadar kematian dalam 30 haribagi pesakit. Ketepatan prognostik dinilai selepas penambahan RDW ke dalam kriteria pemarkahan CRB 65. Di samping itu, beberapa petunjuk seperti sensitiviti, kekhususan, nilai ramalan positif dan nilai ramalan negatif, kawasan di bawah lengkung ciri operasi penerima (ROC) dengan 95% jarak konfidensi dikira untuk setiap sistem pemarkahan dan dibandingkan.

Keputusan :

Pesakit dengan kisaran ukuran sel darah merah yang lebih tinggi mempunyai kadar kematian 30 hari yang lebih tinggi, memerlukan kemasukan di wad ICU dan vasopressor, serta bantuan pernafasan secara mekanikal. Sistem pemarkahan CURB-65 mempunyai

AUC tertinggi (81.8%), diikuti oleh CRB 65 RDW (77.9%) dan CRB 65 (74.3%) dalam meramalkan kematian 30 hari di kalangan pesakit CAP. Apabila membandingkan ROC antara tiga sistem pemarkahan, CURB 65 mempunyai perbezaan yang ketara dengan CRB 65, tetapi tiada perbezaan yang ketara dengan CRB 65 RDW.

Kesimpulan :

Kesimpulannya, pengubahsuaian CRB 65 dengan menambahkan nilai kisaran ukuran sel darah merah meningkatkan prestasi prognostik CRB 65. Lebih banyak kajian perlu dijalankan terutamanya dari pesakit dengan latar belakang sosio-demografi yang berbeza untuk meneroka dan menilai peranan kisaran ukuran sel darah merah sebagai penanda prognostik pada pesakit radang paru – paru komuniti.

Kata Kunci: Radang Paru – Paru Dari Komuniti, Lebar pengedaran sel merah, CURB 65, CRB 65

ABSTRACT

Introduction:

Red cell distribution width (RDW) and mortality are vastly studied in various diseases. However, the connection between RDW and mortality in community-acquired pneumonia (CAP) remains unknown. We aim to use RDW to improve the prognostication of CRB 65 and to compare its accuracy with CURB 65 in forecasting 30-day mortality among CAP patients.

Methodology :

A retrospective cohort analysis of patients hospitalized for CAP is carried out. The CRB 65 and CURB 65 were calculated for each patient. A third score was calculated by adding RDW into CRB 65. The primary outcome is to identify the 30-day mortality. Prognostic accuracy was evaluated after the addition of RDW into CRB 65 scoring. In addition, several indicators such as sensitivity, specificity, positive predictive value and negative predictive value, area under the receiver operating characteristic (ROC) curve with 95% CI were calculated for each scoring system and compared.

Results:

Patients with higher RDW showed higher 30 day mortality, ICU admissions, vasopressor, and mechanical ventilation requirements. CURB-65 scoring system had the highest AUC (81.8%), followed by CRB 65 + RDW (77.9%) and CRB 65 (74.3%) in forecasting 30-days mortality among CAP patients. When comparing the ROC between the three scoring systems, CURB 65 had a significant difference with CRB 65, but no significant difference with CRB 65 + RDW.

Conclusion:

In conclusion, modification of CRB 65 by including RDW improved the prognostic performance of CRB 65. Future studies are needed from patients with different socio-

demographic backgrounds to explore and evaluate the role of RDW as a prognostic marker in CAP patients.

Keywords: Community Acquired Pneumonia, Red cell Distribution Width, CURB 65, CRB 65

CHAPTER 1

INTRODUCTION

Community-acquired pneumonia (CAP) is defined as one of the top factors of morbidity and mortality on a global basis.[1] In the United States, CAP contributed nearly 4.5 million outpatient as well as emergency room visits yearly.[2] In Malaysia, pneumonia is the 2nd highest significant factor of death, with 12.2 % of the population succumbing to the disease in 2019.[3]

CAP not only increases global morbidity and mortality, but it also puts a strain on a country's economy. In Europe, the medical cost for pneumonia is €10.1 billion per year, with inpatient care accounting for €5.7 billion, outpatient care accounting for €0.5 billion, and drugs accounting for €0.2 billion.[4] The secondary costs of missed workdays amounted to a total of €3.6 billion. Based on an analysis from the Spanish national surveillance system of hospital discharge data over two years, the cost of CAP hospitalization in Spain in 2001 [5] was €114.8 million. On the other hand, In Singapore, the projected direct cost of a single CAP hospitalization falls between the range from S$2000 to 16,000 (US$1400–12,000). [6]

With the aim to reduce the possible effect of pneumonia and its economic impact, there were several numbers of predictive score systems developed to improve the care and treatment of CAP. With that, the three most used scoring systems for CAP are CURB-65, CRB 65 as well as the Pneumonia Severity Index (PSI), developed by Fine et al in 1997.

PSI uses 20 clinical variables to compute the severity score.[7] Then, the patients will be

categorized into five severity classes based on an increasing likelihood of death within 30 days. Out of the 5 classes, the first 3 classes (Class I – III) are considered as low risk groups with cumulative mortality rate <1%. On the other hand, the other 2 classes (Class IV and V) are categorized as the intermediate and high-risk groups with mortality rates ranging from 9–30%. Out of all the scoring system, CURB-65 is considered as a simple severity calculator by using only 5 conditions which are confusion, urea respiratory rate, blood pressure and age ⩾65).[8-10] On the other hand, CRB 65 is a simplified version of CURB 65. It is being obtained by removing blood urea measurement from the calculation.[11, 12] The 3 scoring systems - PSI, CURB 65, and CRB 65 have been utilized in various studies and widely used. This has proven the effectiveness of the indicators in severity stratification and mortality prediction.[12-16] In the case of Europe and North America, as part of the clinical guidelines of the standard of care of pneumonia, PSI and CURB 65 are used.[1, 17, 18]

Despite the 3 indicators has been extensively used and validated, these scoring tools do have their limitations. The usage of PSI is complicated and time consuming when it comes to predict low-risk patients.[19] On the flip side, when it comes to identify critically ill patients, the results are limited due to its overestimation of mortality risk among the aged patients with comorbidity whilst the results may lead to underestimation of the need for ICU care among the younger patients who have not been previously ill. Besides that, the usage of CURB 65 is simple to apply and hence make it useful for clinicians when comes to identification of significant sign of abnormalities that may lead to severe illness. Yet, if patients have multiple comorbid illnesses, the detection may not be effective, especially in the existence of decompensated illnesses related with CAP.

As mentioned earlier, the basic version of CURB 65, CRB 65 is gotten by ignoring blood

urea measurement making. This makes CRB 65 an interesting option for doctors from all setting be it community or emergency department. However, like CURB 65 and PSI, CRB 65 has its limitations. In a recent meta-analysis of CRB 65, the reports showed that this indicator shall be used on cautious basis because of its tendency of overpredicts the likelihood of death in the community setting.[20] Overprediction of mortality might lead to unnecessary admission , ED overcrowding and a strain on our already limited resources.

Throughout the years, many widespread efforts were taken. The efforts are mainly to enhance the prognostic performance of these scales. Based on the studies, certain biomarkers such as pro-adrenomedullin, pro - atrial natriuretic peptide, pro - vasopressin and copeptin have been studied and shown to enhance the prognostic performance of severity scales.[15, 21] [15, 21] Nevertheless, to obtain these biomarkers are rather expensive and yet they are not always available instantly. The search for a biomarker that is cost effective, easily available and less time consuming has led us to the next indicator - Red Cell Distribution Width (RDW).

RDW is a coefficient of disparity of circulating red cells. RDW is part of a component of the complete blood count (CBC) by showing the heterogeneous of red cell volume. As of today, RDW has been mainly utilized for the differential diagnosis of anemia in a clinical perspective, though recent reports have also displayed the linkage of higher RDW with outcomes in cardiovascular disease, rheumatoid arthritis, colon cancer, and metabolic syndrome .[22-25] The reports also showed that RDW is a reliable forecaster of death across different study populations.[26] Despite that the exact mechanisms underlying RDW fluctuations remain unknown, the other influential factors that have been suggested are oxidative stress and inflammation.[26] For patients admitted from the emergency

department (ED) with suspected infections, the CBC is regularly carried out which is relatively inexpensive and able to provide valuable information.

In this research, we would like to determine if RDW can be used to improve prognostic performance of CRB 65 and to compare its accuracy with CURB 65 in predicting 30-day death rate in adult patients hospitalized for Community Acquired Pneumonia (CAP) from Emergency Department (ED) of Hospital USM. We hypothesize that RDW can improve the prognostic performance of CRB 65 and there is no difference in predicting 30-day death rate when using CRB 65 + RDW and CURB 65 in patients hospitalized for CAP.

CHAPTER 2

STUDY PROTOCOL

2.1 INTRODUCTION

On a global perspective, CAP is categorized as one of the most common and important factor of morbidity and mortality.[1] In the United States alone, the CAP contributed for over 4.5 million outpatient as well as emergency room visits on a yearly basis and is the most frequent infectious cause of death.[27, 28] Based on the statistics, almost 650 adults are hospitalized with CAP every year per 100,000 population in the United States United States.[29] Out of that, almost 9 percent of patients hospitalized with CAP tend to be re-hospitalized due to a new episode of CAP during the same year. In Malaysia, pneumonia is considered as the 2nd largest cause of death, with 12.2% of the population succumbing to the disease in 2019.[3]

In Europe, based on the estimation by the European Respiratory Society, the annual expenses of pneumonia in the country of Europe is €10.1 billion covering in-patient care expenditure of €5.7billion.[4] The development of predictive scoring system is encouraged by several factors which are the high incidence and mortality as well as the economic impact of CAP. The purposes of the predictive scoring system are to simplify the assessment of disease severity and prognostication in these patients. Currently, there are several prognostic scales in use. Out of all the scales, the one which are commonly use are the pneumonia severity index (PSI), CURB-65 (Confusion, Urea, Respiratory rate, Blood pressure, Age above and equal to 65), and CRB-65 (Confusion, Respiratory rate, Blood pressure, Age above or equal to 65). Nevertheless, each of these scales have several restrictions.[19]

The efforts to enhance the prognostic performance of these scales have been on-going. There were studies recommended that specific biomarkers possibly would enhance the prognostic capacity of pre-existing severity scales.[15, 21] Yet, the price of these biomarkers is high and may not be available instantly. Hence, the RDW which is a coefficient of variation of circulating red cells is being studied. RDW is part of a component of the complete blood count (CBC) by showing the heterogeneous of red cell volume. On top of that, RDW has been reported as a reliable interpreter of death rate across different study populations.[30] Despite that the precise mechanisms underlying RDW instabilities are remain unknown, the other influential factors that have been suggested are oxidative stress and inflammation.[30] For patients admitted from the emergency department (ED) with suspected infections, the CBC is regularly carried out which is relatively inexpensive and able to provide valuable information. In this research, we would like to determine if RDW can be used to improve prognostic performance of CRB 65 and to compare its accuracy with CURB 65 in predicting 30-day death rate among adult CAP patients who were hospitalized. This research can be helpful for doctors, especially in Emergency Departments or Community settings, to risk-stratify their patients in a shorter time and reduce ED overcrowding without incurring additional costs.

2.2 PROBLEM STATEMENT AND STUDY JUSTIFICATION

CAP has not only increased morbidity and mortality globally, but it had also greatly burdened the economy and healthcare sectors of many countries. Several predictive score systems were designed to optimize the care and treatment of CAP namely Pneumonia Severity Index (PSI), CURB-65 and CRB 65. Though extensively used and validated, these scoring tools have their limitations.

Throughout the years, many efforts were taken to level up the prognostic performance of these scales by adding certain biomarkers. Yet, the price of these biomarkers is not cheap to obtain and are not always available instantly. The search for a biomarker that is cost-effective, easily available, and less time consuming has led us to Red Cell Distribution Width (RDW).

RDW is a coefficient of disparity of circulating red cells. RDW is part of a component of the complete blood count (CBC) by showing the heterogeneous of red cell volume. As of today, RDW has been mainly utilized for the differential diagnosis of anemia in a clinical perspective, though recent reports have also displayed the linkage of elevated RDW with outcomes in colon cancer, rheumatoid arthritis, cardiovascular disease, and metabolic syndrome.[22-25]

In this paper, we would like to determine if RDW can be used to enhance the prognostic performance of CRB 65 and to compare its accuracy with CURB 65 in estimating 30-day mortality in adult patients hospitalized for Community-Acquired Pneumonia (CAP) from the Emergency Department (ED) of Hospital USM.

2.2.1 Benefit of the study

- The outcome of this study can be useful for doctors especially in Emergency Departments or Community settings such as family physicians or general practitioners to risk-stratify their patients in a shorter time compared to other scoring tools such as CURB 65 or PSI. This is because CBC analyzers are commonly available in these settings and RDW is testified as a component of CBC, therefore the data is able obtained without experiencing additional cost.

- Results from this paper can also help reduce ED overcrowding as complete scoring and risk stratification of patients can be done within 15 minutes compared to other tools such as PSI and CURB 65 which require at least 1 hour for its laboratory parameters to be reported.

- Results from this study can also be instrumental in developing a future scoring tool to predict mortality among CAP patients which is simple, cost-effective, and convenient for all settings.

2.3 RESEARCH QUESTIONS

1. Can RDW improve the prognostic performance of CRB 65?
2. Does CRB 65 + RDW have similar accuracy with CURB 65 in predicting 30 - day mortality in adult patients hospitalized for Community-Acquired Pneumonia (CAP) from ED Hospital USM?
3. Can RDW predict the likelihood of ICU Admission, Vasopressor, and Mechanical Ventilation Use in adult patients hospitalized for Community-Acquired Pneumonia (CAP) from ED Hospital USM?

2.4 OBJECTIVES

2.4.1 General objective:

To determine if RDW can improve the prognostic performance of CRB 65 and compare its accuracy with CURB 65 in predicting 30 - day mortality in adult patients hospitalized for Community-Acquired Pneumonia (CAP) from ED Hospital USM.

2.4.2 Specific objective:

1. To measure the distribution of RDW among CAP patients requiring hospitalization in ED Hospital USM.
2. To determine 30 days mortality rate between different RDW levels among CAP patients requiring hospitalization in ED Hospital USM.
3. To determine the association between ICU admission, vasopressor use, mechanical ventilation use, and 30 days mortality rate between different RDW levels.
4. To compare CRB 65, CRB 65 + RDW, CURB 65 in predicting 30-day mortality in hospitalized CAP patients.

2.5 LITERATURE REVIEW

Based on previous studies, the RDW is easy and cheap to obtained. This measures the disparity in the size of the erythrocyte. Not only that, RDW is also an index of its collection and are usually used in mixture with various laboratory tests for the different level of diagnosis such as the iron deficiency anemia, hematological system diseases, and bone marrow dysfunction [31] It is not frequent to detect RDW value less than the standard reference value and the results are clinically meaningless, however if the figures beyond the regular range reflect the presence of anisocytosis, probably lead to the presence of small and large red blood cells (RBCs), or both.[32] However, there are more studies and researches show that RDW can be utilized as a strong and independent risk factor for death rate in the general population.

In 2013, in his study of 744 CAP patients, Lee et al suggested that those with higher RDW tend to have higher severity index scores and 30-day mortality .[33] Braun et al. in 2014

also explained that elevated RDW levels on admission has significant relationship with rates of mortality and severe morbidity in adult patients with CAP.[34] RDW has also been identified as a prognostic marker in other diseases.[35] Based on a study by Sun et al., patients with a higher value of RDW displays a higher value in the incidence of all-cause mortality RDW[36] among 329 patients with ST-elevation MI (STEMI). In research conducted by Wang et al., based on the total of 117 patients with sepsis, the RDW was used as an independent variable for mortality among the older patients. Furthermore, as a marker for worse outcomes in patients with a quick sepsis-related organ failure assessment (qSOFA) of less than two, higher RDW levels can be used.[37] Cakal et al. found that RDW was the most substantial indicator of active disease compared to ESR, CRP, fibrinogen, and platelet count.[38]

In another study conducted by Ozsu et al., 702 patients were evaluated with acute pulmonary embolism. The outcome indicated that the higher the values of RDW, the mortality rate increase. To use RDW to predict in-hospital mortality, the optimal cutoff value of RDW was ≥15%. This makes RDW a potential indicator for mortality in these patients.[39] In another study with evaluation of 309 patients with pulmonary emboli, the results explained that RDW is a simple and valuable marker to predict 30-day mortality in this patients.[40] In Malaysia, there was a study by Kassim et al. which evaluated 452 patients displays the results shows higher RDW levels in diabetic patients with coronary artery disease than diabetic patients with no coronary artery disease. However, there was no association between RDW level and coronary artery disease in their study.[41]

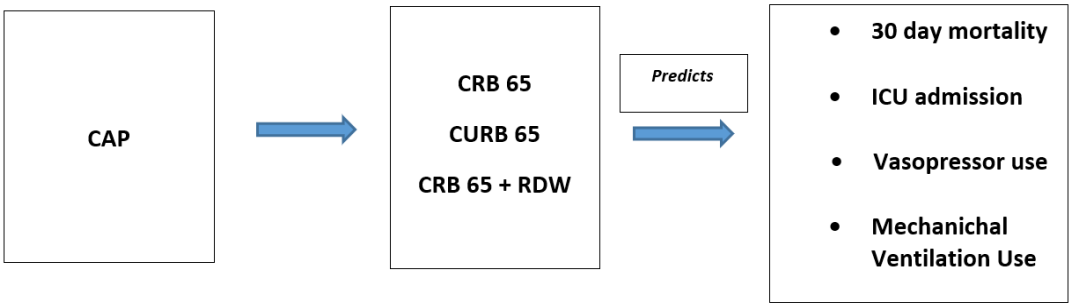
With much recent evidence on the prognostic capabilities of RDW, researchers have

attempted to compare the accuracy of RDW in predicting 30-day mortality with existing scoring tools in various diseases. Lee et al. found that both the PSI and CURB-65 improved the mortality prediction upon addition of RDW as a severity criterion.[33] However, no similar study has been done yet using the CRB 65 scoring tool.

Our study aims to determine if RDW could improve the prognostic performance of the CRB 65 scoring tool and whether it has similar prediction outcomes as the CURB 65 tool.

2.6 METHODOLOGY

2.6.1 Conceptual framework



2.6.2 Study design

This retrospective study includes all patients that fulfill inclusion and exclusion criteria and were treated for Community-Acquired Pneumonia in Emergency Department Hospital USM.

2.6.3 Study setting

Emergency Department Hospital USM Kubang Kerian, Kelantan.

2.6.4 Study population

Reference population: All patients who presented to Emergency Department of Hospital Universiti Sains Malaysia (Hospital USM), Kelantan.

Study population: All CAP patients who presented to emergency department Hospital USM during the study period.

Study Participant: All patients presented to emergency department Hospital USM that were treated for CAP and hospitalized during the study period and fulfilled the inclusion and exclusion.

2.6.5 Sampling duration

From January 2019 till December 2020

2.6.6 Subject criteria

Inclusion criteria

- Age > 18 years old
- Patients diagnosed as CAP by attending emergency physician or medical officer that requires hospitalization in Emergency Department of Hospital USM

Exclusion criteria

- Was discharged from a hospital within the previous 10 days, experienced an episode of pneumonia within the past 30 days
- Active pulmonary tuberculosis
- Chronically immunosuppressed: Known HIV positivity, on immunosuppression for solid organ transplantation, post splenectomy, receiving ≥10 mg/d

prednisolone or equivalent for <30 days, treatment with other immunosuppressive agents, or neutropenia [<1.0 × 109/L neutrophils])

- Severe anemia[42] (Hb < 8g/dL)
- Final diagnosis before discharge from ward is not CAP
- Unable to retrieve data regarding 30-day mortality status of all patients admitted for CAP via online admission records, forensic records, phone interview in the Emergency Department of Hospital Universiti Sains Malaysia (Hospital USM)

2.6.7 Sample size estimation

Objective 1 and 2

- To measure the distribution of RDW among CAP patient requiring hospitalization in ED Hospital USM
- To determine 30 days mortality rate between different RDW level among CAP patient requiring hospitalization in ED Hospital USM

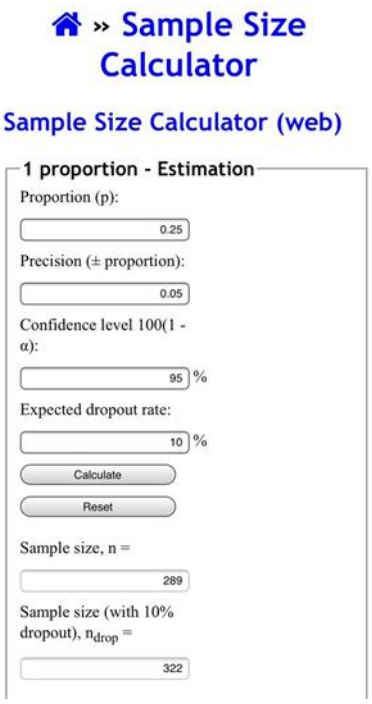
Sample size needed for objective 1 and 2 is ***359*** and ***322*** patients respectively calculated using single proportion estimation based on the available data from Lee et al.[38]

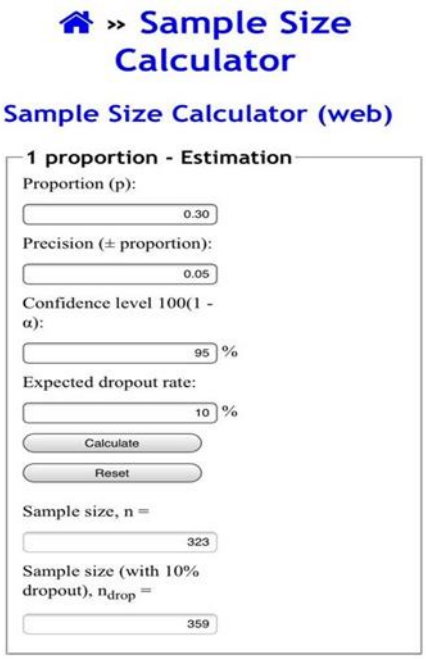
Variable	Proportion	Precision	n	n + 10%
RDW distribution	0.25	0.05	289	322
30 days mortality rate	0.30	0.05	323	359

Confidence Level: 95%

Expected Drop out: 10%

Calculator: Arifin, W. N. (2020). Sample size calculator (web). Retrieved from http://wnarifin.github.io





Objective 3

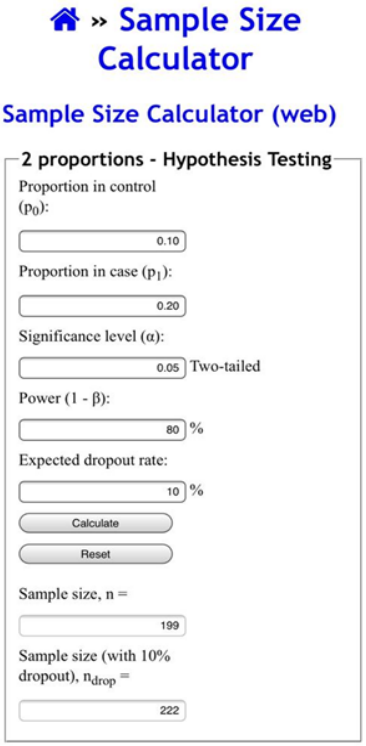
- To find association between ICU admission, vasopressor, mechanical ventilation uses and 30 days mortality rate between different RDW level

Sample size needed for objective 3 is 222 patients, the highest each variable calculated using two proportion estimation based on the available data from Lee et al.[38]

Calculator: Arifin, W. N. (2020). Sample size calculator (web). Retrieved from http://wnarifin.github.

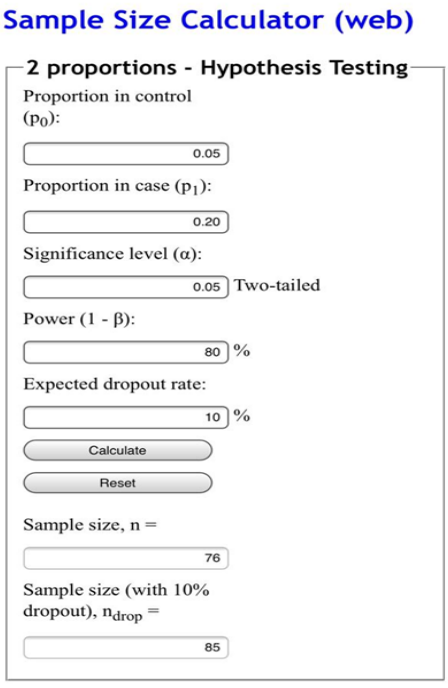
Variable 1: ICU Admission

According to Lee et al, [38] 14.4% of CAP patients had an ICU admission. Sample size required to determine association between ICU admission and 30 days mortality rate between different RDW level is 222 (199 + 10% dropout rate).



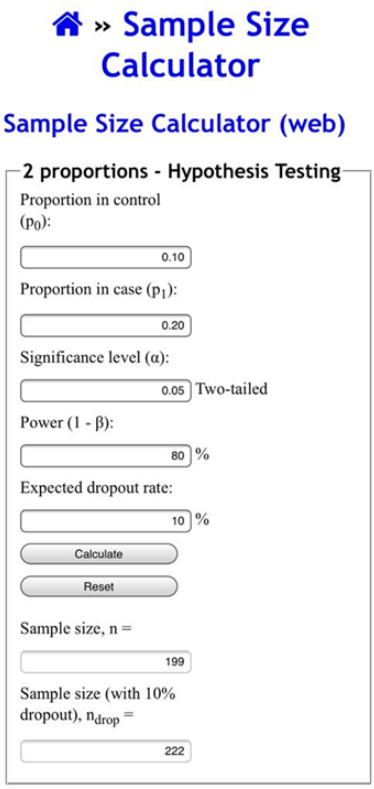
Variable 2: Vasopressor Use

According to Lee et al, [38] 13.8 % of CAP patients had vasopressor use during their admission. Sample size required to determine association between ICU admission and 30 days mortality rate between different RDW level is 85 (76 + 10% dropout rate).



Variable 3: Mechanichal Ventilation Use

According to Lee et al [38], 13.7 % of CAP patients had mechanichal ventilation use during their admission. Sample size required to determine association between mechanichal ventilation use and 30 days mortality rate between different RDW level is 222 (199 + 10% dropout rate)

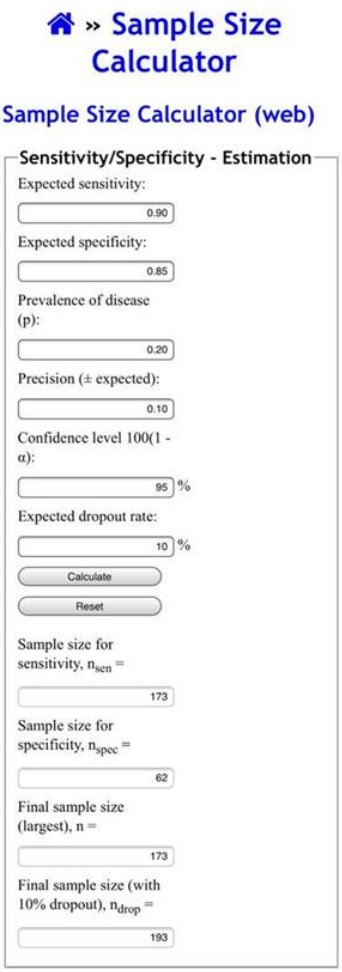


Objective 4:

- To compare CRB 65, CURB 65 and CRB 65 + RDW in predicting 30-day mortality in hospitalized CAP patients.

Sample size needed for objective 4 is 193 patients calculated using sensitivity/specificity estimation based on the available data from Dwyer et al.[49]

Calculator: Arifin, W. N. (2020). Sample size calculator (web). Retrieved from http://wnarifin.github.io



In conclusion, the largest sample size calculated was 359. Therefore, the sample size taken forthis study is 360.

2.6.8 Sampling Technique

All patients treated for CAP in ED Hospital USM and fulfilled the inclusion and exclusion criteria from January 2019 to December 2020 will be included in the study. The minimum sample size required is estimated to be ***360 patients***.

2.6.9 Operational definition

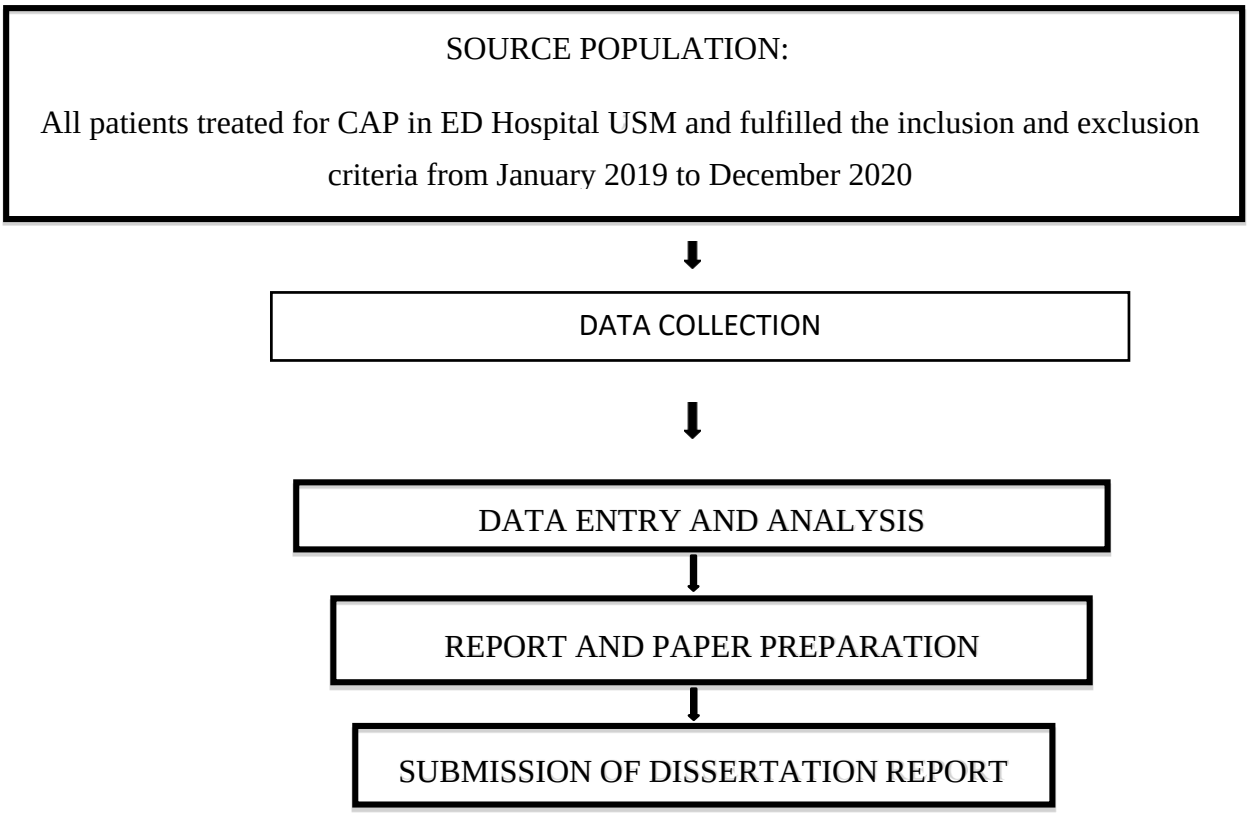
- Community-acquired pneumonia (CAP) is defined as pneumonia acquired outside of hospital or healthcare facilities.[43] Clinical diagnosis is based on a group of signs and symptoms related to lower respiratory tract infection with presence of fever >100ºF (>38ºC), cough, expectoration, chest pain, dyspnea, and signs of invasion of the alveolar space with radiological evidence of a pulmonary infiltrate on chest X-ray.[43]
- RDW normal range is 11.4 to 15.2 as described by Roshah et al[44] in 2008
- Confusion is assessed using Schmid fall risk assessment tool.[45] In this tool , four stages of mentation can be observed. In stage 1, patient is alert, oriented to person, place, and time. In stage 2, patient is observed to have periodic confusion. In stage 3, patient appears always confused. Stage 4 patients are those who are comatose or unresponsive.

2.7 DATA COLLECTION METHOD

- Patients admitted from ED HUSM with a provisional diagnosis of Community-Acquired Pneumonia as defined by BTS from January 2019 till December 2020 are identified from the emergency department registration book.
- Data will be retrieved from the patient's folder for patients who had fulfilled all the inclusion and exclusion criteria using the data collection form in Appendix 1.
- Each of the patients will be assigned a unique study ID to maintain the patient's confidentiality. A separate list of names containing relevant identification data will only be available to the investigator and his team.

- For data on 30-day mortality of patients, an online Forensic Registration System will be checked for death in ED and in wards. The online admission record will be traced for subsequent discharge summaries if the patient is discharged from the ward within 30 days of admission. Suppose death has occurred in subsequent admission before 30 days; date and time will be recorded.
- Suppose the patient is discharged from the ward within 30 days and no further admissions records are available, the investigator will proceed with a phone interview to get the information regarding patient's 30-day mortality.
- If unable to reach the patient or next of kin after three calls in a week, the sample will be omitted.

2.8 FLOW CHART



2.9 DATA ENTRY

Data will be entered and analyzed using Statistical Package for Social Science (SPSS) for windows, version 24.0.

2.10 DATA ANALYSIS

To achieve objective 1, which is to measure the distribution of RDW among CAP patient requiring hospitalization in ED HUSM, Descriptive analysis will be used. Mean (SD) will be used to describe numerical variable and n (%) for categorical variable

Next, to achieve objective 2, which is to determine 30 days mortality rate between different DW level among CAP patient requiring hospitalization in ED, Descriptive analysis will be used. Mean (SD) will be used to describe numerical variable (e.g., number of survival day) and n (%) for categorical variable such as the proportion of patient died within 30 days over all CAP patients.

Furthermore, for objective 3, which is to find association between ICU admission, vasopressor, mechanical ventilation uses and 30 days mortality rate between different RDW level, Chi square test or logistic regression will be used.

Lastly, for objective 4, which is to compare CRB-65, CURB-65 and CRB-65 + RDW in predicting 30-day mortality in hospitalized CAP patients, sensitivity, specificity, positive predictive value (ppv), negative predictive value (npv) will be scored at each score point, comparing predicted mortality and observed mortality (Dwyer 2014). Online calculator will be used to calculate the value (https://www.medcalc.org/calc/diagnostic_test.php). ROC curve will then be plotted using SPSS for comparison.

2.11 EXPECTED RESULTS

Table 1: CAP patients' demographic

Variable	n (%) / mean (SD)
Gender	
Female	
Male	
Age (year)	
Ethnicity	
Malay	
Chinese	
Siamese	

Table 2: Clinical Characteristic of CAP patients

Variable	n (%) / mean (SD)
Heart Rate (bpm)	
Respiratory Rate (per minute)	
Systolic BP (mmHg)	
Diastolic BP (mmHg)	
SpO_2 (%)	
Body Temperature (°c)	
Consciousness Level	
A	
B	
C	
D	
White Cell Count Level (mmol/L)	
Haemoglobin Level (g/dL)	
Haematocrit Level (%)	
MCV (fL)	
MCH (pg)	
RDW Level (%)	
RDW Quartile	
Q1 (RDW < 13.3)	
Q2 (13.3 ≤ RDW < 14.1)	
Q3 (14.1 ≤ RDW < 15.2)	
Q4 (RDW ≥ 15.2)	
Albumin Level (mmol/L)	
Urea Level (mmol/L)	
INR	
PT (s)	
APTT (s)	

Variable	n (%) / mean (SD)
Time for RDW Test result (minute)	
Time for Urea Test result (minute)	

Table 3: Distribution of CAP patient according to each score in the three prognostic tools

Variable	n (%) /Median (IQR)
CRB-65 Score	
0	
1	
2	
3	
4	
CURB-65 Score	
0	
1	
2	
3	
4	
5	
CRB-65 + RDW Score	
0	
1	
2	
3	
4	
5	

Table 4: The outcomes of the CAP patients (n = 417)

Variable	n (%) / mean (SD)
Disposition	
Ward	
ICU	
ED Death	
Duration of Hospital Stay (days)	
Vasopressor Usage	
Mechanical Ventilation Usage	
30-days Mortality	

Table 5: Differences of characteristic between 30-days mortality among CAP patients

Variable	**Survive, n (%) / mean (SD)**	**Died, n (%) / mean (SD)**	**p-value**
Gender			
Female			
Male			
Age (year)			
Ethnicity			
Malay			
Chinese			
Siamese			
Heart Rate (bpm)			
Respiratory Rate (per minute)			
Systolic BP (mmHg)			
Diastolic BP (mmHg)			
SpO_2 (%)			
Body Temperature (c)			
Consciousness Level			
A			
B			
C			
D			
White Cell Count Level			
Haemoglobin Level			
Haematocrit Level			
MCV			
MCH			
RDW Level			
RDW Quartile			
Q1 (RDW < 13.3%)			
Q2 (13.3 ≤ RDW < 14.1)			
Q3 (14.1 ≤ RDW < 15.2)			
Q4 (RDW ≥ 15.2)			
Albumin Level			
Urea Level			
INR			
PT			
APTT			
Time for RDW Test (minute)			
Time for Urea Test (minute)			

[a]Chi-square Test
[b]Independent Welch's t-test

Table 6: Differences of outcomes between 30-days mortality among CAP patients

Variable	**Survive , n (%) / mean (SD)**	**Died , n (%) / mean (SD)**	**p-value**
CRB-65 Score			
0			
1			
2			
3			
4			
CURB-65 Score			
0			
1			
2			
3			
4			
5			
CRB-65 + RDW Score			
0			
1			
2			
3			
4			
5			
Disposition			
Ward			
ICU			
ED Death			
Duration of Hospital Stay (days)			
Vasopressin Usage			
Mechanical Ventilation Usage			

[a]Chi-square Test
[b]Independent Welch's t-test

Table 7: Association between RDW Quartiles level and patients' outcomes among CAP patients

Outcomes	**RDW Q1, n (%)**	**RDW Q2, n (%)**	**RDW Q3, n (%)**	**RDW Q4, n (%)**	**p-value[a]**
ICU Admission					
Vasopressin Usage					
Mechanical Ventilation Usage					