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Survival Trends, Determinants of Mortality, and the Impact of Advance Directives: An Observational Study from the Pakistan Registry of Intensive Care

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ABSTRACT

Objective: This study assesses survival trends and identifies determinants of adverse outcomes (at hospital discharge and 90-day) among ICU patients, for the whole cohort and in the context of advanced directives (AD).

Study Design: Correlational Study.

Place and Duration of Study: Pakistan Registry of Intensive Care (PRICE), National Institute of Cardiovascular Diseases (NICVD) in Karachi, Pakistan, between Jan 22 and Dec 23.

Methodology: Data for a total of 1570 patients were analyzed from the PRICE registry. We included patients of either gender, aged≥ 18 years, who were admitted to the ICU. Patients who deferred consent for participation in the PRICE registry were excluded. Data included clinical and laboratory parameters at ICU admission, treatment details, AD, ICU, and hospital discharge outcomes, and 90-day post-discharge survival.

Results: Of the 1570 patients (mean age 57.6±14.3 years, 945 males), 83.3% required mechanical ventilation (MV), 76.7% needed vasoactive therapy, 2.9% underwent renal replacement therapy, and 34.9% received antibiotics. ICU mortality was 16.6%, and 20.4% died by hospital discharge. At 90 days post-discharge, follow-up was successful for 59.1% of patients, with a 20.6% mortality rate. Among 436 DNR patients, 41.1% died in-hospital. DNR status raised in-hospital and 90-day mortality risks (OR: 4.91, 3.48).

Conclusion: High ICU and hospital mortality rates underscore the challenges in managing critically ill patients, particularly those on MV. The study calls for a culturally sensitive approach to ICU management, emphasizing AD, early risk factor identification, and individualized patient care strategies.

Keywords: Survival Trends, Adverse Outcomes, Intensive Care Unit, Cardiac Care.

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INTRODUCTION

The management of Intensive Care Unit (ICU) services poses a significant financial challenge within the healthcare systems of Low-middle-income countries (LMIC). Given limited resources, the optimization of resource allocation and utilization is crucial to improve patient outcomes and ensure efficient healthcare delivery.[1] Unfortunately, there is frequently a shortage of ICU beds and resources in public sector hospitals, which creates difficulties for healthcare delivery and resource allocation.[2] In critical care settings, healthcare providers often face ethical dilemmas when determining the appropriate course of action for patients with uncertain prognoses. A useful approach to deal with these issues and maximize the use of medical resources in the intensive care unit is the implementation of advanced directives.[3]

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Individuals can express their healthcare preferences and wishes ahead of time through advance directives, which are legal agreements that specifically address end-of-life care. By outlining preferences for specific interventions, advance directives help healthcare providers allocate resources more efficiently.[4] For patients who express a desire to forego certain treatments or interventions that are unlikely to improve their prognosis, resources can be redirected to those who stand to benefit more, thereby optimizing resource utilization in the ICU. Advanced directives provide clear guidance on the patient's wishes, helping clinicians navigate these complex ethical decisions with greater confidence and integrity.[5]

Clinical audits serve as invaluable tools in achieving optimization by offering critical insights. Analyzing survival patterns in ICU patients at a cardiac center is pivotal for optimizing healthcare resource allocation.[6] Understanding factors contributing to adverse outcomes is essential for

improving patient care and cost-effectiveness.[7] There is a pressing need for further analysis of medical admissions and outcomes in intensive care units in low-resource settings to identify common indications and improve patient care.[8] Future research could explore the necessity of routine admission to cardiac intensive care units and the potential for redirecting triage to less costly hospital units.[9] The Pakistan Registry of Intensive Care (PRICE), a clinician-led, real-time national intensive care registry in Pakistan, facilitates comprehensive evaluation of clinical outcomes.[10]

In this study, we aimed to evaluate the clinical and laboratory assessments at ICU admission, therapeutic management strategies, and outcomes at both ICU and hospital discharges for the whole cohort and in the context of advanced directives. Additionally, survival patterns at 90-day post-discharge follow-up were assessed, and the importance of advance directives and other factors contributing to adverse outcomes (at hospital discharge and at 90-day follow-up) in these critically ill patients was also assessed.

METHODOLOGY

This correlational study utilized prospectively collected data from the PRICE registry, National Institute of Cardiovascular Diseases (NICVD) in Karachi, Pakistan, between Jan 22 and Dec 23. It is a comprehensive, clinician-led, real-time national intensive care registry in Pakistan, which is designed to acquire detailed clinical information from intensive care units (ICUs) across the country, providing a valuable resource for clinical research and quality improvement initiatives. The registry was approved by the institutional review board of NICVD (reference #: ERC-13/2020, dated: 30th April 2020). The study evaluated data of ICU survival patterns, identify factors influencing patient outcomes, and provide insights to guide clinical practice and resource allocation in intensive care settings.

A study by Ansari MI *et al.*,[1] reported in-hospital mortality rate of 19.6% among ICU patients, using WHO sample size calculator version 2.0, at 95% confidence level, and 2% margin of error, the required sample size was calculated to be 1514 patients. Two years of data form the PRICE registry was extracted to meet the minimum sample size requirement for the study. The PRICE is an ongoing registry; this study collected comprehensive data on a cohort of 1,570 patients registered in the PRICE registry for two years period.

Inclusion Criteria: For this analysis, data were extracted from the PRICE registry for patients of either gender, age ≥18 years, who were admitted to the intensive care unit for diseases/symptoms etc.

Exclusion Criteria: Patients who admitted to the ICU during same duration but deferred or resulted in mortality and those who were unwilling for participation in the PRICE registry were excluded.

Data collection at the cardiac center involved gathering patient demographics, medical history, and treatments during ICU stays. The primary focus was on all-cause mortality in the ICU, during hospitalization, and at 90-day follow-up. The dataset included clinical evaluations and lab test results at ICU admission and documented treatments like medications, surgeries, and supportive therapies, alongside advanced directives determined collaboratively by the physician and intensivist.

Patient outcomes were recorded at ICU and hospital discharge, capturing mortality, discharge destinations, and complications. Follow-up data on survival status were collected for 90 days post-discharge, using a standardized tool and independent data collectors to minimize bias. Quantitative variables were analyzed with descriptive statistics, reported as Mean±SD or median [interquartile range (IQR)]. Patients were stratified by survival status, and clinical characteristics were compared. Survival patterns were evaluated based on mechanical ventilation status and lab values at admission. Logistic regression analyzed the impact of various factors on survival during hospitalization and at follow-up. Key clinical factors were identified to enhance survival rates and outcomes. All analyses were performed using SPSS version 21, with significance set at $p<0.05$.

RESULTS

Among the 1,570 patients (mean age 57.6±14.3 years, 945 males), 1,308(83.3%) required mechanical ventilation, 1,204(76.7%) needed vasoactive therapy, 45(2.9%) underwent renal replacement therapy and 547(34.9%) received antibiotics. The source of admission was the emergency department (ED) for 1,018(64.8%) patients, while 323(20.6%) were admitted through the ward and 225(14.3%) through the ICU/HDU. At ICU admission, advance directive of code status (Do Not Resuscitate) DNR was for 436(27.8%) patients, out of which 179(41.1%) died

during hospital stay, while among 1134 patients with an advance directive of full code, had a mortality rate of 12.4% (141), (Table-I).

Table-I: Baseline Demographic and Clinical Characteristics at the Time of Admission to Intensive Care Unit (n=1570)

	Total	Discharge Status Hospital		*p*-value
		Alive	Dead	
Total (n)	1570	1250	320	
Mean age (years)	57.6±14.3	56.8±14.3	60.5±13.9	<0.001
Gender				
Female	625(39.8%)	487(39.0%)	138(43.1%)	0.170
Male	945(60.2%)	763(61.0%)	182(56.9%)	
Source of admission				
ED – other hospital	3(0.2%)	3(0.2%)	0 (0.0%)	0.008
ED – same hospital	1,018(64.8%)	797(63.8%)	221(69.1%)	
ICU/HDU – same hospital	225 (14.3%)	196(15.7%)	29(9.1%)	
Ward – other hospital	1(0.1%)	0(0.0%)	1(0.3%)	
Ward – same hospital	323(20.6%)	254(20.3%)	69(21.6%)	
Readmission	4(0.3%)	2(0.2%)	2(0.6%)	0.140
Diagnosis type				
Non-operative	1,565(99.7%)	1,245(99.6%)	320(100.0%)	0.260
Post-operative	5(0.3%)	5(0.4%)	0(0.0%)	
Admission Disorder				
Acute Myocardial Infarction	827(52.7%)	665(53.2%)	162(50.6%)	0.41
Cardiogenic Shock	116(7.4%)	77(6.2%)	39(12.2%)	<0.001
Pulmonary Edema	85(5.4%)	76(6.1%)	9(2.8%)	0.021
Ventricular Failure	85(5.4%)	70(5.6%)	15(4.7%)	0.52
Valvular Heart Disease	80(5.1%)	60(4.8%)	20(6.2%)	0.29
Heart Failure	75(4.8%)	66(5.3%)	9(2.8%)	0.065
Arrhythmias	67(4.3%)	47(3.8%)	20(6.2%)	0.049
Pulmonary Embolism	57(3.6%)	51(4.1%)	6(1.9%)	0.060
Complete Heart Block	56(3.6%)	44(3.5%)	12(3.8%)	0.84
Septic Shock	43(2.7%)	30(2.4%)	13(4.1%)	0.10
Pneumonia	37(2.4%)	28(2.2%)	9(2.8%)	0.55
Chronic Kidney Disease	26(1.7%)	21(1.7%)	5(1.6%)	0.88
COPD	25(1.6%)	21(1.7%)	4(1.2%)	0.58
Acute Kidney Injury	23(1.5%)	18(1.4%)	5(1.6%)	0.87
ARDS	19(1.2%)	13(1.0%)	6(1.9%)	0.22
Respiratory Infection	18(1.1%)	12(1.0%)	6(1.9%)	0.17
ARF	23(1.5%)	14(1.1%)	9(2.8%)	0.025
Hypertensive Urgencies	15(1.0%)	14(1.1%)	1(0.3%)	0.19
Other	144(9.2%)	118(9.4%)	26(8.1%)	0.47
Diabetes	616(39.2%)	481(38.5%)	135(42.2%)	0.23
Cardiovascular disease	233(14.8%)	174(13.9%)	59(18.4%)	0.043
Chronic kidney disease	33(2.1%)	24(1.9%)	9(2.8%)	0.32
Asthma/COPD	11(0.7%)	9(0.7%)	2(0.6%)	0.86
Mechanically ventilated	1,308(83.3%)	996(79.7%)	312(97.5%)	<0.001
ETT	1,238(94.7%)	934(93.8%)	304(97.7%)	0.006
Noninvasive vent	69(5.3%)	62(6.2%)	7(2.3%)	
Advance directive				
Full code	1134 (72.2%)	993 (79.4%)	141 (44.1%)	<0.001
DNR	436 (27.8%)	257 (20.6%)	179 (55.9%)	

**COPD – Chronic Obstructive Pulmonary Disorder, ARDS – Acute Respiratory Distress Syndrome, ARF – Acute Renal Failure, ETT – Exercise Tolerance Test, DNR - Do Not Resuscitate, ICU – Intensive Care Unit, ED – Emergency Department*

The ICU mortality rate was 16.6% (260), with CPR administered in the ICU for 180 (11.5%) patients, and the hospital mortality rate was 20.4% (320). Ninety-day telephonic follow-up was successful for 739(59.1%) patients, among whom 152(20.6%) died post-discharge, Table-II.

The ICU mortality rate was 19.3% (252/1,308) vs. 2.7% (7/262); $p<0.001$, and the hospital mortality rate was 23.8% (311/1,308) vs. 3.1% (8/262); $p<0.001$, among ventilated and non-ventilated patients, respectively. The 90-day mortality rate was 17.8% (117/658) vs. 43.2% (35/81); $p<0.001$, among ventilated and non-ventilated patients, respectively, Figure-1. For patients with serum creatinine levels of <1.5 and ≥1.5 mg/dL, ICU mortality rates were 12.0% (89/744) vs. 20.9% (139/664); $p<0.001$, hospital mortality rates were 14.8% (110/744) vs. 25.6% (170/664); $p<0.001$, and 90-day mortality rates were 19.1% (69/361) vs. 23.9% (73/306); $p=0.136$, respectively.

Among patients with hyponatremia (<135), normal sodium levels (135-145), and hypernatremia (>145), ICU mortality rates were 16.7% (78/467) vs. 14.9% (133/893) vs. 26.0% (19/73); $p=0.040$, hospital mortality rates were 20.8% (97/467) vs. 18.3% (163/893) vs. 31.5% (23/73); $p<0.019$, and 90-day mortality rates were 23.9% (51/213) vs. 18.7% (81/433) vs. 40% (12/30); $p=0.012$, respectively.

Similarly, among patients with hypokalemia (<3.5), normal potassium levels (3.5-5), and hyperkalemia (>5), ICU mortality rates were 12.3% (40/326) vs. 16.5% (158/955) vs. 21.2% (32/151); $p=0.037$, hospital mortality rates were 16.0% (52/326) vs. 20.2% (193/955) vs. 25.2% (38/151); $p=0.053$, and 90-day mortality rates were 18.8% (29/154) vs. 22.2% (102/460) vs. 21.0% (13/62); $p=0.679$, respectively.

On multivariable binary logistic regression analysis, older age (years), acute renal failure, low arterial PH at admission, sedated on admission, vasoactive therapy, low diastolic blood pressure (mmHg), and increased heart rate (bpm) were found to be the independent predictors of hospital mortality with adjusted ORs of 1.02 [1 - 1.03; $p=0.035$], 3.31 [1.16 - 9.44; $p=0.026$], 0.12 [0.03 - 0.49; $p=0.003$], 2.12 [1.19 - 3.78; $p=0.010$], 2.98 [1.4 - 6.36; $p=0.005$], 0.98 [0.96 - 0.99; $p=0.001$], and 1.02 [1.01 - 1.03; $p<0.001$] respectively as shown in Table-III.

On multivariable binary logistic regression analysis, absence of diabetes, no use of mechanical ventilation during ICU stay, high APACHE score at admission to ICU, no use of vasoactive therapy during ICU stay, and low diastolic blood pressure (mmHg) were found to be the independent predictors of 90-day follow-up mortality with adjusted ORs of 0.42 [0.25 - 0.69; p<0.001], 0.32 [0.14 - 0.71; p=0.005], 1.14 [1.05 - 1.24; p=0.002], 0.48 [0.26 - 0.87; p=0.016], 0.98 [0.96 – 1.00; p=0.13], respectively as shown in Table-IV.

Table-II: ICU Course, ICU and Hospital Mortality, and Follow-Up Status (n=1570)

	Total	Discharge Status Hospital		*p*-value
		Alive	Dead	
Total (n)	1570	1250	320	
Mean APACHE at admission	12.0 (9.0-15.0)	12.0 (9.0-14.0)	14.0 (11.0-16.0)	<0.001
Mean FiO2 at admission	0.6 ± 0.3	0.5 ± 0.3	0.7 ± 0.3	<0.001
Mean Arterial PH at admission	7.4 ± 0.1	7.4 ± 0.1	7.3 ± 0.2	<0.001
Sedated on admission	1,120 (71.4%)	828 (66.2%)	292 (91.5%)	<0.001
Vasoactive Therapy	1,204 (76.7%)	897 (71.8%)	307 (96.2%)	<0.001
Dopamine >15, Epinephrine >0.1, or norepinepherine >0.1	843 (70.0%)	614 (68.5%)	229 (74.6%)	0.16
Dopamine >5, Epinephrine ≤0.1, or norepinephrine ≤0.1	323 (26.8%)	254 (28.3%)	69 (22.5%)	
Dopamine ≤5 or Dobutamine (any dose)	3 (0.2%)	3 (0.3%)	0 (0.0%)	
Epinephrine >0.3 or Norepinephrine >0.3	35 (2.9%)	26 (2.9%)	9 (2.9%)	
Renal Replacement	45 (2.9%)	31 (2.5%)	14 (4.4%)	0.068
Antibiotics	547 (34.9%)	419 (33.5%)	128 (40.1%)	0.027
Mean Systolic Blood Pressure (mmHg)	119.0 ± 21.2	120.2 ± 21.3	114.2 ± 20.0	<0.001
Mean Diastolic Blood Pressure (mmHg)	67.1 ± 13.7	68.1 ± 13.7	63.1 ± 13.1	<0.001
Mean Respiratory Rate (%)	18.8 ± 3.9	18.9 ± 4.1	18.2 ± 2.9	0.007
Mean Heart Rate (bpm)	96.9 ± 20.1	95.5 ± 19.3	102.6 ± 22.1	<0.001
Mean Temperature (°F)	98.3 ± 0.9	98.3 ± 0.9	98.4 ± 0.9	0.002
Mean Blood Sugar Level (mg/dl)	181.1 ± 72.4	178.9 ± 72.0	190.1 ± 73.3	0.014
Mean hemoglobin (mg/dl)	12.4 ± 2.7	12.4 ± 2.6	12.2 ± 2.7	0.20
Mean Platelets Count	250.8 ± 114.1	253.4 ± 112.6	240.5 ± 119.3	0.087
Mean Serum Sodium (mmol/l)	136.2 ± 6.9	136.2 ± 6.6	136.4 ± 7.8	0.63
Mean Serum Potassium (meq/l)	4.1 ± 0.8	4.0 ± 0.8	4.2 ± 0.9	0.016
Mean Serum Bicarbonate (meq/l)	21.8 ± 5.2	22.2 ± 4.9	19.8 ± 6.0	<0.001
Mean Serum Creatinine (mg/dl)	1.9 ± 1.7	1.9 ± 1.8	2.2 ± 1.7	0.002
Mean Serum Bilirubin (mg/dl)	1.4 ± 3.6	1.4 ± 3.9	1.5 ± 1.5	0.83
Mean Blood Urea (mg/dl)	67.0 ± 49.3	64.8 ± 48.6	76.5 ± 51.3	0.002
Mean Partial Pressure Arterial Oxygen (mmhg)	156.0 ± 113.0	153.5 ± 111.7	165.0 ± 117.6	0.12
Mean Peep (cmh2o)	5.2 ± 0.7	5.2 ± 0.7	5.2 ± 0.8	0.92
CPR	180 (11.5%)	3 (0.2%)	177 (55.3%)	<0.001
ICU mortality	260 (16.6%)	0 (0.0%)	260 (81.2%)	-
Discharge destination				
HDU	769 (58.7%)	713 (57.0%)	56 (93.3%)	<0.001
Home	84 (6.4%)	84 (6.7%)	0 (0.0%)	
ICU	9 (0.7%)	6 (0.5%)	3 (5.0%)	
Other hospital	46 (3.5%)	46 (3.7%)	0 (0.0%)	
Others	6 (0.5%)	6 (0.5%)	0 (0.0%)	
Transfer for specialist care	32 (2.4%)	32 (2.6%)	0 (0.0%)	
Ward	364 (27.8%)	363 (29.0%)	1 (1.7%)	
90-day follow-Up				
Successful	739 (59.1%)	739 (59.1%)	-	-
90-days not completed	110 (8.8%)	110 (8.8%)	-	-
Lost to follow-up	401 (32.1%)	401 (32.1%)	-	-
Median follow-up days	97.0 [91.0-114.0]	97.0 [91.0-114.0]	-	-
Follow-up Status				
Alive	587 (79.4%)	587 (79.4%)	-	-
Dead	152 (20.6%)	152 (20.6%)	-	-

**APACHE - Acute Physiology and Chronic Health Evaluation, FiO2 - Fraction of Inspired Oxygen,*

Among the 262 non-mechanically ventilated patients with advance directives of DNR had an in-hospital mortality rate of 3.1% (8/262). The 90-day follow-up was successful in 30.9% (81) of these patients with 90-day mortality rate of 43.2% (35/81). However, mechanically ventilated patients whose code status was revised to DNR during ICU stay had mortality rate of 98.3% (171/174), (Table-V).

DISCUSSION

In this study, the ICU and hospital course of patients admitted to the ICU of a tertiary care cardiac center of a low- and middle-income country were evaluated. In addition to the survival patterns, this study aimed to evaluate the role of advance directives in the optimization of resource utilization. Among 1570 patients admitted to ICU, 83.3% required

Table-III: Univariate And Multivariable Logistic Regression Analysis For Hospital Mortality

	Univariate		Multivariable	
	OR [95% CI]	***p*-value**	**OR [95% CI]**	***p*-value**
Age (years)	1.02 [1.01 - 1.03]	<0.001	1.02 [1.00 - 1.03]	0.035
Female	1.19 [0.93 - 1.52]	0.175	1.33 [0.94 - 1.88]	0.104
Admission Disorders				
Acute Myocardial Infarction	0.9 [0.71 - 1.15]	0.410	-	-
Cardiogenic Shock	2.11 [1.41 - 3.18]	<0.001	1.53 [0.92 - 2.52]	0.099
Pulmonary Edema	0.45 [0.22 - 0.90]	0.025	0.40 [0.16 - 1.02]	0.054
Ventricular Failure	0.83 [0.47 - 1.47]	0.520	-	-
Valvular Heart Disease	1.32 [0.78 - 2.23]	0.294	-	-
Heart Failure	0.52 [0.26 - 1.05]	0.069	0.62 [0.26 - 1.47]	0.275
Arrhythmias	1.71 [1.00 - 2.92]	0.052	1.73 [0.91 - 3.29]	0.092
Pulmonary Embolism	0.45 [0.19 - 1.06]	0.067	0.60 [0.15 - 2.38]	0.469
Complete Heart Block	1.07 [0.56 - 2.05]	0.843	-	-
Septic Shock	1.72 [0.89 - 3.34]	0.108	1.45 [0.62 - 3.40]	0.391
Pneumonia	1.26 [0.59 - 2.70]	0.548	-	-
Chronic Kidney Disease	0.93 [0.35 - 2.48]	0.883	-	-
Chronic Obstructive Pulmonary Disease	0.74 [0.25 - 2.17]	0.585	-	-
Acute Kidney Injury	1.09 [0.40 - 2.95]	0.871	-	-
Acute Respiratory Distress Syndrome	1.82 [0.69 - 4.82]	0.230	-	-
Respiratory Infection	1.97 [0.73 - 5.29]	0.178	2.28 [0.63 - 8.22]	0.209
Acute Renal Failure	2.55 [1.10 - 5.96]	0.030	3.31 [1.16 - 9.44]	0.026
Hypertensive Urgencies	0.28 [0.04 - 2.11]	0.215	-	-
Co-Morbid Conditions				
Diabetes	1.17 [0.91 - 1.5]	0.226	-	-
Cardiovascular Disease	1.40 [1.01 - 1.93]	0.043	1.12 [0.74 - 1.72]	0.589
Chronic Kidney Disease	1.48 [0.68 - 3.21]	0.324	-	-
Asthma/COPD	0.87 [0.19 - 4.03]	0.856	-	-
Admission status				
Mechanically ventilated	9.91 [4.85 - 20.27]	<0.001	1.71 [0.53 - 5.55]	0.372
APACHE at admission	1.15 [1.11 - 1.19]	<0.001	1.06 [0.99 - 1.13]	0.098
FiO2 at admission	2.32 [1.79 - 3.01]	<0.001	1.29 [0.91 - 1.82]	0.152
Arterial PH at admission	0.01 [0.01 - 0.04]	<0.001	0.12 [0.03 - 0.49]	0.003
Sedated on admission	5.51 [3.65 - 8.32]	<0.001	2.12 [1.19 - 3.78]	0.010
Vasoactive Therapy	9.29 [5.26 - 16.41]	<0.001	2.98 [1.40 - 6.36]	0.005
Renal Replacement	1.81 [0.95 - 3.44]	0.072	1.27 [0.54 - 3.01]	0.580
Antibiotics	1.33 [1.03 - 1.71]	0.027	1.09 [0.79 - 1.52]	0.596
Systolic Blood Pressure (mmHg)	0.99 [0.98 - 0.99]	<0.001	0.99 [0.98 – 1.00]	0.168
Diastolic Blood Pressure (mmHg)	0.97 [0.96 - 0.98]	<0.001	0.98 [0.96 - 0.99]	0.001
Respiratory Rate (%)	0.94 [0.9 - 0.98]	0.007	0.98 [0.94 - 1.04]	0.539
Heart Rate (bpm)	1.02 [1.01 - 1.02]	<0.001	1.02 [1.01 - 1.03]	<0.001
Blood Sugar Level (mg/dl)	1.00 [1.00 – 1.00]	0.015	1.00 [1.00 – 1.00]	0.926
Hemoglobin (mg/dl)	0.97 [0.92 - 1.02]	0.200	0.97 [0.91 - 1.04]	0.365
Platelets count	1.00 [1.00 – 1.00]	0.087	1.00 [1.00 – 1.00]	0.419
Serum sodium (mmol/l)				
<135 Hyponatremia	Reference category		Reference category	
135-145 Normal	0.85 [0.64 - 1.13]	0.262	1.08 [0.76 - 1.53]	0.668
>145 Hypernatremia	1.76 [1.02 - 3.02]	0.042	1.87 [0.93 - 3.77]	0.081
Serum potassium (mEq/l)				
<3.5 Hypokalemia	Reference category		Reference category	
3.5-5 Normal	1.33 [0.95 - 1.87]	0.092	1.27 [0.85 - 1.89]	0.249
>5 Hyperkalemia	1.77 [1.11 - 2.84]	0.018	1.03 [0.58 - 1.82]	0.932
Serum creatinine > 1.5 mg/dl	1.98 [1.52 - 2.59]	<0.001	1.04 [0.71 - 1.54]	0.826
DNR status	4.91 [3.78 - 6.36]	<0.001	Not included due to wide CI	

**OR: "odds ratio", CI: "confidence interval", bpm – Beats per minute,*

mechanical ventilation, 76.7% needed vasoactive therapy, 34.9% received antibiotics, and 2.9% underwent renal replacement therapy. The mortality rate during ICU stay was 16.6%, with an overall in-hospital mortality rate of 20.4%, and 20.6% mortality was observed among survivors who were successfully followed after 90 days. The advance directive of code status DNR was found to be associated with an increased risk of in-hospital and 90-day mortality with an odds ratio of 4.91 [3.78 - 6.36] and 3.48 [2.16-5.61], respectively. Additionally, among the successfully followed non-mechanically ventilated patients with DNR, the 90-day mortality rate was observed to be 43.2%, and mechanically ventilated patients whose code status was revised to DNR during ICU stay had a mortality rate of 98.3%. Hence, advanced directives

can be an effective strategy for the optimization of resource utilization.

healthcare preferences, particularly concerning life-sustaining treatments such as mechanical ventilation

Table-IV: Univariate and Multivariable Logistic Regression Analysis for 90-day Follow-up Mortality

	Univariate		Multivariable	
	OR [95% CI]	***p*-value**	**OR [95% CI]**	***p*-value**
Age (years)	1.01 [1.00 - 1.03]	0.044	1.01 [0.99 - 1.03]	0.227
Female	1.38 [0.96 - 1.98]	0.079	1.29 [0.81 - 2.06]	0.279
Admission disorders				
Acute myocardial infarction	0.59 [0.41 - 0.84]	0.004	1.3 [0.79 - 2.13]	0.31
Cardiogenic Shock	1.31 [0.68 - 2.53]	0.413	-	-
Pulmonary Edema	2.10 [1.02 - 4.33]	0.044	2.21 [0.86 - 5.64]	0.098
Ventricular failure	0.77 [0.38 - 1.56]	0.474	-	-
Valvular heart disease	0.63 [0.24 - 1.66]	0.350	-	-
Heart failure	2.47 [1.14 - 5.34]	0.022	1.65 [0.62 - 4.39]	0.318
Arrhythmias	0.92 [0.34 - 2.47]	0.864	-	-
Pulmonary Embolism	2.23 [1.01 - 4.93]	0.048	2.26 [0.84 - 6.04]	0.105
Complete heart block	1.62 [0.66 - 3.98]	0.294	-	-
Septic shock	1.68 [0.64 - 4.45]	0.295	-	-
Pneumonia	1.63 [0.57 - 4.7]	0.366	-	-
Chronic kidney disease	5.38 [1.84 -15.75]	0.002	2.27 [0.58 - 8.95]	0.24
Chronic obstructive pulmonary disease	0.86 [0.18 – 4.00]	0.844	-	-
Acute kidney injury	0.97 [0.11 - 8.7]	0.975	-	-
Acute respiratory distress syndrome	0.97 [0.20 - 4.59]	0.964	-	-
Respiratory infection	2.93 [0.65 - 13.25]	0.162	1.85 [0.3 - 11.42]	0.510
Acute renal failure	2.34 [0.55 - 9.92]	0.247	-	-
Hypertensive Urgencies	1.67 [0.43 - 6.53]	0.462	-	-
Co-morbid conditions				
Diabetes	0.61 [0.41 - 0.88]	0.009	0.42 [0.25 - 0.69]	<0.001
Cardiovascular disease	1.39 [0.88 - 2.21]	0.156	1.53 [0.88 - 2.66]	0.131
Chronic kidney disease	1.74 [0.53 - 5.71]	0.364	-	-
Asthma/COPD	2.60 [0.43 -15.67]	0.299	-	-
Admission status				
Mechanically ventilated	0.28 [0.18 - 0.46]	<0.001	0.32 [0.14 - 0.71]	0.005
APACHI at admission	1.10 [1.05 - 1.16]	<0.001	1.14 [1.05 - 1.24]	0.002
FiO2 at admission	0.88 [0.61 - 1.25]	0.472	-	-
Arterial PH at admission	2.66 [0.57-12.43]	0.213	-	-
Sedated on admission	0.34 [0.23 - 0.51]	<0.001	1.09 [0.56 - 2.12]	0.797
Vasoactive therapy	0.37 [0.25 - 0.55]	<0.001	0.48 [0.26 - 0.87]	0.016
Renal replacement	3.21 [1.24 - 8.27]	0.016	1.84 [0.55 - 6.15]	0.319
Antibiotics	1.82 [1.26 - 2.64]	0.002	1.43 [0.9 - 2.28]	0.127
Systolic blood pressure (mmHg)	1.00 [0.99 - 1.01]	0.797	-	-
Diastolic blood pressure (mmHg)	0.98 [0.96 - 0.99]	0.001	0.98 [0.96 – 1.00]	0.013
Respiratory rate (%)	1.05 [1.01 - 1.09]	0.017	1.01 [0.96 - 1.06]	0.804
Heart rate (bpm)	1.00 [0.99 - 1.01]	0.728	-	-
Blood sugar level (mg/dl)	1.00 [0.99 - 1]	0.049	1.00 [1.00 – 1.00]	0.660
Hemoglobin (mg/dl)	0.86 [0.8 - 0.92]	<0.001	0.92 [0.84 - 1.01]	0.080
Platelets count	1.00 [1.00 – 1.00]	0.293	-	-
Serum sodium (mmol/l)				
<135 Hyponatremia	Reference category		Reference category	
135-145 Normal	0.73 [0.49 - 1.09]	0.122	0.81 [0.51 - 1.3]	0.386
>145 Hypernatremia	2.12 [0.96 - 4.69]	0.064	2.12 [0.8 - 5.63]	0.131
Serum potassium (mEq/l)				
<3.5 Hypokalemia	Reference category		Reference category	
3.5-5 Normal	1.23 [0.78 - 1.95]	0.381	-	-
>5 Hyperkalemia	1.14 [0.55 - 2.38]	0.720	-	-
Serum creatinine > 1.5 mg/dl	1.33 [0.91 - 1.92]	0.137	0.66 [0.38 - 1.14]	0.133
DNR status	3.48 [2.16 - 5.61]	<0.001	Not included due to wide CI	

OR: "odds ratio", CI: "confidence interval"

In Pakistan, the recognition of advance directives faces obstacles due to religious, cultural, and societal factors. Family autonomy often takes precedence over patient autonomy, impeding the establishment of a sound decision regarding end-of-life care. These directives play a pivotal role in delineating patients' and dialysis.[11] Conflicts may arise when the designated healthcare power of attorney (HcPOA) disagrees with the patient's documented preferences, leading to legal and ethical quandaries. Addressing these complexities is essential for healthcare providers

to ensure patient wishes are honored while complying with legal and ethical standards.[12]

Advance directives may encompass preferences regarding mechanical ventilator assistance, CPR, renal support, or vasopressors, stemming from a variety of factors.[14] Patients may specify these exclusions in their advance directives to ensure their end-of-life wishes are respected. Some individuals may prioritize a comfortable death without burdens on their family, leading them to decline aggressive life-sustaining treatments like ventilator support or dialysis.[15] Additionally, patients with chronic illnesses or those facing critical care situations may choose to forego these interventions to align with their values and preferences, as documented in their advance directives. The choice to omit these treatments can also arise from considerations regarding the quality of life during end-of-life care and a wish to avoid prolonged suffering or intrusive medical procedures.[16]

Similar to our findings, various studies have reported an association of DNR status with an increased risk of poor outcomes. A study by April *et al*., found that 39% of COPD patients had a DNR order; the death rate for patients with a DNR at baseline was 82%, and the death rate for patients with a DNR throughout follow-up was 76%.[13] In another study by Piscitello *et al*., on COVID-19 patients, the mortality rate was 49% for patients with a DNI order, which is related to DNR status and was three times higher than that of other patients.[14] Our results found that the in-hospital mortality rate for the 262 non-mechanically ventilated patients who had a DNR advance directive was 3.1% (8/262). Of these patients, 30.9% (81) had a successful 90-day follow-up, while the 90-day death rate was 43.2% (35/81). On the other hand, 98.3% of mechanically ventilated patients whose coding status was changed to DNR during their ICU stay died.

Overall, the mortality rate during ICU stay, hospital stay, and post-discharge follow-up observed in our study is in the range of the reported mortality rate by various studies. However, survival rates post-ICU discharge may vary in the literature, as reported by Davison *et al*., highlighting the need to understand and address factors influencing patient outcomes. Our study revealed significant disparities in mortality rates among ventilated and non-ventilated patients, underscoring the impact of interventions on survival. ICU survivors have decreased long-term survival rates compared to the general population, prompting the FROG-ICU study to assess one-year mortality post-ICU discharge.[15] In Victoria, Australia, the long-term survival of ICU patients post-discharge was worse compared to the general population, except for elderly patients following cardiac surgery, as concluded by Doherty *et el*.[16] A study in Korea by Hyun *et al*., found an in-hospital mortality rate of 11.7% among ICU survivors, with respiratory failure being the most common cause of death. These findings highlight the importance of understanding and addressing factors influencing post-ICU survival.[17]

We identified patient subsets at increased mortality risk during hospital stays and discharge, including older patients, those with acute renal failure, low arterial pH, sedation at admission, need for vasoactive therapy, low diastolic blood pressure, and elevated heart rate. Early risk stratification and targeted management can enhance outcomes for these groups.[11] Similar to our observations, Avdeen *et al*., studied the risk factors for COVID-19 adverse outcomes, which were evaluated by logistic regression, and the most significant risk factors were the severity of lung damage based on CT quantification, the number of antibiotics used in the course of treatment, and patients' age.[18] Another study by Rockenschaub *et al*., found that the incidence of adverse events among ICU patients is associated with higher patient mortality and elevated costs, with hospital-acquired infections and cardiac-related adverse events being the most impactful subtypes from a cost- and patient-perspective.[19] These findings emphasize the importance of early identification and

Table-V: In-Hospital And 90-Day Mortality Rate by Mechanical Ventilation Status Stratified by Advance Directive

	Non-mechanical Ventilated			Mechanical Ventilated		
	Full Code	**DNR**	***p*-value**	**Full Code**	**DNR**	***p*-value**
Total (N)	0	262	-	1133	174	-
In-hospital Mortality	-	8 (3.1%)	-	140 (12.4%)	171 (98.3%)	<0.001
90-day follow-up status						
Successful	-	81 (30.9%)	-	655 (57.8%)	3 (1.7%)	<0.001
90-days not completed	-	11 (4.2%)		99 (8.7%)	0 (0%)	
Lost to follow-up	-	162 (61.8%)		239 (21.1%)	0 (0%)	
90-day mortality	-	35 (43.2%)	-	116 (17.7%)	1 (33.3%)	0.480

targeted management of these risk factors to mitigate adverse outcomes and improve patient survival.

The study by Nateghi *et al*., identified several predictors of 90-day mortality in ICU patients, including the absence of diabetes, non-use of mechanical ventilation, high APACHE score at admission, non-use of vasoactive therapy, and low diastolic blood pressure. These findings emphasize the importance of considering both acute physiological factors and pre-existing conditions in patient care.[20] Additionally, Ashry *et al.,* highlighted that acute kidney injury, lung damage severity, age, arterial oxygen tension, antibiotic use, and conditions like preeclampsia, eclampsia, cerebral infarction, myocardial infarction (MI), and HELLP syndrome are linked to poor outcomes in the ICU. AKI is linked to a higher death rate in COVID-19 patients.[21] However, our research revealed that variables like advanced age, acute renal failure, and sedation upon admission were predictive of detrimental outcomes, highlighting the significance of early detection and focused treatment.

ICU fatality rates varied among patients with abnormal sodium levels, highlighting the complexity of managing critically ill patients and the need for individualized care. In a study of patients with spontaneous subarachnoid hemorrhage, conducted by Shah *et al*., showed that a J-shaped association was observed between serum sodium at ICU admission and minimum sodium values during ICU stay, with in-hospital mortality.[22] Sodium fluctuation above 8.5 mmol/L was independently associated with in-hospital mortality.[23] The body sodium imbalance (dysnatremias) may be associated with increased mortality of critically ill patients, and changes in serum sodium level on admission to the ICU may lead to a poor outcome.[24] In our analysis, we discovered that patients with hyponatremia had an ICU mortality rate of 16.7%, a hospital mortality rate of 20.8%, and a 90-day mortality rate of 23.9%. Similarly, patients with hypernatremia had ICU mortality rates of 26.0%, hospital mortality rate of 31.5%, and day mortality rate of 40%.

Studies similar to Huang *et al*., examined the correlation between serum potassium levels and mortality. In one particular investigation, it was found that lower potassium levels at discharge were associated with an increased risk of all-cause mortality in both short- and long-term scenarios, with a hazard ratio of 1.668 at a 95% confidence interval of 1.081–2.574.[25] In our study, the ICU mortality rates were 12.3% for hypokalemia and 21.2% for hyperkalemia; hospital mortality rates were 16.0% for hypokalemia and 25.2% for hyperkalemia; and 90-day mortality rates were 18.8% for hypokalemia and 21.0% for hyperkalemia.

This study highlights the crucial role of advanced directives in optimizing resource utilization in an ICU setting within a tertiary care cardiac center in a low- and middle-income country. The findings emphasize the significant impact of DNR status on in-hospital and post-discharge mortality, particularly among mechanically ventilated patients. Additionally, the identification of various mortality risk factors, such as advanced age, acute renal failure, and low arterial pH, provides valuable insights for early risk stratification and targeted management strategies to improve patient outcomes.

The strengths of this study include the analysis of a substantial sample size of 1570 ICU patients, providing robust insights into survival patterns and the role of advance directives; the inclusion of diverse patient demographics, which offers a detailed understanding of various factors influencing patient outcomes; a focus on advance directives, particularly DNR status, which adds significant value by linking patient preferences with clinical outcomes and resource utilization; and the effective identification of critical mortality risk factors, aiding in the development of targeted intervention strategies.

LIMITATIONS OF STUDY

The limitations of this study include a low follow-up rate of 30.9% among non-mechanically ventilated patients with a DNR status, which limits the generalizability of post-discharge mortality findings; the single-center design, which may not fully represent other settings or regions; the unique cultural and societal context of Pakistan, which may limit the applicability of the findings to other low- and middle-income countries with different cultural dynamics; potential selection bias due to the retrospective nature of the study; and a primary focus on DNR orders, potentially overlooking other important aspects of advance directives that could influence patient care and outcomes.

CONCLUSIONS

The study sheds light on the high ICU and hospital mortality rates, particularly among mechanically ventilated patients, in a low- and middle-income country. It calls for a comprehensive and culturally sensitive approach to ICU management, emphasizing the importance of advanced directives, early risk factor identification, and individualized patient care strategies. By addressing these factors, healthcare providers can enhance the quality of care for ICU patients, especially in resource-limited settings. The findings

advocate for the integration of patient and family wishes into clinical decision-making to improve resource allocation and patient outcomes.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

FI & MIA: Data acquisition, data analysis, critical review, approval of the final version to be published.

LT & NAL & MSA: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

MYB & MU & JA: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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