International Journal of Aging Research (ISSN:2637-3742)

Predictors of in-hospital mortality in critically ill Geriatric patients

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ABSTRACT

Objective: To determine the predictors of in-hospital mortality in critically ill older patients. **Participants and Methods:** A prospective cohort study including 305 critically ill older adults (age ≥60 years) who were admitted to High Dependency Units (HDUs) in a tertiary care university hospital from March 22, 2019 to January 4, 2020. Demographic, clinical and laboratory data of participants were collected thought a review of medical records and clinical observation at HDUs till either death or discharge alive. Statistical analysis included univariate analysis of selected potential predictors such as various comorbidities, C- reactive protein / Albumin ratio (CAR), Neutrophil-lymphocyte ratio (NLR), Red cell distribution width (RDW), Po2/Fio2 ratio (PFR), Simplified acute physiology score II (SAPS II), Charlson comorbidity index (CCI) and multidrug-resistant Gram-negative bacterial (MDR-GNB) infection to ascertain their association with mortality, followed by multivariable logistic regression to derive the final prediction model. The discriminative ability of the model was evaluated by using the receiver operating characteristic (ROC) curve. **RESULTS:** Overall mortality was 53.1%. Multivariate regression analysis revealed independent predictors of mortality including dementia in clinical history with an odds ratio (OR) of 4.86 (95% CI: 1.28-18.34), total protein with an OR of .53 (95% CI: .30-.95) and the use of mechanical ventilation (MV) and/or intravenous cardiovascular support with an OR of 148.34 (95% CI: 34.28-641.77), formulating a novel prognostic model with an area under the ROC curve of .93 (95% CI: .89-.96, P.000). **CONCLUSION:** History of dementia, total protein and the use of MV and/or intravenous cardiovascular support are predictors of mortality in critically ill geriatric patients. It provides a novel prognostic model which needs validation in other multicenter prospective studies.

Keywords: Mortality, prognostic model, older adults, critical illness, dementia.

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INTRODUCTION

Look at the past to predict the future is a convenient concept for prognosis in critically ill older adults [1]. Traditional scoring systems lack accuracy in geriatric patients because of focusing on acute illness severity and lacking specific geriatric assessments [2]. As preexisting geriatric syndromes such as frailty, cognitive impairment and functional limitations are closely related to poor outcomes rather than age alone [3]. Cognitive impairment and comorbidity are common in critically ill older patients and could lead to the provision of less aggressive treatment or even treatment restriction, in addition to the increased risk of MDR-GNB infection and mortality [4-8]. MDR-GNB infection poses a clinical challenge because of resistance to nearly all antibiotics except colistin, some aminoglycosides, and variably tigecycline [9] and it is associated with increased risk of mortality [10]. Also, there is increasing evidence that certain laboratory markers of inflammation such as RDW, C- reactive protein (CRP), NLR and CAR could also be associated with mortality in critically ill patients with various aetiologies [11-14]. Despite these concepts in prognosis, they are commonly neglected in various scoring systems. This study aims to identify predictors of in-hospital mortality among critically ill geriatric patients through investigating the potential prognostic role of comorbidity, acute illness severity score, MDR-GNB infection and novel inflammatory markers including RDW, CRP, NLR and CAR.

METHODOLOGY

Study Design, Setting and participants

A prospective observational study including critically ill elderly patients who were admitted to HDUs including intermediate care unit and intensive care unit at Geriatrics hospital from March 22, 2019, to January 4, 2020. Geriatrics Hospital is a tertiary care hospital, designated for medical care of older adults (aged ≥60 years). Exclusion criteria included patients with missing outcome or first admission data, and those who were transferred to another hospital or discharged against medical advice. Patients who were readmitted throughout the follow-up period till the end of January 2020 were included for one time, utilizing their first admission data.

Demographic and clinical data collection

Review of medical records was done for extraction of first admission clinical data including the main cause of admission, medical history of chronic diseases including dementia, initial vital signs and random blood glucose on admission to HDUs. Follow up was done through checking their clinical status for receiving renal replacement therapy and the use of MV and/or intravenous cardiovascular support (defined as the use of vasopressors and/or inotropes including Epinephrine, Norepinephrine, Dopamine and Dobutamine) during the period of stay at HDUs till either discharge alive or death. The primary outcome was mortality at HDUs.

Laboratory Data collection

Biological samples were collected by nursing staff members and assessed at the clinical laboratories of Ain Shams University hospital. Laboratory data collection was done through checking for laboratory results in medical records including arterial blood gases (ABG), CRP, total protein, albumin, aspartate transaminase, alanine transaminase, total bilirubin, blood urea nitrogen (BUN), creatinine, sodium, potassium, calcium, haemoglobin, hematocrit, white blood cell, RDW, and platelet. Diagnosis of MRD-GNB infection was confirmed by the available bacterial cultures and sensitivity either at admission or during the observation period. Different cultures and sensitivity to antibiotics were done by disc diffusion method. MDR was defined as acquired resistance to at least one agent in three or more antimicrobial categories [15].

Measurements and covariates of interest:

Comorbidities assessment was based on the obtained medical history followed by CCI determination [16]. History of dementia was considered positive based on clinical symptoms

obtained from patient's proxy coinciding with Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [17]. Calculation of acute illness severity score was done by SAPS II score [18]. Laboratory parameters on admission were used for calculation of inflammatory indicators. NLR is defined as the ratio of relative neutrophil to relative lymphocytes count [19]. The CAR was calculated by dividing the CRP level (mg/L) by the serum albumin level (g/L) [20]. RDW was reported as part of a standard complete blood count to measure anisocytosis [12]. PFR was calculated by dividing Po_2/Fio_2 to assess initial oxygenation [21]. Estimation of PaO_2/FiO_2 from oximeters is used for patients who had normal oxygen saturation on admission without available PaO_2 in ABG parameters [22].

Statistical analysis

The analysis was performed by statistical package software IBM- SPSS version 21.

Values were presented as means ± SD or as numbers and proportions, as appropriate. The relations between qualitative variables were evaluated by Chi-square test or Fisher's exact test, as indicated. Continuous variables were checked for normality by using Shapiro-Wilk test. As data were normally distributed, unpaired t-test was used. Variables with P values <0.05 in univariate analysis were introduced in a logistic regression model to detect independent predictors of mortality. Based on that prediction model was formulated as stated below. ROC curve was conducted to assess the sensitivity and specificity of the model in detecting mortality. All tests were bilateral and a P value of 5% was the limit of statistical significance.

Ethical consideration

The study protocol was revised and approved by the Geriatrics hospital ethics review board and the ethical committee of the faculty of medicine at Ain Shams University.
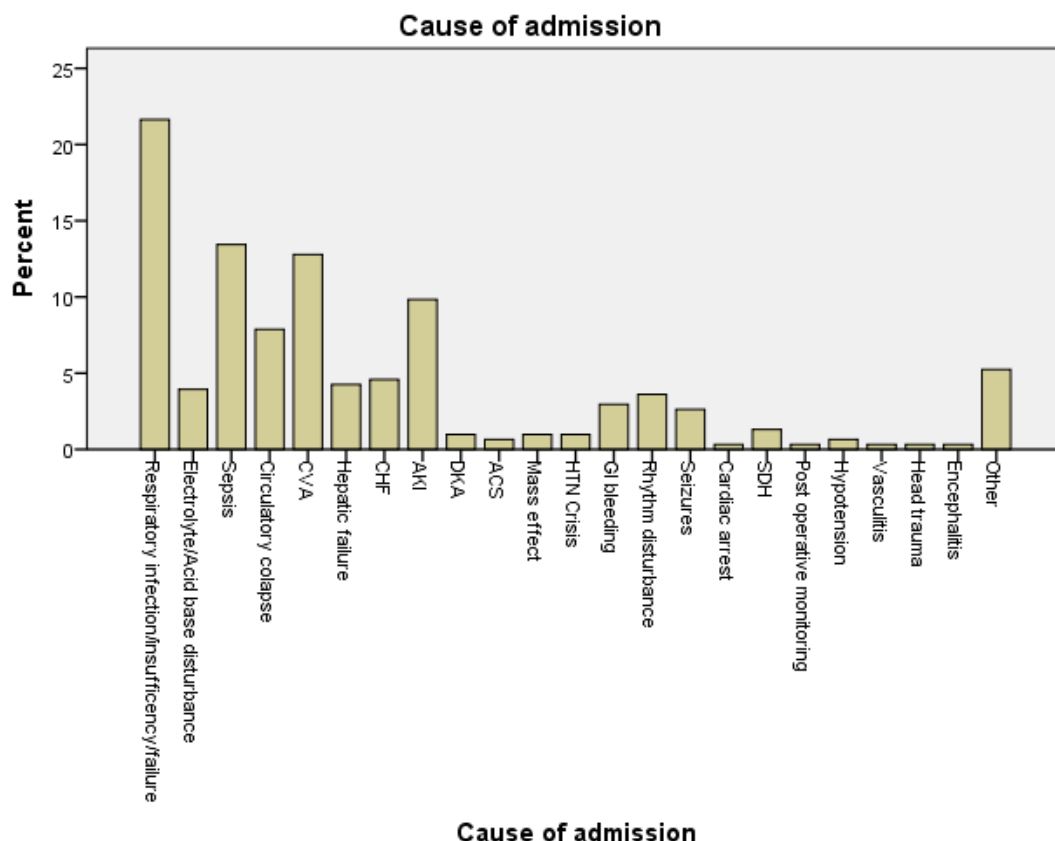

Figure 1 Principal causes of admission in critically ill older adults

Abbreviations: Cerebrovascular accident (CVA), Congestive heart failure (CHF), Acute kidney Injury (AKI), Diabetic ketoacidosis (DKA), Acute coronary syndrome (ACS), Hypertensive crisis (HTN crisis), Gastrointestinal bleeding (GI bleeding), Subdural hemorrhage (SDH).

RESULTS

A total of 305 critically ill patients including 104 male (34.1%) and 201 female (65.9%) with an overall mortality rate of 53.1%. Mean age of participants was 74.1±8.8 years.   The most common principal causes of admission were acute respiratory insufficiency/infection (ARI) (21.6%), followed by sepsis (13.4%), cerebro-vascular accidents (12.8%), acute kidney injury (9.8%), circulatory collapse (7.9%), congestive heart failure (4.6%), hepatic failure (4.3%) and electrolyte/acid-base disturbance (3.9%) **(Figure 1).** Baseline characteristics and univariate analysis of quantitative and qualitative variables are described in **Tables 1 and 2 respectively.**

The variables significantly associated (<0.05) with in-hospital mortality were history of dementia, history of malignancy, BUN, CAR, PFR, CCI, total protein, albumin, SAPS II score, sodium categories, the use of MV and/or intravenous cardiovascular support and the presence of MRD-GNB infection.

After multivariate analysis, history of dementia (OR= 4.86; 95% CI: 1.28-18.34; P =.020), total protein (OR= .53; 95% CI: .30- .95; P= .035), and the use of MV and/or intravenous cardio-vascular support (OR =148.34; 95% CI: 34.28-641.77; P= .000) were predictors of in-hospital mortality and a novel predictive model has been formulated (table 3). This model can correctly predict 88.7% of mortality in the studied cohort and it was able to explain 71.5% of the variability of mortality (Nagelkerke R Square =.715) (**Supplementary Dataset S1**). Using a cut-off score .70, this model predicted in-hospital mortality with a sensitivity 95.8% and a specificity 83.3%. The area under the ROC curve (AUC) of this novel model was .93 (95% CI: .89-.96, P=.000), while AUC of SAPS II score was .67 (95%CI: .59-.74, P=.000) (**Figure 2A**). A ROC curve was plotted also for inflammatory markers but none was significant for prediction of mortality at HDUs. The AUC of RDW, NLR and CAR was .57 (95%CI: .46-.69, P=.174), .58 (95%CI:.47-.70,P=.125), and .49 (95%CI: .38–.61, P=.953), respectively (**Figure 2B**).
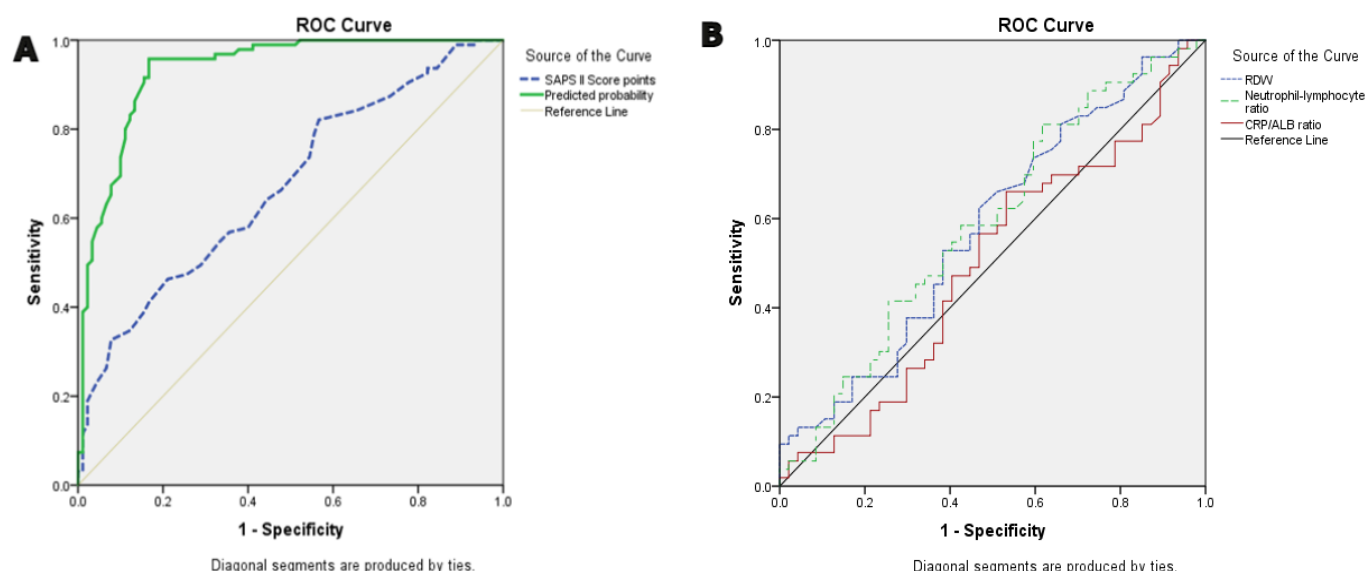

Figure 2 Receiver operating characteristic (ROC) curve of (A) the novel prediction model and SAPS II Score (B) Inflammatory indicators: Red cell distribution width. Neutrophil-lymphocyte ratio and CRP/albumin ratio. (A) Area Under the Curve (AUC) of the novel prediction model is .93 (95% Confidence Interval. .89-.96) while it is .67 (95% Confidence Interval. .59-.74) for SAPS II Score; (B) AUC of inflammatory indicators: Red cell distribution width .57 (95% Confidence Interval. .46-.69), Neutrophil-lymphocyte ratio .58 (95% Confidence Interval. .47-.70), and CRP/ALB ratio.49 (95% Confidence Interval. .38-.61)

Table 1 Baseline characteristics and univariate analysis for quantitative variables in critically ill older adults

Quantitative Variables	Mean±SD (Number)	Survivors 46.9 % (n=143)	Nonsurvivors 53.1% (n=162)	P
Age	74.1±8.8 (305)	73.0±8.7(143)	75.0±8.9 (162)	.055
TLC	12.1±8.8 (305)	11.3±7.2(143)	12.9±10.0(162)	.116
NLR	12.2±16.1(137)	9.9±11.0 (66)	14.4±19.5(71)	.105
Hemoglobin	10.5±2.2(304)	10.5±2.1(143)	10.4±2.4(161)	.680
Hematocrit	32.0±8.8 (264)	32.0±7.3 (125)	31.9±9.9 (139)	.926
Platelets	236.5±113.2(304)	236.6±112.6(143)	236.3±114.0(161)	.978
BUN	44.3±33.6 (297)	39.8±29.6 (140)	48.3±36.4 (157)	.029
Creatinine	1.8±1.7 (303)	1.8±1.4 (142)	1.8±1.9 (161)	.999
RDW	17.2±13.3 (203)	17.9±19.8 (90)	16.6±3.1 (113)	.471
CRP	100.3±92.1 (275)	90.8±96.2(130)	108.8±87.7(145)	.107
Albumin	2.7±.6 (282)	2.8±.6 (132)	2.6±.6 (150)	.001
CAR	4.0±4.0 (261)	3.5±3.9 (123)	4.5±4.0 (138)	.030
Sodium	134.8±9.2 (303)	134.2±7.2 (142)	135.4±10.6 (161)	.227
Potassium	4.0±.8 (302)	4.0±.9 (142)	4.0±.8 (160)	.729
Corrected Calcium	9.1±1.0 (266)	9.0±.9 (130)	9.1±1.1 (136)	.489
Phosphorus	3.6±1.5 (235)	3.6±1.4 (112)	3.6±1.6 (123)	.979
Magnesium	1.9±.4 (255)	1.9±.4 (121)	1.9±.5 (134)	.986
Total protein	5.9±1.0 (224)	6.2±1.1 (107)	5.7±.8 (117)	.000
Total bilirubin	1.1±1.7 (269)	.9±1.1 (127)	1.3±2.1 (142)	.063
ALT	31.1±77.3 (274)	22.9±27.7 (128)	38.3±102.4 (146)	.082
AST	48.8±118.7 (265)	38.3±67.3 (120)	57.4±148.1 (145)	.194
PH	7.4±.0 (297)	7.4±.0 (137)	7.3±.0 (160)	.071
PFR	341.3±130.6(285)	361.2±113.4(132)	324.1±141.9(153)	.016
RBS	177.1±92.8 (297)	169.1±76.5(141)	184.4±105.1(156)	.150
CCI	7.8±2.5 (293)	7.4±2.3 (136)	8.2±2.5 (157)	.010
SAPS II Score	36.9±10.1 (241)	33.1±8.3 (114)	40.3±10.5 (127)	.000

Abbreviations: Total leukocyte count (TLC), Neutrophil-lymphocyte ratio (NLR), Blood Urea Nitrogen (BUN), Red cell distribution width (RDW), C-reactive protein (CRP), C-reactive protein/ Albumin ratio (CAR), Alanine aminotransferase (ALT), Aspartate transaminase (AST), Po2/Fio2 ratio (PFR), Random blood sugar (RBS), Charlson comorbidity index(CCI)., simplified acute physiology score II (SAPS II).

Normal range of TLC (4-10 x 10^3/µL), Hemoglobin (12-15g/dl), Hematocrit (36-46%), Platelets (150-410x 10^3/µL), BUN (5-23mg/dl), Creatinine (0.6-1.2mg/dl), RDW (11.5-14%), CRP (< 6mg/l), ALB (3.5-5.7g/dl), Sodium (136-145Mmol/l), Potassium (3.5-5.1Mmol/l), Total Calcium (8.6-10.3mg/dl), Phosphorus (2.5-5mg/dl), Magnesium (1.8-2.6mg/dl), Total protein (6-8.3g/dl), Total bilirubin (0.3-1mg/dl), ALT (7-52IU/L), AST (3-35IU/L), RBS (80-140mg/dl).

Table 2 Baseline characteristics and univariate analysis for qualitative variables in critically ill older adults

Qualitative Variables	Percentage (Number)	Survivors 46.9 % (n=143)	Nonsurvivors 53.1% (n=162)	P
Men: women	34.1(104):65.9(201)	47.1(49):46.8(94)	52.9(55):53.2(107)	.954
Comorbidities				
CVD				.938
(Yes)	76.7 (234)	47.0 (110)	53.0 (124)	
(No)	23.3 (71)	46.5 (33)	53.5 (38)	
DM				.826
(Yes)	46.9 (143)	47.6 (68)	52.4 (75)	
(No)	53.1 (162)	46.3 (75)	53.7 (87)	
CVA/TIA				.829
(Yes)	32.8 (100)	46.0 (46)	54.0 (54)	
(No)	67.2 (205)	47.3 (97)	52.7 (108)	
CKD/ESRD				.249
(Yes)	24.3 (74)	52.7 (39)	47.3 (35)	
(No)	75.7 (231)	45.0 (104)	55.0 (127)	
Chronic hepatic disease (Yes)				.894
	21.3 (65)	46.2 (30)	53.8 (35)	
(No)	78.7 (240)	47.1 (113)	52.9 (127)	
History of malignancy				.006
(Yes)	15.1 (46)	28.3 (13)	71.7 (33)	
(No)	84.9 (259)	50.2 (130)	49.8 (129)	
History of dementia				.006
(Yes)	33.1 (101)	35.6 (36)	64.4 (65)	
(No)	66.9 (204)	52.5 (107)	47.5 (97)	
Chronic respiratory disease (Yes)				.646
	15.1 (46)	50.0 (23)	50.0 (23)	
(No)	84.9 (259)	46.3 (120)	53.7 (139)	
MRD-GNB infection				.001
(Yes)	42.6 (130)	35.4 (46)	64.6 (84)	
(No)	57.4 (175)	55.4 (97)	44.6 (78)	
Use of MV and/or intravenous cardiovascular support (Yes)	58.5 (175)	15.4 (27)	84.6 (148)	.000
(No)	41.5 (124)	92.7 (115)	7.3 (9)	
Sodium Categories				.014
Hyponatremia	50.8 (153)	49.0 (75)	51.0 (78)	
Hypernatremia	7.6 (23)	17.4 (4)	82.6 (19)	
Normal	41.5 (125)	48.8 (61)	51.2 (64)	
High Creatinine				.503
(Yes)	49.0 (148)	48.6 (72)	51.4 (76)	
(No)	51.0 (154)	44.8 (69)	55.2 (85)	
Hemodialysis during stay				.453
(Yes)	8.3 (25)	40.0 (10)	60.0 (15)	
(No)	91.7 (276)	47.8 (132)	52.2 (144)	

Abbreviations: Cardiovascular disease (CVD), Diabetes mellitus (DM), Cerebrovascular accidents/Transient ischemic attacks (CVA/TIA), Chronic kidney disease/End Stage Renal disease (CKD/ESRD), Multidrug-resistant Gram-negative bacteria (MDR-GNB), Mechanical ventilation (MV).

Table 3 Predicted probability of in-hospital mortality of critically ill older adults

Predictors: History of dementia (X_1: Yes= 1 , No= 0)

Total protein (X_2: in g/dl)

Use of MV and/or IV cardiovascular support: (X_3: Yes= 1 , No= 0)

$$\text{Outcome} = \frac{e^{-0.106 + 1.582 X_1 - 0.624 X_2 + 5 X_3}}{(1 + e^{-0.106 + 1.582 X_1 - 0.624 X_2 + 5 X_3})}$$

Outcome: Dead, if predicted probability ≥50%

Alive, if predicted probability <50%

DISCUSSION

The study assessed the potential prognostic role of comorbidity, MRD-GNB infection and novel inflammatory indicators including CAR, RDW and NLR in critically ill older adults. History of dementia, total protein and the use of MV and/or intravenous cardiovascular support were independent predictors of in-hospital mortality and a novel predictive model has been developed. AUC of this model showed higher discriminative ability in comparison to SAPS II.

Both dementia and malignancy in the clinical history were significantly associated with mortality (P value .006). 101 patients (33.1%) had a history of dementia and it predicted in-hospital mortality. In comparison to other comorbidities, only history of dementia was associated with increased mortality hazard independent of other mortality risk factors and it is consistent with previous studies reporting this significant association between cognitive impairment and in-hospital mortality as in another prospective cohort study including hospitalized elderly patients [23], and a retrospective cohort study using databases of older people in England [24]. The importance of cognitive impairment in outcome prediction is also supported by large scale studies utilizing data from the Chinese Longitudinal Healthy Longevity Survey [25], and an integrative review of 104 articles reporting poorer hospital outcomes of older people with cognitive impairment [26]. This information confirms the value of cognitive screen at the time of admission of critically ill older patients.

Besides investigating the prognostic role of various comorbidities, this study investigated the impact of MRD-GNB infection on critically ill geriatric patients. MRD-GNB is the most dangerous group among MDR bacteria as infection with these bacteria is associated with significant morbidity and mortality worldwide [27]. This study showed that mortality in those who were infected with MRD-GNB was high, reaching 64.6% (84 patients), confirming the real challenge of this problem in the clinical settings and coinciding with data provided by The Global Point Prevalence Survey [28]. These findings are supported by other studies involving different age groups [29, 30].

Study results showed that non-survivors had statistically significant lower serum albumin than the survivors (2.6±.6 versus 2.8±.6, P value .001) supporting the results of previous studies [31, 32]. These serum protein markers reflect an acute phase response and may not accurately represent the nutritional status in critical illness [33]. Also, non-survivors had a statistically significant lower serum total protein in comparison to survivors (5.7±.8 versus 6.2±1.1, P value .000), a finding supported by another prospective study showing a relationship between total protein and mortality in hospitalized patients [34]. Despite these statistically significant associations between low serum albumin, low total protein and observed

mortality, only low total protein has remained as an independent predictor in the regression model that elicits the search for the potential role of the albumin-globulin ratio as a novel prognosticator and a reflective of both malnutrition and inflammation as reported in a previous study including patients with chronic kidney disease [35].

The third independent predictor of mortality in the study was the use of MV and/or intravenous cardiovascular support which is a well-known finding and supported by several previous studies [36, 37].

In this study comorbidity and acute illnesses severity assessments were conducted by CCI and SAPS II calculation, respectively and both were significantly associated with mortality at HDUs coinciding with other studies [29, 36].

The study did not show significant differences (P value <0.05) concerning the use of hemodialysis during stay at HDUs, but non-survivors had statistically significant higher mean BUN (48.3±36.4) coinciding with the results of other studies [34]. There were no significant differences (P value <0.05) concerning different serum electrolyte parameters on admission between the deceased patients at HDUs and those who were discharged alive, except for sodium categories on admission. The study showed that sodium categories had a significant association with death at HDUs (P value .014) coinciding with the reported importance of sodium level abnormalities on mortality among older adults [38, 39]. Additionally, non-survivors had a statistically significant lower PFR than the survivors (324.1±141.9 versus 361.2±113.4), supporting the reported negative linear association between oxygenation and mortality [40].

The study also estimated the prognostic value of various inflammation-based markers. First, CAR represents a combination of markers for systemic inflammation and nutritional status [14]. Although it was significantly associated with mortality in the univariate analysis, it didn't remain as a predictor of mortality in the regression model and its AUC was .49 (95% CI: .38-.61). Also, there was no significant association between CRP and in-hospital mortality. On the contrary, there are several studies demonstrating the prognostic value of CAR and CRP among hospitalized adults [14, 41, 42]. Second, the study didn't reveal a significant association between RDW, NLR and in-hospital mortality. ROC curves for RDW and NLR were used to assess their predictive ability and both had low AUC. It was .57 (95% CI: .46-.69) and .58 (95% CI: .47-.70) for RDW and NLR, respectively. This finding is inconsistent with other studies demonstrating their significant prognostic value [43, 44].

Despite the prognostic role of age among hospitalized elderly patients [23] and the associated risk of treatment restriction in older adults [37], this study showed that chronologic age is not a predictor of mortality and should not lead to treatment restriction. This finding is supported by other studies [7, 45, 46] as frailty, comorbidity and severity of illness are more important than age per se [47]. Also, gender was not found to be a predictor of mortality, supporting other findings of another prospective cohort study including hospitalized older adults [23, 46].

There were overlapping causes of admission at HDUs; this study demonstrated that ARI and sepsis are the 2 most common principal causes of admission among critically ill older adults, following previous reports [48, 49]. The association between different principal causes of admission and mortality can't be assessed in this study as Chi-Square test was invalid for the analysis of this categorical variable also Fisher's Exact test wasn't applicable as the used SPSS statistical package in the study provides analytical results for 2 × 2 contingency tables only [50].

Strengths and Limitations: major strengths of this study include its prospective design and involvement of older adults only. This is the first study incorporating the search for the predictive role of comorbidity, novel inflammatory markers and MDR-GNB infection among older adults during critical illness to provide a simple

prognostic model for this vulnerable group of patients. The key finding is the provision of an age-specific predictive model. The study has several limitations; first, it is a single institute study including a relatively small sample size especially for some variables such as NLR and without excluding patients with don't resuscitate orders. Second, diagnosis of dementia was merely based on clinical history and obtained by different clinicians from a proxy of each patient without objective cognitive assessment tools. Third, this novel prognostic model includes data that may not be attained on the first day of admission at HDUs that makes its application at the time of entry to HDUs limited in some degree, besides the combination of the use of MV with intravenous vasopressors / inotropes into one variable could lead to an inflation of its value in the model. Future studies should be conducted on a larger sample size and at more than one institutional centre as this study lacks a validation sample.

CONCLUSION: Dementia in clinical history, total protein and the use of MV and/or intravenous cardiovascular support are independent predictors of mortality in critically ill older adults that formulates a novel prognostic model. The model has strong discriminative abilities for mortality prediction. It could help clinicians dealing with geriatric patients, but it is not a self-fulfilling prophecy of death at the hospital and should not substitute clinical intuition and guidelines of management. It needs to be elucidated in other prospective multicenter studies with the investigation of additional variables for higher accuracy and better applicability.

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