UNIVERSITY OF MALAYA
ORIGINAL LITERARY WORK DECLARATION

Name of Candidate: Kanargahraj a/l Vetaryan

Matric No: MGE150003

Name of Degree: Masters of Anaesthesiology

Title of Project Paper/Research Report/Dissertation/Thesis ("this Work"): A tool for predicting outcomes of patients admitted to ICU – "Battery of life"

Field of Study:

I do solemnly and sincerely declare that:

(1) I am the sole author/writer of this Work;
(2) This Work is original;
(3) Any use of any work in which copyright exists was done by way of fair dealing and for permitted purposes and any excerpt or extract from, or reference to or reproduction of any copyright work has been disclosed expressly and sufficiently and the title of the Work and its authorship have been acknowledged in this Work;
(4) I do not have any actual knowledge nor do I ought reasonably to know that the making of this work constitutes an infringement of any copyright work;
(5) I hereby assign all and every rights in the copyright to this Work to the University of Malaya ("UM"), who henceforth shall be owner of the copyright in this Work and that any reproduction or use in any form or by any means whatsoever is prohibited without the written consent of UM having been first had and obtained;
(6) I am fully aware that if in the course of making this Work I have infringed any copyright whether intentionally or otherwise, I may be subject to legal action or any other action as may be determined by UM.

Candidate's Signature Date:

Subscribed and solemnly declared before,

Witness's Signature Date:

Name:

Designation:

ACKNOWLEDGEMENTS

I would like to express my gratitude to Professor Dr Yoo Kuen Chan, consultant anaesthesiologist, of University Malaya who encouraged and directed me in planning and completing my study. This study came into existence only due to her continuous guidance. I would also like to thank my supervisor, Professor Dr Marzida for her support and guidance.

I would like to extend my thanks to lecturers and colleagues who guided me and provided assistance when I needed them most. I am thankful to all my study subjects, for the information they have provided in completing this study.

I am grateful to my family members for their patience and time to pursue and complete my study. Most importantly, I would like to thank my wife, Dr Sangeetha for her encouragement and support.

ABSTRACT

Design: This is a prospective study on all patients admitted to ICU UMMC from April to July 2018.

Method: Data for 280 patients was collected. Patient's physiological status was scored daily for 30 days, or until discharge or death – whichever comes first. Scoring was done based on BOL parameters which included airway, breathing, circulation, haemoglobin, microcirculation and glucose. Each parameter had 4 grades of severity – 25%, 50%, 75%, 100%, with the lowest score at 25% and the highest score at 100%. The lowest score of all six parameters were taken as the final score for each day. Statistical analysis on parameters affecting the final status (alive or dead) was done. Patients who died were further divided into those who died in ICU and those who died in the ward. Individual BOL parameters were analysed for these patients on first day of ICU admission and last day of ICU admission.

Results: Patients who scored a BOL of 25% on the first day were 3.699 times more likely to die compared to patients who scored >25%. The leading physiological causes of deterioration/death was circulation, microcirculation followed by breathing.

Conclusion: The six physiological parameters of airway, breathing, circulation, haemoglobin, microcirculation and glucose, which are captured through a scoring system called the "Battery of Life", are able to identify the potential cause of deterioration in the critically ill patients, as well as those in the wards.

ABSTRAK

Reka bentuk: Ini adalah kajian prospektif semua pesakit yang dimasukkan ke ICU UMMC dari April hingga Julai 2018.

Kaedah: Data telah dikumpulkan daripada 280 pesakit dalam tempoh masa ini. Status fisiologi pesakit direkod setiap hari selama 30 hari / sehingga discaj atau kematian - yang mana lebih awal. Markah diberi berdasarkan parameter BOL yang terdiri daripada saluran udara, pernafasan, sistem peredaran darah, hemoglobin, sistem peredaran mikro dan glukosa. Setiap parameter mempunyai empat skor - 25%, 50%, 75%, 100%. Skor terendah ialah 25% dan skor tertinggi 100%. Skor terendah daripada enam parameter ini diambil sebagai skor akhir untuk setiap hari. Analisis statistik mengenai faktor yang mempengaruhi status akhir pesakit (hidup atau mati) telah dilakukan. Pesakit yang meninggal dunia dibahagikan kepada mereka yang meninggal dunia di ICU atau mereka yang meninggal dunia di wad. Parameter BOL individu dianalisa untuk pesakit-pesakit ini pada hari pertama kemasukan ke ICU dan hari terakhir di ICU.

Keputusan: Kebarangkalian pesakit yang mendapat skor BOL sebanyak 25% pada hari pertama untuk mati adalah 3.699 kali lebih berbanding pesakit yang mencatat BOL > 25%. Penyebab utama kemerosotan / kematian fisiologi ialah sistem peredaran darah diikuti dengan sistem peredaran mikro dan akhirnya pernafasan.

Kesimpulan: Enam parameter fisiologika, iaitu saluran udara, pernafasan, sistem peredaran darah, hemoglobin, sistem peredaran mikro dan glukosa, yang dikumpulkan melalui “Battery of Life”, boleh mengenal pasti penyebab kemerosotan dalam pesakit ICU dan juga dalam wad.

CONTENTS

LIST OF FIGURES AND TABLES

LIST OF SYMBOLS AND ABBREVIATIONS

BoL: Battery of life

ICU UMMC: Intensive care unit University Malaya Medical Centre

MOH: Ministry of health

ATP: Adenosine triphosphate

ADL: Activities of daily living

EWS: Early warning system

PF ratio: Partial pressure of oxygen divided by oxygen concentration in fraction

ABG: Arterial blood gas

LIST OF APPENDICES

Appendix A: Demographic parameters

Appendix B: BOL for non-intubated patients

Appendix C: BOL for intubated patients

Appendix D: Daily BoL follow-up chart

CHAPTER 1: INTRODUCTION

All living organisms require energy to function (1). The two main components of energy (adenosine triphosphate; ATP) production in a living organism are oxygen and glucose (and other energy substrates, such as fats and proteins). When there is an impairment in oxygen delivery or glucose intake, energy production becomes inadequate at cellular level, which in turn would threaten the function of the cells, tissues, organs and ultimately the whole organism. This process inevitably leads to the irreversible process of death (2).

The process of ATP generation requires different organs and systems to work in coordination to deliver oxygen and glucose to the cytoplasm of a cell where the process of glycolysis begins. This process begins from the respiratory system where the oxygen is inhaled from the atmosphere, followed by the circulatory system which coordinates the transportation of oxygen via haemoglobin to different cells of the body (3). This enables oxygen to reach the microcirculatory system where it diffuses into the cell cytoplasm. The digestion of food to produce glucose, and ultimately its absorption, is facilitated by the gastrointestinal system and glucose is also transported to the cells via the circulatory and microcirculatory systems (1,4).

The Battery of Life (BoL) is a scoring system which has been able to identify the failure or deterioration in the different systems that transport oxygen and glucose. This could help the care provider to target their treatment approach more effectively and thereby address and manage the deterioration process in a timely manner.

CHAPTER 2: LITERATURE REVIEW

The intensive care unit (ICU) is staffed with specialized health-care professionals, containing equipment and monitoring devices which are necessary to provide continuous and optimal care for the critically ill patient (5). Discharge from ICU at the earliest appropriate time reduces unnecessary use of these expensive health care facilities and generally improves patient outcomes (6). However, some patients may deteriorate in the wards after having been discharged from ICU. Such patients may require ICU readmission, which is associated with worse clinical and economic outcomes (7,8). Patients who are readmitted have a higher mortality rate compared to those not readmitted – up to five times greater (9,10). Readmission rate within the first 48 hours of ICU discharge for the 49 Ministry of Health (MOH) centres was 1.5% in 2015 (11). The crude in-hospital mortality rate for UMMC was 25.8% in year 2015 (11).

A majority of deaths in hospital are predictable and therefore preventable (12,13). Physiological deterioration occurs gradually before the patient becomes critically ill (13,14). However, delayed recognition leads to a delay in intervention, increased morbidity and mortality. Modified early warning systems (MEWS) are scoring systems used to assess basic physiological parameters to identify patients with potential or established critical illness.

In contrast, the Battery of Life (BOL) is a scoring tool designed to rapidly identify how the oxygen and energy needs of a patient have been compromised at various levels in the pathway to delivery to the cells. This score in turn may be used to predict outcomes and provide appropriate care for the patient.

BOL has 6 parameters, which include airway (cough), breathing (respiratory rate), circulation (blood pressure, heart rate), haemoglobin, microcirculation (lactate) and blood sugar level. The function at each level of oxygen delivery are then further subdivided into 4 levels, i.e. 25%; 50%; 75% and 100%. These levels are guided by several prognostic studies in acutely ill patients where these parameters (and their scoring system) have been correlated with outcome (15-22). These levels have been chosen to allow providers to recognize the urgency of the situation in a language that can even be translated for easier use by the general public. The BOL level for each part of the pathway is scored according to a predetermined table (that has been verified through prognostic studies) and the ultimate prevailing BOL level is determined by the lowest level throughout all six domains.

CHAPTER 3: METHODS

3.1 AIM

We aim to develop a new early warning system to achieve the following goals:

1) To determine patient's BOL score after ICU admission and identify the physiological cause of deterioration.
2) To alert the healthcare provider in advance of patients who may be deteriorating physiologically, and may need early intervention.
3) To identify physiological cause of death.

3.2 Study Design

This was a prospective study. Patients were recruited on the day of admission to ICU (designated as day 0) and followed up until either day 30, discharge from hospital, or death, whichever came first. Subsequently, alive patients were followed up 30 days after the last BOL scoring was done.

3.3 Study Population

Inclusion criteria

- All patients admitted to ICU UMMC

Exclusion criteria

- Patients transferred out to other hospital

Patients admitted to ICU UMMC from 10 April 2018 to 24 July 2018 were analysed. Patients that fit the inclusion criteria were recruited. Upon recruitment, patient's demographic data were recorded (Appendix A). Each patient's BOL levels were scored. Six parameters were included – airway, breathing, circulation, haemoglobin, microcirculation, and blood glucose level. These six parameters were

given a score of 25%, 50%, 75% and 100%, depending on their physiological parameters, with the lowest score being 25% and the highest being 100%. The lowest score of these six parameters were taken as the final score for each day. Data was collected daily from each patient's care chart.

3.3 Statistical analysis

The data was analysed using IBM SPSS Statistics version 25 to produce descriptive statistics and expressed as count (percentage). Patients were divided into 2 main groups – ADL independent and ADL dependent on ICU admission. The proportion of patients that scored a BOL value of 25% compared to more than 25% were calculated in these two groups.

Patients were divided into two groups based on the final status (alive or dead). Univariate analysis was done using five factors which includes gender, age group, race, intubation status and first day BOL.

Finally, patients who passed away were further divided into two groups – patients who died in ICU and those who died in the ward. Their first and last day BOL scores were analysed to identify the physiological factor(s) contributing to their death.

CHAPTER 4: RESULTS

4.1 Demographics

A total of 280 patients were recruited with a mean age of 54.1, with a predominantly non-geriatric population of less than 65 years old (64.6%) and most of the patients recruited were male (61.1%). At baseline, prior to admission to hospital, 258 (92%) of patients were ADL independent whereas 22 (7.9%) were dependent.

Table 1: Demographics and hospital admission status (n=280)

Demographic	**n (%)/Mean (SE)**
Age	54.1 (1.1) [#]
Age category	181 (64.6)
≤ 65	99 (35.4)
> 65	
Gender	
Male	171 (61.1)
Female	109 (38.9)
Race	
Malay	92 (32.9)
Chinese	97 (34.6)
Indian	69 (24.6)
Others	22 (7.9)
Hospital admission status	
Admission ADL	
ADL independent	258 (92.1)
ADL dependent	22 (7.9)

= Mean (SE) where SE = Standard error.

4.2 ICU status

A total of 157 patients (56.1%) were intubated on admission to ICU. Patients were in the normal ward for a mean duration of 3.3 days before being admitted to ICU. Patients spent a mean duration of 4.9 days in ICU. A total of 10 patients (4.3%) were discharged from ICU, and subsequently readmitted. Mean BOL score prior to ICU readmission was 35.0.

Table 2: ICU patient status

Clinical	**n (%)/ Mean (SE)**
Intubation	
No	123 (43.9)
Yes	157 (56.1)
Mean duration of hospital stay prior to ICU admission (days)	3.3 (0.4) #
ICU discharge status	
Discharged	231 (82.5)
Died	49 (17.5)
ICU admission (days)	4.9 (0.4) #
ICU readmission status (n = 231)	
No	221 (95.7)
Yes	10 (4.3)
Mean BoL prior to ICU readmission (n=10)	35.0 (12.91)

= Mean (SE) where SE = Standard error..

4.3 Outcome

By day 30 following admission into ICU, 64 patients (22.9%) had died, and 16 patients (5.7%) had not been discharged. Of the remaining 200 patients who were discharged from ICU, 141 (50.4%) were ADL independent, and 59 (21.1%) were ADL dependent. Patients were admitted for a mean of 17 days.

At 30-day follow-up of those who were alive, 9 more patients had died. A total of 20 patients (7.1%) were lost to follow-up. In total, 187 patients (66.8%) were still alive, whereas 73 patients (26.1%) had died.

Table 3: Patient outcome	**n (%)/ Mean (SE)**
Hospital discharged status	
ADL independent	**141 (50.4)**
ADL dependent	**59 (21.1)**
Died	**64 (22.9)**
Not discharged yet	**16 (5.7)**
Hospital admission (days) (n=265)	17.0 (1.0)[#]
*16 participants still not discharged	
After 30 days follow up	
ADL independent	139 (49.6)
ADL dependent	45 (16.1)
Died	9 (3.2)
Died before 30 days follow up	64 (22.9)
Lost follow up	23 (8.2)
Final status	
Alive	187 (66.8)
Died	73 (26.1)
Lost to follow up	20 (7.1)

= Mean (SE) where SE = Standard error.

4.4 First day BOL score

Table 4: Patients with BOL score of 25% on ICU admission(n=135)

Hospital admission	n (%)	Hospital discharged	n (%)	30 days status Follow up	n (%)
ADL (I)	118 (45.7)	ADL (I)	45 (32.6)	ADL (I)	36 (30.8)
				ADL (D)	4 (44.4)
				ND	5 (45.5)
		ADL (D)	19 (38.8)	ADL (I)	9 (47.4)
				ADL (D)	5 (27.8)
				Died	2 (66.7)
				Lost follow up	3 (33.3)
		Died	44 (80.0)	D (30)	44 (80.0)
		ND	10 (62.5)	ADL (I)	2 (100.0)
				ADL (D)	5 (50.0)
				Died	2 (66.7)
				Lost follow up	1 (100.0)
ADL (D)	17 (25.0)	ADL (I)	3 (100.0)	ADL (I)	1 (100.0)
				ADL (D)	1 (100.0)
				Lost follow up	1 (100.0)
		ADL (D)	7 (70.0)	ADL(I)	4 (57.1)
				Died	2 (100.0)
				Lost follow up	1 (100.0)
		Died	7 (77.8)	D (30)	7 (77.8)

ADL (I) = ADL Independent , ADL (D) = ADL dependent, ND = Not yet discharged, D (30) = Died before 30 days follow up

A total of 135 patients scored 25% on the first day of ICU admission. 80% of the patients who died scored a BOL of 25% in the ADL independent group. 77.8% of patients who died scored 25% BOL in the ADL dependent group. There was a strong correlation between first day BOL and mortality irrespective of the ADL status.

4.5 Factors associated with final status

Table 5: Factors associated with final status (n=260)

Factors	Patients final status		HR (95% CI)	p value	AHR (95% CI)	p value
	Alive (n=187) n (%)	Died (n=73) n (%)				
Gender			0.746 (0.451-1.232)	0.252	0.916 (0.550-1.528)	0.738
Male(R)	109 (68.1)	51 (31.9)				
Female	78 (78.0)	22 (22.0)				
Age group			1.234 (0.775-1.963)	0.375	1.213 (0.747-1.969)	0.435
≤ 65(R)	124 (74.7)	42 (25.3)				
> 65	63 (67.0)	31 (33.0)				
Race				0.848		0.944
Malay(R)	62 (70.5)	26 (29.5)				
Chinese	68 (71.6)	27 (28.4)	0.916 (0.534-1.569)	0.748	1.168 (0.668-2.044)	0.586
Indian	45 (71.4)	18 (28.6)	1.023 (0.561-1.867)	0.940	1.067 (0.583-1.952)	0.834
Others	12 (85.7)	2 (14.3)	0.548 (0.130-2.311)	0.413	0.872 (0.202-3.762)	0.855
Intubation			1.697 (1.029-2.799)	0.038	1.528 (0.913-2.557)	0.106
No(R)	91 (80.5)	22 (19.5)				
Yes	96 (65.3)	51 (34.7)				
First day BoL			3.863 (2.217-6.731)	< 0.001	3.699 (2.094-6.534)	< 0.001
25%	69 (54.8)	57 (45.2)				
> 25% (R)	118 (88.1)	16 (11.9)				

(R) = Reference;HR = Hazard ratio; AHR = Adjusted hazard ratio; CI = Confidence interval.20 patients were removed from analysis due to lost follow-up.

Univariate analysis showed that a higher number of intubated patients die (p value 0.038). When both intubation status and first-day BOL score were taken into consideration in multivariate analysis, only the first-day BOL score remained significant (p<0.001). Patients who scored 25% were 3.699 times more likely to die compared to patients who score >25%.

4.6 Individual BOL score for patients who died in ICU

Table 6: Comparison of proportion with each individual domain at 25% for deceased patients in ICU on the 1st day versus the last day (n = 48)

Subcomponent	First day	Last day
Airway	0(0 %) 1 missing	2 (4.2%) 95% CI -1.5 – 9.8
Breathing	3(6.3%) 95% CI -0.6 – 13.1	12 (25.0%) 95%CI 12.8-37.2
Circulation	37 (77.1%) 95%CI 65.2-89.0	45 (93.8%) 95%CI 86.9-100.6
Hemoglobin	1 (2.1%) 95%CI -2.0-6.1	0 (0%) 3 missing
Micro-circulation	22 (45.8%) 95%CI 31.7-59.9	29 (65.9%) 4 missing 95%CI 51.9-79.9
Sugar	3 (6.3%) 95%CI -0.6-13.1	7 (15.9%) 4 missing 95%CI 5.1-26.7

The majority of patients who died in ICU scored poorly in circulation and microcirculation followed by breathing.

4.7 Individual BOL score for patients who died in the ward

Table 7: Comparison of proportion with each individual domain at 25% for deceased patients in the wards on the 1st day versus the last day (n = 25)

Subcomponent	First day	Last day
Airway	0 (0%)	1 (4.2%) 1 missing 95%CI -3.8-12.1
Breathing	0 (0%)	1 (4.0%) 95%CI -3.7-11.7
Circulation	17 (68.0%) 95%CI 49.7-86.3	12 (48.0%) 95%CI 28.4-67.6
Hemoglobin	0 (0%)	0 (0%) 6 missing
Micro-circulation	8 (33.3%) 1 missing 95%CI 14.5-52.2	2 (15.4%) 12 missing 95%CI -4.2-35.0
Sugar	0 (0%)	3 (13.6%) 3 missing 95%CI -0.7-28.0

In the wards, patients also scored poorly in circulation and microcirculation.

CHAPTER 5: DISCUSSION

Multivariate analysis done on the final status of patients (whether alive or dead) did not show any difference for gender, age group, race and intubation status. We expected elderly patients (age > 65 years) to have poorer outcomes compared to younger patients as they had lower physiological reserves and would have been unable to compensate physiologically in the event of a critical illness (23). However, our study showed there is no significant difference between these two groups. One possible explanation would be that younger patients admitted to ICU were usually more ill, with presentations such as motor vehicle accidents (MVA) with multiple organ injuries. So, they also tended to do as poorly as the elderly. Generally intubated patients were more ill compared to non-intubated patients. However, based on our analysis, there was no significant difference between these two groups. Since intubation status were only recorded on day one, there might be patients who deteriorated and required intubation later on during their stay in hospital, hence the insignificant result.

The first system involved in the delivery of oxygen from the environment to the blood is the respiratory system. BOL scoring system assesses two parameters in the respiratory system, which are airway and breathing. Airway patency is of paramount importance for the transport of oxygen (3). In this study, most patients scored more than 25% for airway. This is due to prompt identification and treatment of patients that need airway support by healthcare providers. Breathing was assessed differently for intubated and non-intubated patients. For intubated patients, it was assessed by their PF ratio, according to Berlin classification (24). For non-intubated patients, breathing was assessed by using the respiratory rate as it is the most sensitive and observable marker of a deteriorating patient (25). A significant proportion of patients showed poor score

for this parameter. This supports the use of this parameter for early assessment of the respiratory system.

The next system is circulatory system and it was assessed based on blood pressure, heart rate and requirement for inotropes/vasopressors. Transportation of oxygen and nutrients to the microcirculation is accomplished by this system. Our study shows that the leading physiological cause for deterioration of patients who died in ICU and in the wards was failure in the circulatory system.

Once the circulatory system transports oxygen and glucose to the cell vicinity, microcirculation allows for delivery into the cell. We assessed microcirculation through base excess and lactate levels (26). In our analysis of patients who died, microcirculatory failure is the second leading cause for physiological death in the patients who died in ICU and in the wards.

Once oxygen is inhaled through the respiratory system, it is transported mainly via haemoglobin. Adequate haemoglobin levels are necessary for oxygen delivery (3). In our study, all patients who died scored >25% in this domain on their last day and it was not assessed to be a primary cause of physiological death. This is due to swift identification and transfusion of anaemic patients by the healthcare provider.

The last crucial factor in energy production is glucose. Energy cannot be produced without glucose in the body. However, high levels of glucose in the blood also cause endothelial dysfunction and vascular inflammation, impairing the microcirculation (27). We gave the scoring based on the level of glucose in the body, either too high or too low was given the lowest score. In our study, glucose level does not appear to be a significant factor in causing patient death, either in the wards or in ICU.

CHAPTER 6: Conclusion

Patients can be assessed physiologically using six main parameters, namely, airway, breathing, circulation, haemoglobin, microcirculation and glucose, which are captured through a scoring system called the Battery of Life. A low score informs the healthcare provider of the patient's immediate need for attention. Care can be delivered more optimally to address the particular physiological parameter. This study showed that the main parameters contributing to the deterioration of a patient were abnormalities in the circulation, followed by microcirculation, and breathing.

In future, the Battery of Life score may be incorporated to monitoring devices to alert the healthcare provider as well as the patients regarding their physiological wellbeing. This would ultimately help to improve outcomes of patients, especially those in the wards as both can utilize this "easy to use" parameter to alert upwards or their care providers respectively.

REFERENCES

1. Hall, John E. Guyton and Hall textbook of medical physiology e-Book. Elsevier Health Sciences, 2015.

2. Chan, Yoo Kuen, and Kwee Peng Ng, eds. Physiological Basis of Acute Care-E-Book. Elsevier Health Sciences, 2012.

3. Treacher, D. F., and R. M. Leach. "Oxygen transport—1. Basic principles." Bmj 317.7168 (1998): 1302-06.

4. Caspary, Wolfgang F. "Physiology and pathophysiology of intestinal absorption." (1992): 299S-308S.

5. Simchen, Elisheva, et al. "Survival of critically ill patients hospitalized in and out of intensive care units under paucity of intensive care unit beds." Critical care medicine 32.8 (2004):1654-61.

6. Stricker, K., H. U. Rothen, and J. Takala. "Resource use in the ICU: short-vs. long-term patients." Acta Anaesthesiologica Scandinavica 47.5 (2003): 508-15.

7. Rosenberg, Andrew L., et al. "Who bounces back? Physiologic and other predictors of intensive care unit readmission." Critical care medicine 29.3 (2001): 511-8.

8. Chan, Khee-Siang, et al. "Readmission to the intensive care unit: an indicator that reflects the potential risks of morbidity and mortality of surgical patients in the intensive care unit." Surgery today 39.4 (2009): 295-9.

9. Renton, J., et al. "Factors associated with increased risk of readmission to intensive care in Australia." Intensive care medicine 37.11 (2011): 1800.

10. Utzolino, Stefan, et al. "Unplanned discharges from a surgical intensive care unit: readmissions and mortality." Journal of critical care 25.3 (2010): 375-81.

11. Malaysian Registry of Intensive Care Report for 2015. Available from: http://mric.org.my/publications/mric-annual-report-2015/

12. McGloin, Helen, Sheila K. Adam, and Mervyn Singer. "Unexpected deaths and referrals to intensive care of patients on general wards. Are some cases potentially avoidable?." Journal of the Royal College of Physicians of London 33.3 (1999): 255-9.

13. Smith, Andrew F., and Jeremy Wood. "Can some in-hospital cardio-respiratory arrests be prevented? A prospective survey." Resuscitation 37.3 (1998): 133-7.

14. FranklinC, MatthewJ. "Developing strategies to prevent in hospital cardiac arrest: analyzing responses of physicians and nurses in the hours preceding the event." Crit Care Med 22 (1994): 244-7.

15. Oliveros Rodríguez, Henry, and Édgar Beltrán Linares. "Preoperative Hemoglobin Levels and Outcomes in Cardiovascular Surgical Patients; systematic review and meta-analysis." Revista Colombiana de Anestesiología 40.1 (2012): 27-33.

16. Luk, J. K. H., P. K. C. Chiu, and L. W. Chu. "Hemoglobin level as a predictor of rehabilitation outcome in older Chinese patients." European Geriatric Medicine 4 (2013): S107.

17. Cretikos MA, Bellomo R, Hillman K, Chen J,Finfer S, Flabouris A. Respiratory rate: the neglected vital sign. Med J Aust 2008; 188(11): 657-9

18. Bakker, Jan, Maarten WN Nijsten, and Tim C. Jansen. "Clinical use of lactate monitoring in critically ill patients." Annals of intensive care 3.1 (2013): 12.

19. Kay, H. H., S. Zhu, and S. Tsoi. "Hypoxia and lactate production in trophoblast cells." Placenta 28.8-9 (2007): 854-60.

20. Williams, B., et al. "National Early Warning Score (NEWS): Standardising the assessment of acute-illness severity in the NHS." London: The Royal College of Physicians (2012).

21. Practice guidelines for sedation and analgesia by Non-Anesthesiologists. An updated report by the American Society of Anesthesiologists Task Force on sedation and analgesia by Non-Anesthesiologists. Anesthesiology 2002; 96(4); 1004-17

22. Force, ARDS Definition Task, V. M. Ranieri, and G. D. Rubenfeld. "Acute respiratory distress syndrome." Jama 307.23 (2012): 2526-33.

23. King, Mitchell S. "Preoperative evaluation of the elderly." The Journal of the American Board of Family Practice 4.4 (1991): 251-8.

24. Agrifoglio, A., et al. "Acute respiratory distress syndrome-the Berlin definition: impact on an ICU of a university hospital." Critical Care 17.2 (2013): P94.

25. CG50, N. I. C. E. "Recognition of and response to acute illness in adults in hospital. National Institute of Clinical Excellence." (2007).

26. Smith, I., et al. "Base excess and lactate as prognostic indicators for patients admitted to intensive care." Intensive care medicine 27.1 (2001): 74-83.

27. Sena, Cristina M., Ana M. Pereira, and Raquel Seiça. "Endothelial dysfunction—a major mediator of diabetic vascular disease." Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease 1832.12 (2013): 2216-31.