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Predictors of Survival Among the Oldest Old Following Acute Hospital Admission: Insights From Clinical and Biochemical Factors

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Abstract

Understanding the factors influencing survival in oldest old population is crucial for providing appropriate care and improving outcomes. This prospective observational study aimed to investigate the determinants of survival in acutely ill oldest old patients during acute hospitalization and 1-month follow-up. Various geriatric domains and biochemical markers were assessed. Among the 70 included patients with a median age of 87 (Inter quartile range: 85–90), the presence of diabetes, delirium, tachypnea, and high sirtuin-5 levels were associated with reduced in-hospital survival. Non-survivors had raised levels of Sirtuin 1 and Sirtuin 5, with an increase of 43% and 70%, respectively. At 1 month, delirium and diabetes were still associated with reduced survival. These findings suggest that type-2 diabetes, delirium, tachypnea, and high sirtuin-5 levels could serve as predictors of reduced survival in acutely ill, hospitalized oldest old patients.

Keywords

oldest old, acute illness, Acute Physiology and Chronic Health Evaluation (APACHE) III, survival, Sirtuins, Sestrins

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Introduction

Advancements in healthcare have contributed to an increase in life expectancy, resulting in a growing population of older individuals, particularly those aged 80 years and above (Boudoulas et al., 2017). The population of older people with multimorbidity is increasing partly due to improved survival at higher ages (Barnett et al., 2012). This population needs a high level of individual assessment and personalized care planning as disease count alone does not grasp the individual patient's complex health and life situation very well (Marengoni et al., 2019). Also, this age group is often susceptible to acute illnesses, leading to hospital admissions and an increased mortality risk (Esme et al., 2019). In prior studies done on young old adults(>65 years), functional status of the older patients has been found to be important factor predicting survival after acute hospitalization (Cebollero et al., 2021; Ryg et al., 2021). Other factors such as malnutrition, delirium, premorbid impaired instrumental activity of daily living, high fall risk score and high Charlson's comorbidity score have been found to associated with increased mortality after hospitalization (Buurman et al., 2011).

Biochemical markers like Sirtuins are vital in cellular processes such as genomic stability and stress response. Sirtuin1 protects adipose tissue and the liver, regulating glucose homeostasis and fat metabolism for metabolic health (Pedersen et al., 2008). Sirtuin3 manages energy demand and eliminates reactive oxygen species to maintain cellular balance (Ansari et al., 2017). Sirtuin5 controls protein functions through various processes.

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Expression levels of Sirtuin1, Sirtuin3, and Sirtuin6 genes have implications for predicting survival outcomes in triple-negative breast cancer (Uzelac et al., 2020). Sestrin proteins, including Sestrin1 (sesn1) and Sestrin2 (sesn2), reduce reactive oxygen species and regulate autophagy under stress conditions. Sesn1 plays a role in DNA damage and oxidative stress response, maintaining genomic integrity (Chen et al., 2022). Sesn2 is associated with improved skeletal muscle function and is potentially a survival predictor in cancer patients (Wei et al., 2015).

The present study aimed to identify the factors that predict in-hospital and 1-month survival in older patients aged 85 years and above who were admitted with acute illnesses. We comprehensively examined a range of demographic factors, comorbidities, the diagnosis of acute illness, and the Acute Physiology and Chronic Health Evaluation (APACHE III) score (Knaus et al., 1991) and its individual components. Additionally, we investigated the influence of geriatric syndromes, including delirium, activities of daily living (ADL), nutritional status, depression, fall risk, and frailty. Recognizing the role of biomarkers in predicting patient outcomes, we also explored the association between survival sirtuin 1, 3, and 5 and sestrin 1 and 2.

By analyzing a comprehensive set of factors, we aimed to provide insights into the predictors of survival in oldest old patients admitted with acute illnesses. The findings from this study will contribute to a better understanding of the complex interactions between these factors. They may have implications for tailoring interventions and improving patient outcomes in this vulnerable population.

Materials and Methods

Subject Characteristics

This prospective observational study was conducted at a tertiary care hospital in New Delhi, India, in the inpatient department of Geriatric Medicine. Enrollment for the study occurred between October 2018 and March 2020. All patients aged 85 years and above admitted with acute illness during the enrollment period were eligible to participate. The study received approval from the Institute Ethics Committee and followed the ethical guidelines of the Declaration of Helsinki and Good Clinical Practice Guidelines.

Inclusion criteria encompassed the presence of acute illness and consent from the patient or a legally authorized representative (LAR). Acute illness was defined as illness of less than 1 month duration. Exclusion criteria involved individuals who died within 24 hr of hospitalization, those with a history of admission in the previous month, and patients on mechanical ventilators at the time of admission.

The study aimed to determine the factors associated with decreased in-hospital survival in patients aged above 85 years who were admitted with acute illness. The secondary objectives were to identify factors associated with decreased 1-month survival and investigate the association of serum markers (sirtuin and sestrin). The possible factors affecting in-hospital outcome and cumulative outcome were age, gender, comorbidities, the diagnosis of acute illness, APACHE III score and its individual components, geriatric syndromes, including delirium, activities of daily living (ADL), IADL, nutritional status, depression, fall risk, frailty and biomarkers sirtuin 1, sirtuin 3, sirtuin 5, sestrin1, and sestrin 2.

Sample Size

It is worth noting that no a priori sample size calculation was conducted for this study. Instead, a sample size of 70 cases was determined based on the available hospitalization data from previous years and considerations of feasibility.

Assessment

Written informed consent was obtained from patients or their legally authorized representatives (LAR) before conducting a comprehensive assessment. This assessment included demographic information, socioeconomic status, presenting complaints, APACHE III score, and evaluation of comorbidities like hypertension, type-2 diabetes, chronic obstructive lung disease, coronary artery disease, chronic kidney disease and cerebrovascular accidents, Geriatric assessment components covered activities of daily living (ADL) using the Barthel ADL Index (Collin et al., 1988), instrumental activities of daily living (IADL) using Lawton's IADL (Lawton & Brody, 1969), depression using the geriatric depression scale (GDS) (Sheikh & Yesavage, 2012), nutritional status using the Mini-nutritional assessment-short form (MNA-SF) (Kaiser et al., 2009), delirium using the confusion assessment method (CAM) (Inouye et al., 1990), cognition using the Hindi Mental Status Examination (HMSE) (Ganguli et al., 1995), falls using the Morse Fall risk score (Morse et al., 1989), frailty using the Rockwood scale (Rockwood et al., 2005), and comorbidities using Charlson's comorbidity index (CCI) (Frenkel et al., 2014).

Biochemical Analysis

Blood samples were collected from participants to assess initial laboratory parameters, including complete blood count (CBC), arterial blood gas analysis, and liver and renal function tests. Two milliliters (ml) of venous blood were collected and allowed to clot for 1 hr. The samples were then centrifuged at 800*g* for 10 min to obtain serum, which was stored at −80°C in multiple small aliquots to maintain sample integrity and avoid freeze-thaw cycles.

Surface Plasmon Resonance (SPR)

For SPR analysis, the serum specimen was gradually thawed once and analyzed immediately. Biacore 3000

system (Wipro GE Healthcare, UK) was used to quantify SIRT1, SIRT3, SIRT5, Sesn1, and Sesn2 levels in the serum of study participants. SPR provides a unique platform for analyzing specific bimolecular interactions in a real-time, label-free manner. The mouse anti-human SIRT1 monoclonal IgG (Santa Cruz Biotechnology, CA, USA), rabbit anti-human SIRT3 polyclonal IgG (Santa Cruz Biotechnology), rabbit anti-human SIRT5 polyclonal IgG (Santa Cruz Biotechnology), mouse anti-human Sesn 1 IgG (Santa Cruz Biotechnology, USA) and rabbit anti-human Sesn 2 IgG (Santa Cruz Biotechnology, USA), were immobilized using the amine coupling reaction kit (Wipro GE Healthcare, Sweden) on two different flow cells of CM5 sensor chip (Wipro GE Healthcare, Sweden). The different concentrations of recombinant SIRT1, SIRT3, SIRT5, Sesn1, and Sesn2 proteins were passed over their respective flow cell with an immobilized antibody that interacted specifically with the protein and generated an SPR signal (measured as the response unit, RU). The standard curve was generated by plotting the RU against known concentrations of recombinant SIRT1, SIRT3, SIRT5, Sesn1, and Sesn2 proteins. The serum samples were diluted (1:70) in HBS EP buffer before running on the sensor chip, and generated RU was noted. The serum protein concentrations of SIRT1, SIRT3, SIRT5, Sesn1, and Sesn2 in all the samples were determined from their standard curve. All the interaction experiments were performed at 25°C with HBS-EP (Wipro GE Healthcare, UK) as a running buffer.

In-Hospital Management and Follow-Up

A multidisciplinary team of geriatricians, nurses, dieticians, and physiotherapists provided comprehensive care for hospitalized patients. Patient outcomes were categorized as discharge, discharge to long-term care facilities, or in-hospital death. Surviving patients were followed up via telephone 4 weeks after discharge to assess their functional status and gather information on re-hospitalization and mortality. Caregivers were also interviewed to obtain details on the cause of death for non-surviving patients. The collaboration of the multidisciplinary team and post-discharge assessments provided valuable insights into patient outcomes, including functional status, re-hospitalization rates, and causes of mortality.

Statistical Analysis

The data collected was recorded in an Excel spreadsheet and analyzed using STATA version 14.0 (StataCorp, 2015). The subjects included in the study were categorized into two groups: survivors and non-survivors. Categorical variables were presented as numbers with percentages. In contrast, continuous variables were reported as either mean (standard deviation) or median (range).

To compare the differences of quantitative variables between the two groups, the Student *t*-test or Wilcoxon rank sum test was employed, while the Chi-square test or Fisher's exact test was used to assess the association between categorical variables. Furthermore, multivariable Cox regression analysis was conducted to identify the factors associated with the time to event outcome, with the results presented as hazard ratios (HR) along with their corresponding 95% confidence intervals (95% CI). The candidate variables for the multivariable analysis were selected through bivariate analysis, using a threshold probability of .20. The stepwise procedure was then applied, with an entry probability of 5% and a removal probability of 10%. Statistical significance was set at a *p*-value less than .05.

Results

Patient Characteristics

During the designated study period, 94 patients aged 85 years and above were admitted to the hospital. Among them, 70 patients met the inclusion criteria and were included in the analysis. The median age of the participants was 87 years, with 36 (51.4%) being male. The median duration of hospitalization was 7 days (range 6–11). Regarding comorbidities, hypertension was the most prevalent, observed in 43 patients (61.4%), followed by type-2 diabetes in 21 patients (30%) and chronic obstructive pulmonary disease in 14 patients (20%) (Table 1). The leading causes of admission were lower respiratory tract infections, accounting for 70 cases (25.7%), and urinary tract infections, accounting for 14 cases (20%).

In-Hospital Outcome

Among the study participants, there were 11 events during the hospital stay. The median age of survivors (87 years) and non-survivors (89 years) was comparable. Univariate analysis (Figure 1) revealed that factors such as type-2 diabetes, high APACHE III score (>66), tachypnea, and delirium were associated with a higher risk of mortality. Additionally, both sirtuin 1 and sirtuin 5 were found to be associated with mortality. In the multivariate analysis, diabetes, tachypnea, delirium, and sirtuin 5 were identified as significant predictors of survival. Though, APACHE III score was significantly associated with reduced survival on univariate analysis, it was not found to significantly associated with reduced survival on multivariable analysis.

Altered Expression of Metabolic Regulator Protein-Sirtuins

The Sirtuin 1 and Sirtuin 5 protein expression analysis revealed a significant increase in non-survivors. When comparing survivors and non-survivors, the expression

Table 1. Baseline Characteristics of Participants With In-Hospital and Cumulative Outcome.

Variables		$n=70$	In-hospital outcome			Cumulative outcome		
			Survivors ($n=59$)	Non-survivors ($n=11$)	p-Value	Survivors ($n=52$)	Non-survivors ($n=18$)	p-Value
Demographic details								
Age, median (range)			87 (85–103)	89 (85–100)	.50	88(85–103)	86(85–89)	.64
Age	≤90	56	47 (79.7)	9 (81.8)		40 (76.92)	16 (88.89)	
	>90	14	12 (20.3)	2 (18.2)		12 (23.08)	2 (11.11)	
Gender	Male	36	31 (52.5)	5 (45.5)	1	26 (50.00)	10 (55.56)	1
	Female	34	28 (47.5)	6 (54.5)	.75	26 (50.00)	8 (44.44)	.78
MKS, median (range)			18 (5–29)	18 (5–29)	.54	16 (5–29)	18 (8–28)	.63
Comorbidities								
Hypertension		43	34 (57.6)	9 (81.8)	.18	30 (57.7)	13 (72.2)	.4
Type-2 diabetes		21	14 (23.7)	7 (63.6)	.01	12 (23.1)	9 (50.0)	.04
COPD		14	10 (16.9)	4 (36.4)	.21	8 (15.4)	6 (33.3)	.16
CAD		13	12 (20.3)	1 (0.1)	.36	9(15.25)	3(30.00)	.47
CKD		4	2 (3.4)	2 (18.2)	.11	2 (3.9)	2 (11.1)	.27
CVA		7	6 (10.2)	1 (9.1)	1.00	5 (9.6)	2 (11.1)	1.00
Acute illness								
LRTI		18	13 (22.0)	5 (45.5)	.13	10 (19.2)	8 (44.4)	.05
AECOPD		5	4 (6.78)	1 (9.09)	.58	3 (5.8)	2 (11.1)	.59
UTI		14	13 (22.0)	1 (9.1)	.44	12 (23.1)	2 (11.1)	.49
Fall		8	6 (10.2)	2 (18.2)	.60	5 (9.7)	3 (16.7)	.41
Acute gastroenteritis		4	4 (6.8)	0 (0)	.49	2 (3.9)	1 (5.6)	.56
Electrolyte imbalance		6	6 (10.2)	0 (0)	.58	10 (19.2)	8 (44.4)	.32
CVA		3	3 (5.1)	0 (0)	.59	3 (5.8)	2 (11.1)	1
Physiological and lab parameters, median (range)								
APACHE III	<66	44	41 (69.49)	3 (27.27)	1	46(79.31)	8(44.44)	1
	≥66	26	18 (30.51)	8 (72.73)	<.001	12(20.69)	10(66.66)	<.001
Pulse (beats per min)			86 (45–120)	90 (60–121)	.94	86.5 (45–120)	88 (60–121)	.76
MAP			93 (56–149)	88 (60–121)	.71	92.5 (56–146)	94 (60–121)	.4
Temperature (degree Celsius)			37 (37–39.4)	37 (37–38)	.28	37 (37–39.4)	37 (37–39.4)	.72
Respiratory rate (per min)			18 (12–38)	20 (16–45)	<.001	18 (12–38)	20 (14–45)	.11
WBC ($\times 10^3$)			7.7 (3.2–22.8)	13.12(4.9–17.4)	<.001	7.75 (3.2–22.8)	12.17 (3.52–17.18)	.1
Serum sodium (mmol/l)			136 (122–157)	139 (120–148)	.32	136 (122–157)	137.5 (119–148)	.74
GCS			15 (5–15)	15 (10–15)	.1	15 (5–15)	15 (8–15)	.08
Geriatric syndrome								
Delirium		18	11 (18.6)	7 (63.6)	<.001	8 (15.4)	10 (55.6)	<.001
ADL before the onset of illness			20 (0–20)	19 (0–20)	.12	20 (0–20)	19 (0–20)	.25
ADL after admission			11 (0–20)	10 (0–20)	.02	10.30 (0–20)	5 (0–11)	<.001
MNS			9 (2–14)	5 (2–12)	.11	9 (2–14)	6 (2–12)	.01
GDS			3 (0–14)	3 (0–4)	.7	3 (0–14)	3 (0–7)	.99
MFS			25 (0–105)	15 (0–55)	.58	25 (0–105)	22.5 (0–75)	.99
RS			13 (4–20)	15 (7–20)	.15	13 (4–19)	16 (7–20)	.01

Note. MKS = Modified Kuppuswamy Scale; COPD = chronic obstructive pulmonary diseases; CAD = coronary artery disease; CKD = chronic kidney disease; CVA = cerebrovascular accident; LRTI = lower respiratory tract infection; AECOPD = acute exacerbation of COPD; UTI = urinary tract infection; APACHE III = acute physiology and chronic health evaluation III; MAP = mean arterial pressure; WBC = white blood cells; GCS = Glasgow coma scale; ADL = activity of daily living; MNS = mini nutritional scale; GDS = geriatric depression scale; MFS = Morse fall scale; RS = Rockwood scale.

of Sirtuin 1 showed a 43% increase. In comparison, the expression of Sirtuin 5 exhibited a larger increase of 70% (Figure 2). On the other hand, a relatively smaller increase of 14% in the expression of Sirtuin 3 was observed in non-survivors. These findings suggest a notable upregulation of Sirtuin 1 and Sirtuin 5, and a lesser upregulation of Sirtuin 3, in non-survivors compared to survivors.

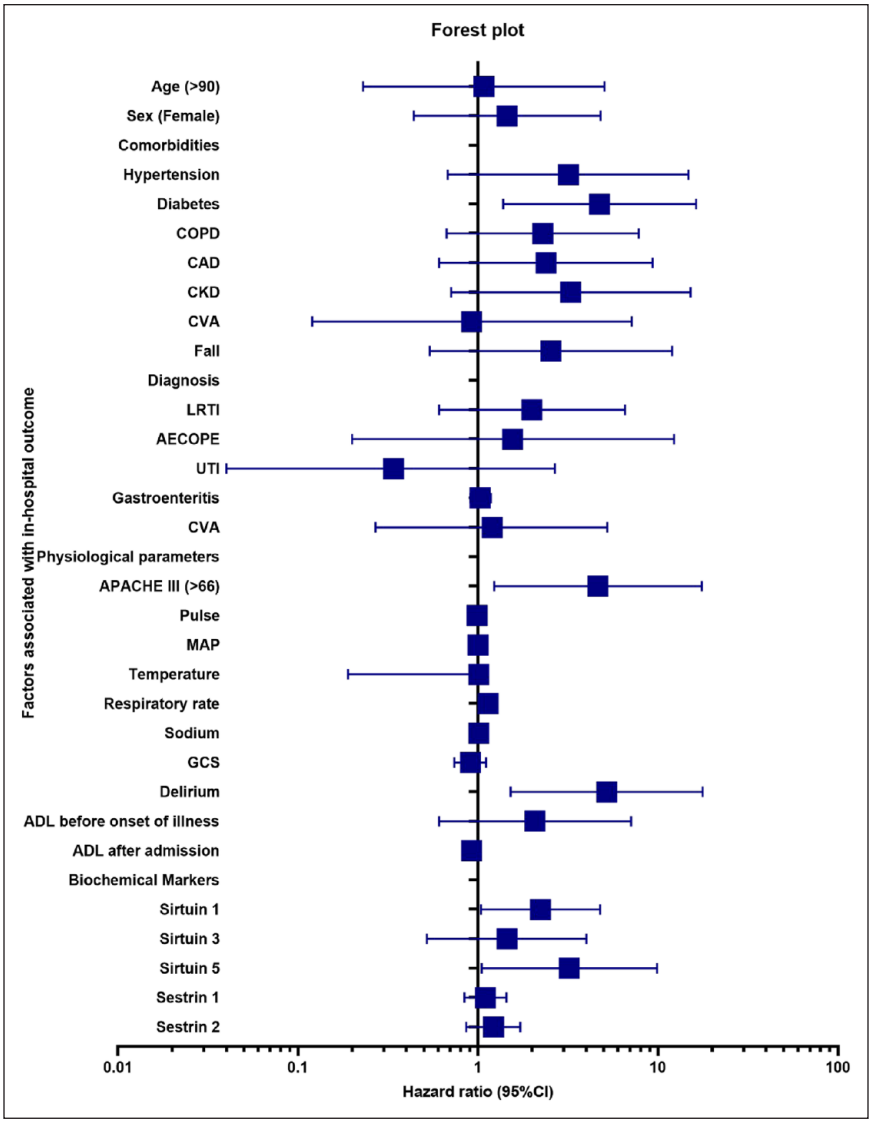

Figure 1. Forest plot representing the association between variables and in-hospital outcome -univariate analysis.

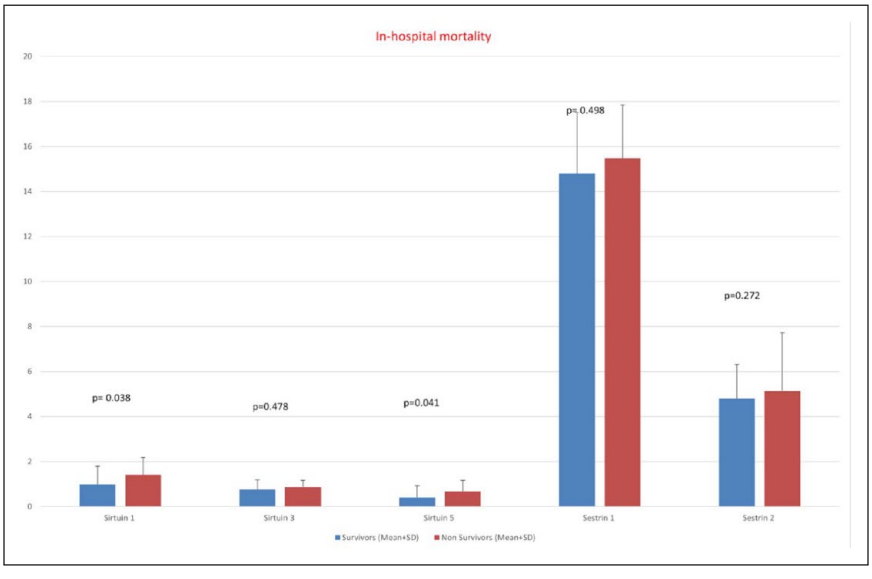

Figure 2. Represents the bar diagram comparing the biomarker levels between survivors and non-survivors, univariate analysis.

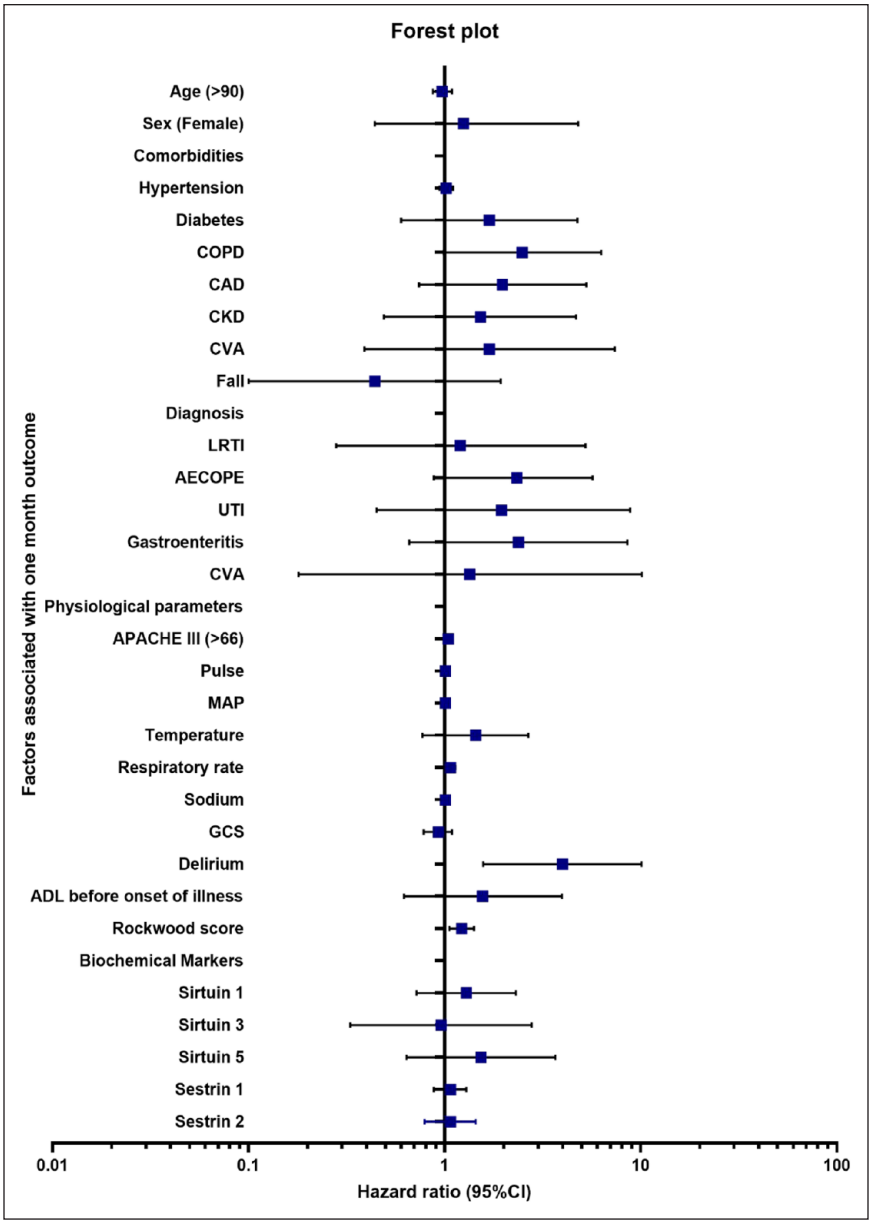

Figure 3. Forest plot representing the univariate analysis of variables with outcome at 1 month.

Comparable Expression of Stress-Induced Proteins Sestrins

In our quantitative analysis, there was no significant difference in Sestrin 1 and Sestrin 2 expression between the survivors and non-survivors. When comparing the two groups, a slight increase of 4% was observed in the expression of Sestrin 1, while an 8% increase was noted for Sestrin 2.

In summary, the analysis of biochemical predictors revealed that Sirtuin 1 and Sirtuin 5 showed significant elevation in non-survivors, with hazard ratios of 2.23 (95% CI [1.04, 4.77]) and 3.22 (95% CI [1.05, 9.88]), respectively. On the other hand, the protein molecules Sirtuin 3, Sestrin 1, and Sestrin 2 showed comparable expression levels between the two groups.

Cumulative Outcome

At 1-month follow-up, 52 patients were still alive, and seven new events occurred. Univariate analysis (Figure 3) revealed that a high APACHE III score (70.8%vs. 55.6%, HR: 1.04; 95% CI [1.01, 1.07]), tachypnea (HR: 1.07; 95% CI [1.01, 1.13]), delirium (55.6%vs. 15.4%, HR: 3.99; 95% CI [1.6, 10.1]), and a high score on the Rockwood scale (16 vs. 13, HR: 1.22; 95% CI [1.06, 1.41]) were significantly associated with lower 1-month survival. However, the biochemical markers did not correlate with survival at 1 month.

In the multivariate analysis, diabetes (HR: 4.36; 95% CI [1.4, 13.3]) and the presence of delirium (HR: 4.20; 95% CI [1.5, 11.7]) were found to be significantly associated with 1-month survival (Table 2). Though APACHE

Table 2. Multivariate Analysis for In-Hospital Outcome and Cumulative Outcome.

	In-hospital outcome	Cumulative outcome
Variables	Hazard ratio [95% CI]	Hazard ratio [95% CI]
Diabetes	13.85 [2.63, 72.88]	4.36 [1.43, 13.29]
Respiratory rate	1.12 [1.02, 1.22]	-
Delirium	8.32 [1.63, 42.35]	4.20 [1.51, 11.7]
Sirtuin 5	6.2 [1.26, 30.52]	-

III score and high Rockwood score were statistically significant on univariate analysis, they were not found to significantly associated with reduced survival on multivariable analysis.

Discussion

This study aimed to identify factors associated with survival in the oldest old population following hospital admission for acute illness. It is the first study from the Indian subcontinent and yielded significant findings: (i) Respiratory and urinary tract infections were the most common causes of hospitalization, (ii) Delirium, tachypnea, and diabetes significantly predict lower in-hospital survival, (iii) Delirium and diabetes also predicted survival after 1 month, indicating their impact on longer-term prognosis, and (iv) Sirtuin 5 emerged as a promising biochemical marker for predicting in-hospital survival.

Diabetes is recognized as a significant complication risk factor, including mortality, among hospitalized patients. Individuals who develop diabetes after the age of 65 are found to have a reduced life expectancy of at least 4 years (Bellary et al., 2021). Furthermore, in older adults, long-standing diabetes exerts a substantial and independent influence on short-term mortality compared to their non-diabetic counterparts of the same age group, as supported by studies such as the one conducted by Tang et al. (2020).

Our study observed a similar trend where non-diabetic patients exhibited better survival rates during their hospital stay and at the 1-month follow-up. These findings align with the results of other studies conducted in high-income countries, such as Shehab et al. (2019) and Donahoe et al. (2007). Taken together, these findings emphasize the significant impact of diabetes on patient outcomes, particularly in the context of older adults. Identifying diabetes as a predictor of lower survival rates highlights the importance of effective management and targeted interventions for this population to improve overall patient outcomes and reduce mortality.

Delirium is a condition that carries significant implications for patient outcomes, including increased morbidity, mortality, and loss of independence. In our study, we observed a significant association between the diagnosis of delirium upon admission and reduced survival rates during the hospital stay and 1 month after discharge. It is important to note that delirium may not simply serve as a marker for individuals with underlying severe illnesses who are more likely to die, but rather, it may confer its own independent risk of mortality.

The presence of delirium disrupts an individual's ability to effectively engage with their environment, leading to a detrimental cycle of declining functionality and adverse events that can ultimately culminate in death, as highlighted by the research conducted by Kiely et al. (2009). Furthermore, delirium increases the likelihood of requiring long-term care. It significantly impacts both subjective and measured cognition, contributing to additional complications and diminishing overall survival, as demonstrated by the findings of Bickel et al. (2008). These findings underscore the critical importance of recognizing and addressing delirium in older patients, as it not only serves as a consequence of underlying illness but also acts as an independent risk factor for adverse outcomes, including mortality.

Tachypnea, characterized by rapid breathing, is a prevalent clinical abnormality observed in critically ill adult patients, as evidenced by a study conducted by Goldhill and McNarry (2004). The significance of tachypnea as a contributing factor to mortality in older patients (aged 75 years and above) with community-acquired pneumonia was assessed in a prospective cohort study by Calle et al. (2014). Our own investigation aligns with the previous studies. These collective findings further underscore the relevance of tachypnea as a significant clinical parameter and its potential impact on patient outcomes.

Oxidative stress and inflammation have been considered factors in age-associated diseases and mortality (Petersen & Smith, 2016). Interestingly, NAD+-dependent Sirtuins play an essential role in inflammation and are a double-edged sword. Low levels accentuate early acute inflammation-related autotoxicity by increasing NFκB RelA/p65 activity. A prolonged increase in SIRT1 during late inflammation is associated with immunosuppression and increased mortality (Liu et al., 2018). As seen in acute illness, fasting or reduced food intake activates SIRT5. During fasting, NAD in liver mitochondria increases, triggering SIRT5 activation (ScienceDirect Topics, n.d.). Another study has previously reported the association of high SIRT5 expression with poor patient survival and further highlighted a potential role of SIRT5 in promoting Warburg-type metabolism by repressing SUN2 expression (Lv et al., 2015).

An acute inflammatory state is a prothrombotic state leading to ischemia. As stated previously, tachypnea was significantly prevalent in the non-survivor group in the hospital, suggesting hypoxia in the patients. Zhu et al. (2012) showed that intermittent hypoxia leads to increased cardiac SIRT5 expression in rats. SIRT5

expression increases after ischemia in proximal tubular epithelial cells in vivo and in vitro (Haschler et al., 2021). In our study, we found that levels of SIRT5 were significantly higher in non-survivors, suggesting a potential association between elevated SIRT5 expression and adverse outcomes. This observation may reflect the complex interplay between SIRT5, ischemia, and the pathophysiological processes leading to poor survival in acute illness. Further research is needed to fully elucidate the role of SIRT5 in ischemia and its implications for patient outcomes.

Strengths and Limitations

Strengths of our study include being one of the few studies focusing exclusively on the oldest old population (age >85 years), a group that is underrepresented in the existing literature. Our study fills a gap in the literature and provides a foundation for future research in this area. Moreover, our findings challenge the notion that chronological age alone should guide treatment decisions for older patients. By identifying physiological parameters that predict survival, our study encourages a shift toward individualized decision-making based on objective factors rather than relying solely on age as a determinant of prognosis.

However, our study has certain limitations that should be acknowledged. Firstly, the sample size is relatively small, which may affect the generalizability of our results. Secondly, our study was conducted in a single center, which may limit the generalizability of our findings to other healthcare settings or populations with different characteristics. Collaborative multicenter studies are warranted to validate and extend our results across diverse populations.

Conclusion

In conclusion, our study contributes novel insights into survival prediction among the oldest old population. It challenges the conventional approach of using chronological age as the sole determinant of treatment decisions. Despite its limitations, our study underscores the need for further research in this area and highlights the potential to improve patient care and reduce age-related disparities through a more individualized approach based on physiological parameters rather than chronological age.

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Declaration of Conflicting Interests

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Research Ethics and Research Participant Consent

The study was approved by Institute Ethics Committee for Post Graduate Research, All India Institute of Medical Sciences, New Delhi (Ref. No. IECPG-377/30.08.2018). This study was conducted according to the ethical guidelines established by the Declaration of Helsinki and Good Clinical Practice Guidelines.

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