ACC Acute and Critical Care

Acute and Critical Care 2024 August 39(3):390-399
https://doi.org/10.4266/acc.2024.00640

| pISSN 2586-6052 | eISSN 2586-6060

The impact of age on mortality in the intensive care unit: a retrospective cohort study in Malaysia

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Background: Age is a significant consideration for intensive care unit (ICU) admission. However, the reported associations between increasing age and mortality vary across studies, and data in the local context of Malaysia are lacking. The objective of the present study was to determine the impact of increasing age on ICU mortality.

Methods: A retrospective cohort study of ICU patients was conducted between January 2020 and November 2023 at a university hospital in Malaysia. Patients were classified into two categories according to age (years) and into four groups according to National Library of Medicine Medical Subject Headings (MeSH): young adult (19–24), adult (25–44), middle age (45–64), and elderly (≥65). The Cochran-Armitage test for trend and Cox proportional hazards regression analyses were performed to evaluate the impact of increasing age on ICU mortality.

Results: A total of 1,661 patients was analyzed. The Cochran-Armitage test showed a significant positive association between ICU mortality rate and age group ($Z=-4.86$, $P<0.01$) or MeSH category ($Z=-5.36$, $P<0.01$). After adjusting for other confounders, the strongest predictor for ICU mortality in the Cox proportional hazards regression analyses was age, with the elderly age group having the highest adjusted hazard ratio of 4.777 (95% CI, 1.128–20.231; $P=0.03$).

Conclusions: Age had a significant impact on ICU mortality in our cohort of critically ill patients.

Key Words: age groups; aged; intensive care units; mortality; prognosis

Original Article

Received: April 12, 2024
Revised: June 16, 2024
Accepted: June 27, 2024

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INTRODUCTION

The aging population presents a significant challenge to healthcare systems worldwide, with a growing number of elderly patients requiring intensive care unit (ICU) admission [1]. Elderly patients often present with complex medical conditions and are at increased risk of adverse outcomes compared to younger patients [2]. Understanding the outcomes of elderly patients admitted to the ICU is crucial for optimizing their care and resource allocation [3]. However, the reported associations of increasing age with clinical outcomes in this population vary across studies.

Some studies have suggested that increasing age is independently associated with higher ICU mortality rates, highlighting the physiological changes and comorbidities that often accompany aging as contributing factors [4,5]. It is hypothesized that advanced age is a marker of increased frailty and vulnerability to stressors that make elderly patients more susceptible to adverse outcomes in the ICU. However, other studies have challenged this notion, suggesting that age alone may not be a significant predictor of ICU mortality once other factors, such as comorbidities, severity of illness, and length of stay, are considered [6,7]. These studies have instead emphasized the importance of overall health status and functional capacity of elderly patients, rather than focusing solely on chronological age, when assessing their prognosis in the ICU [6]. Furthermore, as global demographics shift toward older populations, the impact of increasing age on ICU mortality needs to be closely studied in regional and local settings [8]. To our knowledge, there is a dearth of data regarding the impact of age on ICU mortality in the local context of Malaysia.

The primary objective of this study was to determine the impact of age on the risk of ICU mortality in our local setting. Secondary objectives were to determine if there are other variables that independently predict ICU mortality after adjusting for confounders when the study population was analyzed as a whole and when non-elderly and elderly groups were analyzed separately.

KEY MESSAGES

- Increasing age has a significant impact on intensive care unit (ICU) mortality. As age increases, the rate of mortality increases almost linearly.
- The highest risk of ICU mortality after adjusting for other confounders was elderly age (≥65 years old) with an adjusted hazard ratio of 4.777 (95% CI, 1.128–20.231; P=0.03).
- Severity of illness was also a significant risk factor for ICU mortality but had lower hazard ratio scores than for advanced age.

MATERIALS AND METHODS

Study Design, Settings, and Populations

This was an observational cohort study involving retrospective data retrieval conducted in the ICU of a teaching university hospital in Malaysia between January 1, 2020, and November 30, 2023. The hospital where the study was conducted is a major tertiary and teaching university hospital in the state of Kelantan, Malaysia. The inclusion criteria were adult patients (aged 18 years or older), admission to the ICU, and availability of follow-up data regarding the outcome at ICU discharge, either alive or deceased. Patients with significant amounts of missing data and those who were admitted to the ICU a second or subsequent time were excluded from the analyses to prevent duplication in calculation of the ICU mortality rate.

Data Collection

The variables retrieved were categorized into (1) baseline clinical characteristics, (2) clinical conditions on ICU admission, and (3) laboratory investigations on ICU admission. With respect to baseline clinical characteristics, data were retrieved regarding age, sex (male or female), comorbidities, admission source (Emergency Department, Ward, Operating Theatre, or Other Critical Care Units), operative status (postoperative or nonoperative), and emergency surgery before ICU admission.

With respect to clinical condition upon ICU admission, data were retrieved regarding the presence of an infection-related primary diagnosis, sepsis or septic shock, cardiac arrest upon or prior to ICU admission, diabetic ketoacidosis, and/or acute kidney injury; use of sedative-agent infusion, vasopressor or inotropic agents, renal replacement therapy, antibiotic, and/or mechanical ventilation; mean arterial pressure, heart rate, Glasgow Coma Scale, and the ratio of the partial pressure of oxygen in arterial blood (PaO_2) and fraction of inspired oxygen (FiO_2) delivered (PaO_2/FiO_2 ratio).

With respect to laboratory investigations on ICU admission, data were also collected on arterial blood pH, capillary blood glucose, hemoglobin, hematocrit, platelet and total white cell counts, urea, creatinine, total bilirubin, and electrolyte concentrations (sodium, potassium and bicarbonate).

Definitions of Elderly and Age Groupings

We defined the “elderly” as individuals aged 65 years and older, in accordance with the World Health Organization's definition. Two methods of age grouping were performed to study the impact of age on ICU mortality. The first age grouping method was according to decade: 18–29, 30–39, 40–49, 50–59, 60–69, 70–79, and 80–99 years; the last category combined two decades given there were only three patients in the 90–99 year group. The second age grouping method was based upon the age groups defined in the internationally recognized Medical Subject Headings (MeSH) from the National Library of Medicine: young adult (19–24 years old), adult (25–44 years old), middle-aged (45–64 years old), and aged (>65 years old). In this research, 18-year-olds were included in the young adult age group to align with Malaysia's Age of Majority Act 1971, which classifies 18-year-olds as adults [9]. Additionally, the term "aged" was changed to "elderly" for the purpose of clarity.

Statistical Analyses

Preliminary analyses

Preliminary analyses were conducted to convert age from years and months to years with a decimal point. Additionally, all quantitative variables were checked for uniformity of significant figures to three decimal points. The ratio between PaO_2 and FiO_2 was calculated using the values recorded at ICU admission.

Primary analyses

Primary analyses were conducted to assess the impact of increasing age on the risk of mortality during ICU stay. The Cochran-Armitage test was performed using age groupings according to decade and MeSH category to analyze any significant increasing or decreasing association in terms of the frequency of an event occurring in ordinal groups.

To adjust for potential confounders to predict ICU mortality, subsequent survival analyses were performed to study the impact of age on ICU mortality. These analyses were performed according to MeSH age group in proportional hazards multivariable Cox regression, with an event defined as mortality during ICU stay and the time-to-event as the number of days from ICU admission until mortality. All data retrieved from the ICU registry were first analyzed using simple Cox regression and are expressed as hazard ratios (HRs), with confidence intervals (CIs). Variables with P-values less than 0.05 were included in the final multivariable Cox regression analysis. The survival function curve plot was split into four age groups to study the impact of the ordinal pattern of increasing age group on the survival risk of patients adjusted for other potential confounders for mortality. During the multivariable Cox regression analysis, other risk factors for ICU mortality were also reported.

Statistical software

Primary analyses were performed using R, version 4.4.1 (R Foundation for Statistical Computing) with the DescTools package to perform the Cochran-Armitage test for trend to analyze ordinal patterns of independent variable impacts on a binary outcome. Secondary multivariable Cox regression analyses and survival function curve generation were performed using SPSS version 29.0 (IBM Corp.).

Research Ethics

This research received ethical approval from the Human Research Ethics Committee USM of Hospital Universiti Sains Malaysia (No. USM/JEPeM/KK/23121009). As this research involved only retrospective data collection, the requirement for informed consent was waived.

RESULTS

Baseline Characteristics

During the study period, from 1 January 2020 to 30 November 2023, 1969 patients were admitted to our ICU. Of these, 1,661 patients were included in the analysis after excluding those younger than 18 years, those with significant amounts of missing data, and those with second or subsequent ICU admissions during the same hospitalization. Figure 1 shows the flow diagram for inclusion of patients in the study. A comparison of the baseline characteristics of the study patients according to ICU survival is shown in Table 1.

Impact of Age on 30-Day ICU Mortality Rate

The effect of age group on 30-day ICU mortality rate was significant and was observed both when age was grouped as decade categories, as shown in Figure 2, or when using MeSH age categories, as shown in Figure 3. The Cochran-Armitage test showed a significant increase in ICU mortality rates as age group increased when using decade categories (Z=–4.86, dim=7, P<0.001) or MeSH age categories (Z=–5.36, dim=4, P<0.001), highlighting increasing age as a key factor in ICU mortality risk.

Survival Analyses to Evaluate the Impact of Increasing Age on ICU Mortality

All independent variables were tested to predict the outcome of ICU mortality using simple Cox regression, and all variables with P<0.05 were imputed into multivariable Cox regression modelling to adjust for all potential confounders to determine the most significant factors in predicting ICU mortality (Table 2).

The overall fit of the model was evaluated using the SPSS omnibus tests of model coefficients. The results indicated that the model was significant ($\chi^2(26)=167.649$, P<0.001), suggesting that the included predictors significantly improved the fit of the model compared to a model with no predictors. The significant chi-square values at each step reinforce the robustness of the model in predicting ICU mortality based on the includ-

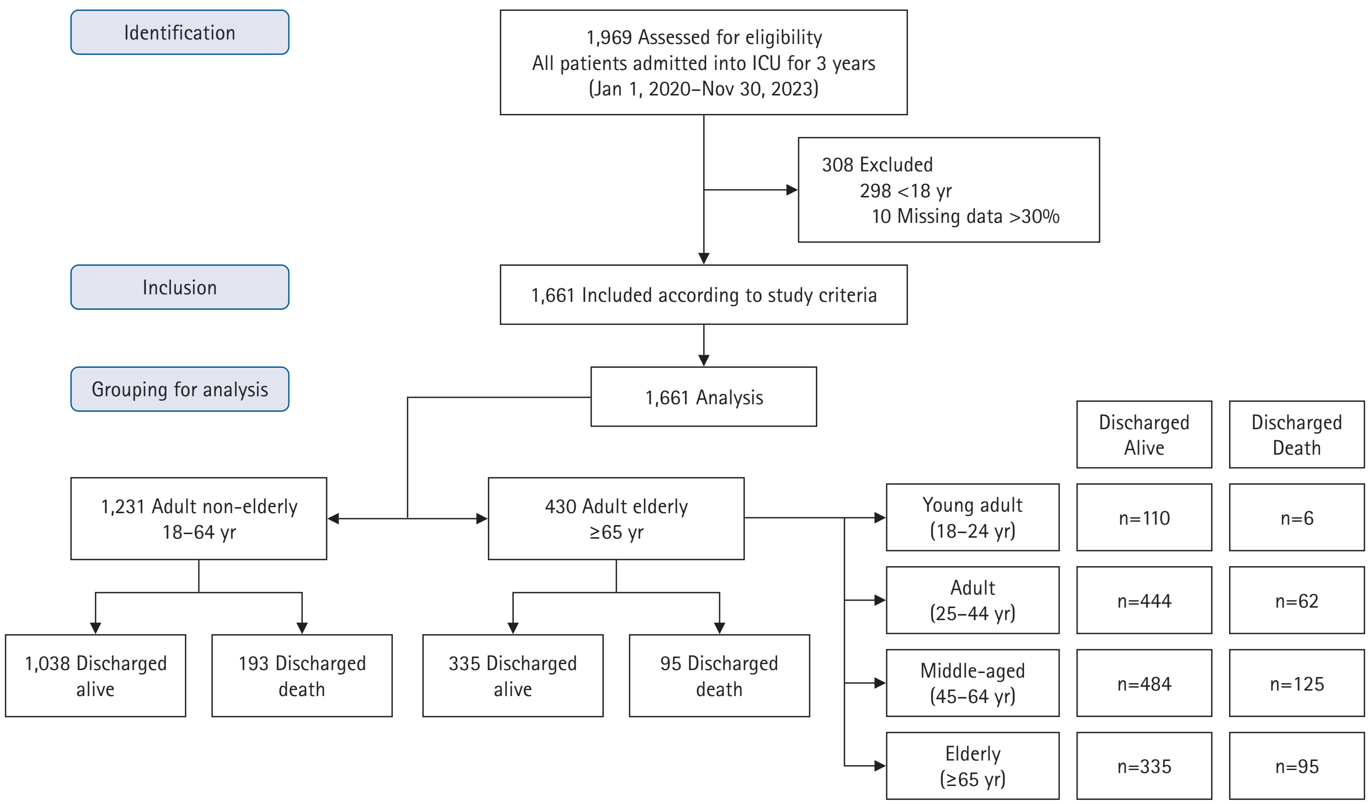

Figure 1. Flowchart of inclusion of patients and grouping for analysis. ICU: intensive care unit.

Table 1. Baseline characteristics and univariate analysis of study participants

Risk factor	Survivor	Non-survivor	P-value
Age group by decades (yr)			<0.001
18–29	228 (91.6)	21 (8.4)	
30–39	226 (85.6)	38 (14.4)	
40–49	215 (86.3)	34 (13.6)	
50–59	229 (79.0)	61 (21.0)	
60–69	263 (77.1)	78 (22.9)	
70–79	180 (78.6)	49 (21.4)	
80–99	32 (82.1)	7 (17.9)	
Age group by MeSH categories (yr)			0.03
18–24	110 (94.8)	6 (5.2)	
25–44	444 (87.7)	62 (12.3)	
45–64	484 (79.5)	125 (20.5)	
>65	335 (77.9)	95 (22.1)	
Sex			0.35
Male	642 (46.8)	159 (55.2)	
Female	731 (53.2)	129 (44.8)	
Comorbidity risk factor			
Diabetes mellitus	429 (31.2)	127 (44.1)	0.01
Hypertension	541 (39.4)	147 (51.0)	0.14
Chronic kidney disease	144 (10.5)	58 (20.1)	0.10

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Table 1. Continued

Risk factor	Survivor	Non-survivor	P-value
Admission source			0.07
Emergency department	428 (31.2)	115 (39.9)	
Ward	456 (33.2)	115 (39.9)	
Other critical care units	63 (4.6)	33 (11.5)	
Operating theater	426 (31.0)	25 (8.7)	
Diagnosis type			<0.001
Postoperative admission	556 (40.5)	27 (9.4)	
Nonoperative admission (medical)	817 (59.5)	261 (90.6)	
Type of surgery			0.39
Emergency surgery	198 (92.1)	17 (5.9)	
Elective surgery	1,175 (81.3)	271 (18.7)	
Clinical condition on ICU admission			
Infection-related primary diagnosis	745 (54.3)	212 (73.6)	0.61
Sepsis/septic shock	297 (21.6)	151 (52.4)	<0.001
Presence of cardiac arrest before admission	8 (0.6)	15 (5.2)	<0.001
Presence of DKA	66 (4.8)	12 (4.2)	0.61
Presence of AKI	135 (9.8)	53 (18.4)	0.78
Presence of sedation medication infusion	821 (59.8)	230 (79.9)	0.15
Presence of vasopressor or inotropic agents	498 (36.6)	212 (73.6)	<0.001
Cardiovascular component of SOFA score of 4	238 (17.3)	120 (41.7)	<0.001
Patients on RRT on day of admission in ICU	69 (5.0)	31 (10.8)	0.94
Antibiotics started	1,235 (89.9)	264 (91.7)	0.99
Invasive mechanically ventilation on admission	1,064 (77.5)	261 (90.6)	<0.001
Glasgow Coma Scale on admission	8.7±5.6	5.9±4.8	<0.001
PaO_2/FiO_2 ratio	337.3±134.0	245.1±125.0	<0.001
Mean arterial pressure (mm Hg)	90.2±15.1	83.5±14.7	<0.001
Heart rate on admission (beats/min)	92.8±20.5	102.2±24.9	<0.001
Laboratory investigations on ICU admission			
Arterial blood pH	7.35±0.10	7.26±0.16	<0.001
Capillary blood glucose (mmol/L)	9.0±4.0	9.1±4.3	0.88
Hemoglobin level (g/dl)	10.7±2.2	10.0±2.6	<0.001
Hematocrit (%)	32.5±6.8	30.5±7.7	<0.001
Platelets count ($\times 10^9$/L)	247.6±134.6	215.1±142.0	<0.001
White cells count ($\times 10^9$/L)	15.3±8.7	19.0±12.5	<0.001
Sodium level (mmol/L)	137.6±4.9	137.8±6.1	0.25
Potassium level (mmol/L)	4.1±0.7	4.4±1.0	<0.001
Urea level (mmol/L)	9.4±9.0	16.6±11.4	<0.001
Creatinine (umol/L)	176.5±251.5	303.4±290.8	<0.001
Bicarbonate level (mmol/L)	21.1±5.0	17.7±6.3	<0.001
Total bilirubin level (mmol/L)	20.6±36.1	30.4±43.4	<0.001

Values are presented as number (%) or mean±standard deviation. All variables were tested for statistical significance to predict outcome of ICU mortality individually using simple univariable Cox regression.
MeSH: Medical Subject Headings; ICU: intensive care unit; DKA: diabetic ketoacidosis; AKI: acute kidney injury; SOFA: Sequential Organ Failure Assessment; RRT: renal replacement therapy.

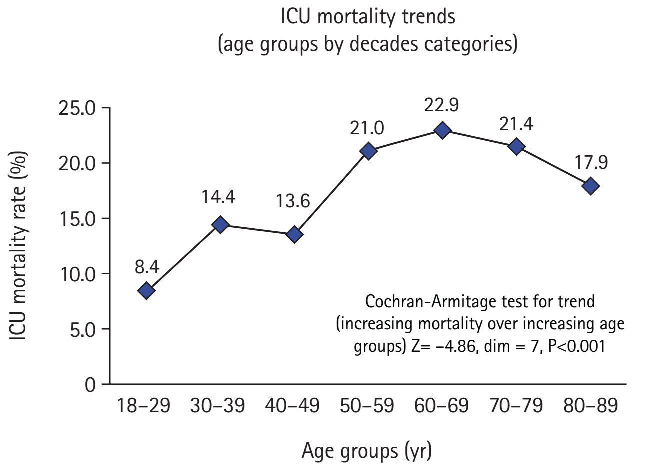

Figure 2. Intensive care unit (ICU) mortality trends (age groups by decade).

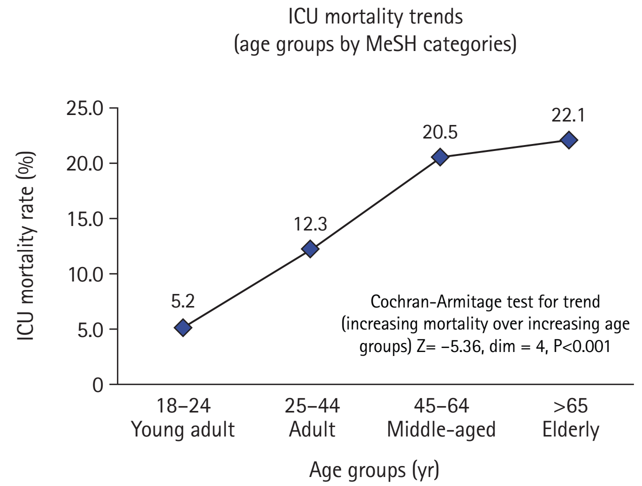

Figure 3. Intensive care unit (ICU) mortality trends (age groups by MeSH category).

Table 2. Cox proportional hazard regression analysis of predictor variables

Risk factor	Simple cox regression			Multivariable cox regression		
	Crude HR	95% CI	P-value	Adjusted HR	95% CI	P-value
Age	1.008	1.001–1.016	0.03			
Age group (yr): decade category	0.420					
18–29		Reference				
30–39	1.527	0.894–2.608	0.12			
40–49	1.401	0.813–2.416	0.22			
50–59	1.569	0.954–2.581	0.07			
60–69	1.716	1.058–2.783	0.03			
70–79	1.645	0.985–2.747	0.06			
80–99	2.118	0.899–4.990	0.09			
Age groups (yr): MeSH category			0.03			
18–24		Reference				
25–44	2.478	1.079–5.731	0.03			
45–64	2.899	1.277–6.581	0.01	3.877	1.213–12.392	0.02
>65	3.151	1.380–7.195	0.01	4.777	1.128–20.231	0.03
Sex						
Male		Reference				
Female	0.896	0.710–1.130	0.35			
Comorbidity risk factor						
Diabetes mellitus	1.362	1.079–1.721	0.01			
Hypertension	1.194	0.946–1.505	0.14			
Chronic kidney disease	1.277	0.956–1.706	0.10			
Admission source			0.07			
Emergency department		Reference				
Ward	0.925	0.555–0.925	0.56			
Other critical care units	1.198	0.365–1.198	0.37			
Operating theater	0.603	0.023–0.603	0.02			

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Table 2. Continued

Risk factor	Simple cox regression			Multivariable cox regression		
	Crude HR	95% CI	P-value	Adjusted HR	95% CI	P-value
Diagnosis type						
Postoperative admission		Reference				
Nonoperative admission	2.221	1.485–3.322	<0.001	1.753	1.141–2.694	0.01
Emergency surgery before admission	0.804	0.491–1.317	0.39			
Clinical condition on ICU admission						
Infection-related primary diagnosis	1.072	0.820–1.400	0.61			
Sepsis/septic shock	1.602	1.265–2.030	<0.001			
Presence of cardiac arrest before admission	2.971	1.762–5.010	<0.001	2.004	1.151–3.490	0.01
Presence of DKA	0.858	0.481–1.531	0.61			
Presence of AKI	1.043	0.773–1.409	0.78			
Presence of sedation medication infusion	1.244	0.927–1.669	0.15			
Presence of vasopressor or inotropic agents	1.943	1.487–2.539	<0.001			
Cardiovascular component of SOFA score (0–4)	1.202	1.121–1.288	<0.001			
Patients on RRT on day of admission in ICU	1.015	0.696–1.479	0.94			
Antibiotics started	0.997	0.656–1.515	0.99			
Glasgow coma scale on admission	0.970	0.946–0.994	0.01			
Invasive mechanically ventilation on admission	1.370	1.005–1.868	0.045			
PaO_2/FiO_2 ratio	0.997	0.996–0.998	<0.001	0.998	0.997–0.999	<0.01
Mean arterial pressure	0.983	0.975–0.991	<0.001			
Heart rate on admission	1.009	1.004–1.014	<0.001	1.007	1.001–1.012	0.01
Laboratory investigations on ICU admission						
Arterial blood pH	0.028	0.012–0.060	<0.001			
Capillary blood glucose	0.998	0.969–1.030	0.88			
Hemoglobin level	0.920	0.875–0.970	<0.001	0.931	0.882–0.982	0.01
Hematocrit	0.978	0.962–0.990	0.01			
Platelets count	0.998	0.998–0.999	<0.001	0.998	0.997–0.999	<0.01
White cells count	1.016	1.006–1.026	<0.001			
Sodium level	0.988	0.968–1.008	0.25			
Potassium level	1.347	1.192–1.522	<0.001	1.247	1.069–1.455	<0.01
Urea level	1.019	1.009–1.028	<0.001			
Creatinine	1.001	1.000–1.001	<0.001			
Bicarbonate level	0.928	0.928–0.948	<0.001	0.950	0.927–0.974	<0.01
Total bilirubin level	1.003	1.001–1.005	<0.001			

All variables were tested for statistical significance to predict outcome of ICU mortality individually using simple univariable cox. Regression, subsequently all predictors with P-value <0.05 were imputed into multivariable cox regression to adjust for confounders to generate adjusted hazard ratio for the most significant prediction of ICU mortality.
HR: hazard ratio; MeSH: Medical Subject Headings; ICU: intensive care unit; DKA: diabetic ketoacidosis; AKI: acute kidney injury; SOFA: Sequential Organ Failure Assessment; RRT: renal replacement therapy.

ed variables.

The most significant risk factor predicting ICU mortality was increasing age according to MeSH age category. The survival curve in Figure 4 demonstrates that the youngest age group exhibited the highest survival probability over time. Moreover, a distinct trend was evident: as age increased, the survival probability decreased, indicating that age plays a role in time to mortality in this analysis.

The 30-day ICU mortality rates were 14% for young adults, 30% for adults, 44% for middle-aged, and 51% for elderly, as shown in Figure 4. The disparity between the curves of the middle-aged and elderly groups was significant compared directly to the young-adult age group (adjusted HR, 3.877 and 4.777 for the middle-aged and elderly groups, respectively,

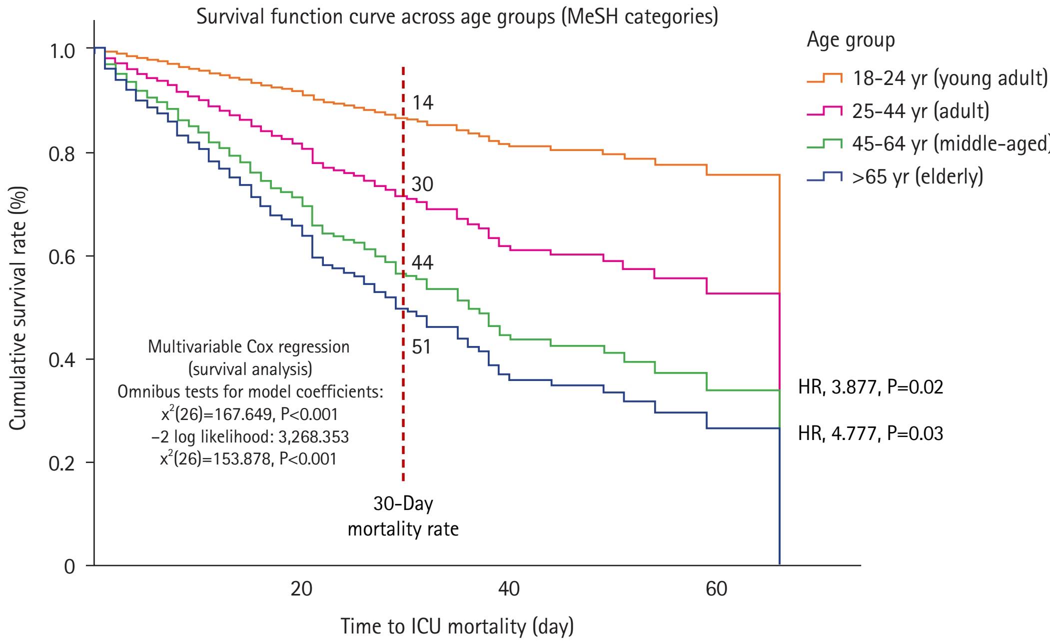

Figure 4. Survival curve function for intensive care unit (ICU) mortality by MeSH age category. HR: hazard ratio.

with a P<0.05 for both).

In addition to increasing age, other risk factors were also significant predictors of ICU mortality. These were non-operative (medical) cases (adjusted HR, 1.73; 95% CI, 1.13–2.67; P=0.01), presence of cardiac arrest prior to admission (adjusted HR, 2.05; 95% CI, 1.17–3.56; P=0.01), low PaO_2/FiO_2 ratio (adjusted HR, 0.998; 95% CI, 0.997–0.999), high heart rate (adjusted HR, 1.006; 95% CI, 1.001–1.011; P=0.03), low hemoglobin concentration (adjusted HR, 0.93; 95% CI, 0.88–0.98; P=0.01), low platelet count (adjusted HR, 0.998; 95% CI, 0.998–0.999), high potassium (adjusted HR, 1.212; 95% CI, 1.03–1.43; P=0.02), and low bicarbonate (adjusted HR, 0.96; 95% CI, 0.93–0.99; P=0.02).

DISCUSSION

Our results from various analyses consistently demonstrated that increasing age was significantly associated with rate of ICU mortality whether analyzed using age grouped by decade categories or the MeSH age group categories. After adjusting for potential confounders in multivariable Cox regression survival analyses, increasing age (from young adult to elderly) was the most significant risk factor predicting ICU mortality; elderly age was the most significant risk factor in our study, with the highest HR of 4.777.

The association of increasing ICU mortality rates with advancing age groups in our study aligns with findings from a retrospective study conducted in the Republic of Korea [10]. In that study, patients admitted to the ICU demonstrated progressively greater HRs for each 10-year increase in age group compared with the reference group (20–29 years old), with the highest HR reported for the group older than 80 years. In the previous study, the endpoint for measuring the death outcome was set at 90 days after ICU admission, while our study focused on mortality in the ICU. In our study, although a univariable statistical test (Cochran-Armitage test) showed increasing mortality to be significantly associated with increasing age when using decade categories, this trend not significant when analyzed using multivariable Cox regression survival analyses to adjust for other potential confounders.

The multi-center retrospective "CIMbA-LT" study conducted in Portugal employed comparable statistical analyses to both our study and the aforementioned Korean study and reported a similar trend of increasing ICU mortality with increasing patient age [10]. However, the CIMbA-LT study age groupings appear to have emphasized elderly patients rather than employing equally distributed age groupings. The investigators demonstrated a significant divergence in cumulative survival curve functions among the age groups, with the most elderly group (>80 years old) exhibiting the highest hazard ratio. This finding was consistent with those of our study, in which the elderly had the highest hazard ratio for ICU mortality.

In addition to increasing age as the strongest risk factor for ICU mortality, the severity of illness also was also significant associated with ICU mortality. The presence of cardiac arrest prior to admission, lower PaO_2:FiO_2 ratio, higher heart rate, lower hemoglobin concentration, lower platelet count, and higher potassium and lower bicarbonate concentrations all significantly predicted ICU mortality, with higher hazard ratios for increasing age groups. These risk factors are consistent with the typical features of critically ill patients with increasing severity of illness.

Our study revealed that both increasing age and severity of illness were significantly associated with ICU mortality. These findings were consistent with those of a previous comprehensive systematic review that highlighted age, disease severity score, functional status, and comorbidities as significant risk factors for mortality in the ICU, especially in the elderly age groups [11].

The main strength of our study lies in the recruitment of all consecutive ICU admissions over a 3-year study period, resulting in inclusion of a relatively large number of patients in the analyses. However, our study did have two significant limitations. First, the results obtained were specific to our single-center dataset, and their generalizability to external populations remains uncertain. Second, due to the retrospective nature of our study design, we were unable to gather additional data beyond that routinely available. The data did not include variables that are particularly relevant in the elderly population, such as frailty, nutritional status, and functional status, or illness severity scores like the Sequential Organ Failure Assessment Score, which are not regularly assessed in our clinical setting. Therefore, a future prospective multi-center study is warranted to confirm the impact of increasing age on ICU mortality in our local population.

Our study demonstrates that age is a robust predictor of ICU mortality, particularly highlighting the heightened risk within the elderly age group. These results underscore the importance of age as a key factor in predicting outcomes in ICU settings. Such insights can significantly improve the decision-making process regarding future ICU admissions, aiding healthcare providers in making more informed and tailored choices to optimize patient care and outcomes. This information could ultimately lead to more targeted interventions and strategies aimed at improving the prognosis and quality of care for elderly patients in the ICU.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

FUNDING

This research was partially funded by a grant from the Malaysian Ministry of Higher Education (FRGS/1/2020/SKK01/USM/ 03/1).

ACKNOWLEDGMENTS

None.

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Conceptualization: AJI, MBMN, WFWMS. Data curation: MBMN, WFWMS. Formal analysis: AJI. Funding acquisition: WFWMS. Methodology: AJI, WMNWH. Project administration: WMNWH, MBMN, WFWMS. Visualization: AJI. Writing – original draft: AJI. Writing – review & editing: all authors. All authors read and agreed to the published version of the manuscript.

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