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Simple scoring for acute necrotizing pancreatitis: mortality in acute necrotizing pancreatitis during admission (MANP-A)

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Abstract

Background Acute necrotizing pancreatitis (ANP) can result in a significant healthcare burden. The present study aimed to develop a new scoring system to accurately and promptly identify patients with a high likelihood of mortality to determine the need for aggressive measures.

Methods We retrospectively analyzed patients diagnosed with ANP using the National Inpatient Sample (NIS). The mortality in ANP during admission (MANP-A) scoring system was derived using multivariate Cox regression analysis and validated using receiver operating characteristic (ROC) curves in a validation cohort.

Results A total of 22,980 hospitalizations were identified in the derivation cohort. There was a predominance of males (65%) and white race (73%). Five variables showed significant association with mortality and were selected for developing the MANP-A scoring system: age ≥60 years; acute renal failure/kidney injury; sepsis with shock; vasopressor use; and disseminated intravascular coagulation. The MANP-A score has a maximum of 5 points and the cutoff for predicting mortality was set at 2 points. The area under the curve (AUC) using the ROC curve of the derivation cohort was 0.9195, 95% confidence interval [CI] 0.8838-0.9551 (P<0.001) for 7- and 0.8954, 95%CI 0.8723-0.9185 (P<0.001) for 30-day periods. The AUC of the Validation Cohort was 0.9204, 95%CI 0.8937-0.9469 (P<0.001) for 7- and 0.9059, 95%CI 0.8893-0.9223 (P<0.001) for 30-day periods.

Conclusion We propose a simple and objective score for predicting ANP inpatient mortality at 7- and 30-day intervals with high validity.

Keywords Acute necrotizing pancreatitis, prognostic scoring system, national inpatient sample, mortality predictors

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Introduction

Acute pancreatitis (AP) is the most common gastroenterology-related cause of inpatient admissions in the United States (US) [1]. Each year, the global incidence of AP is 340 cases per one million people and this rate continues to rise [2,3]. AP results from inflammation of the pancreas and is commonly associated with gallstones and alcohol use [4]. Acute pancreatitis severity can be categorized as mild, moderate or severe using the Atlanta classification system, with moderate to severe AP requiring transient or persistent multiple organ dysfunction [5,6]. Acute necrotizing pancreatitis (ANP) is categorized as moderate to severe, as it is often associated with organ failure [7]. In most cases, AP presents with limited symptoms, but occasionally it is accompanied by complications that include peripancreatic fluid collection, pancreatic pseudocysts, pancreatic necrosis, and systemic problems (respiratory, cardiovascular, or acute renal failure) [8,9].

Given AP's variable and often severe presentation when necrosis is present, clinical decisions need to be made urgently. Different scoring systems for the early identification of AP include the Acute Physiology and Chronic Health Evaluation (APACHE-II), Ranson's score, Modified Computed Tomography Severity Index (MCTSI), and Bedside Index of Severity in Acute Pancreatitis (BISAP) [10]. However, each scoring system has its own distinctive application and limits. For example, APACHE-II has high predictive accuracy, and it cannot be used exclusively for pancreatic necrosis (infected or noninfected). Likewise, the Ranson score needs exhaustive evaluation on admission and 48 h later. The BISAP score has poor sensitivity for severe AP, limiting its applicability to ANP [11]. MCTSI requires imaging and relies on a radiologist's subjective analysis to measure the area involved in pancreatic necrosis/inflammation. We aimed to develop a simple and effective scoring system to predict the ANP inpatient mortality at 7- and 30-days of admission using the US population.

Materials and methods

Design and data source

For the derivation cohort, we carried out a retrospective analysis using the National Inpatient Sample (NIS) database, evaluating adult (≥18 years) hospitalizations for ANP in the US from January 1 to December 31, 2019 [12]. The NIS was developed as a stratified probability sample to represent all nonfederal hospitals in the US. Detailed information on the design and sampling methods of NIS are available at https://www.hcup-us.ahrq.gov. The NIS database was queried for the principal discharge diagnosis of ANP using ICD-10 codes (Supplementary Table 1) over the study period. Individuals ≤17 years old were excluded from the study.

Outcome measures and statistical analysis

We determined independent predictors that had a >50% increased hazard ratio to develop a risk scoring system for 7- and 30-day inpatient mortality for AP hospitalizations. Additional variables, including acute renal failure, mechanical ventilation, disseminated intravascular coagulopathy, sepsis with shock, acute peritonitis, pseudocyst, paralytic ileus, thromboembolism, respiratory distress syndrome and vasopressor use, were incorporated in the hierarchal multivariate Cox regression analysis. Based on this regression analysis, a specific score was assigned to these variables and the mortality rate for aggregate scores was obtained. Kaplan-Meier curves were generated based on the study findings. We also utilized receiver operating characteristics (ROC) analysis to assess the model's performance in terms of the area under the curve (AUC) [13]. The models' predictive performance was assessed using the validation cohort from the NIS study period January 1, 2016, to December 31st, 2017. Any difference between the 2 models was compared using a standard non-parametric test (Delong Test), with statistical significance when P<0.001 [14]. The regression models were tested for over-dispersion using a Pearson goodness-of-fit test before our analysis, and these models were not over dispersed.

Analyses were performed using STATA version 16.0. Hierarchal multivariate Cox regression models were built based on univariate analysis to adjust confounding variables. Only variables associated with the outcome of interest on univariable regression analysis at P<0.2, or known potential confounders despite the P-value indicating no significance, were used in multivariate Cox regression to assess mortality during admission. Our analysis set 0.05 as the threshold for statistical significance and all P-values were 2-sided. All outcomes were adjusted for patient and hospital-level confounders, including age, race, sex, insurance type, residential region, Elixhauser Comorbidity Index comorbidities, hospital teaching status, and hospital size.

The NIS has been used previously to report inpatient outcomes and to derive predictive scoring models [15-17]. Since the NIS contains de-identified patient data, it was deemed exempt from review as per institutional review board guidelines. Patient consent was also waived in view of the public availability of the data.

Results

A total of 22,980 cases were identified in the derivation cohort for the study period, with a mortality of 4.8%. In the mortality cohort, there was a predominance of male sex (65%) and white race (73%). This was followed by African Americans/Blacks (9%), Hispanics (8%), and other races (9%). The mean age was 61.40±1.1 years. The median age of the patients was 52 years (interquartile range 18-90 years). Most hospitalizations were reported at urban teaching hospitals (86%). Medicare was the largest payer (51%), followed by private insurers (30%) and Medicaid (13%) (Table 1). Further demographic characteristics are summarized in Table 1.

Univariate analysis identified several variables associated with an increased risk of inpatient mortality (Supplementary Table 2). The multivariate Cox regression analyses of all common clinical data indicated that 5 variables were significantly associated with patient death at 7- and 30-day intervals during hospitalization (Supplementary Table 3). These variables included age ≥60 years (adjusted hazard ratio [aHR] 2.75, 95% confidence interval [CI] 2-3.79; P<0.001), acute renal failure/kidney injury (aHR 2.1, 95%CI 1.34-3.24; P<0.001), sepsis with shock (aHR 3.72, 95%CI 2.32-5.96; P<0.001), vasopressor use (aHR 1.97, 95%CI 1.29-3.03, P<0.001), and disseminated intravascular coagulation (aHR 1.92, 95%CI 1.01-2.76; P=0.006). These were used to develop the "mortality in acute necrotizing pancreatitis during admission" (MANP-A) scoring system for inpatient mortality at 7- and 30-day intervals for ANP (Table 2). The new scoring system yields a total maximum score of 5 points and is derived from the sum of the variable scores. Based on the calculated highest sensitivity and specificity values from the ROC curves,

Table 1 Biodemographic characteristics of hospitalizations for ANP in the derivation cohort

Patient characteristics	ANP-associated survivor cohort	ANP-associated mortality cohort	P-value
Total hospitalizations	21875	1105	
Sex			0.5
Male	13825 (63%)	720 (65%)	
Female	8050 (37%)	385 (35%)	
Mean age (years) ± SE	51.69±0.27	61.40±1.1	<0.001
Race/ethnicity			0.06
White	14165 (67%)	785 (73%)	
Black	2660 (13%)	100 (9%)	
Hispanic	2825 (13%)	90 (8%)	
Asian or Pacific Islander	750 (4%)	60 (6%)	
Native American	255 (1%)	5 (<1%)	
Other	600 (3%)	30 (3%)	
Elixhauser comorbidity index score			<0.001
0	720 (3%)	0 (0%)	
1	2070 (9%)	10 (1%)	
2	3350 (15%)	30 (3%)	
≥3	15735 (72%)	1065 (96%)	
Median annual income in patient's zip code, US$			0.2
$1-24,999	5970 (28%)	355 (33%)	
$25,000-34,999	5395 (25%)	295 (27%)	
$35,000-44,999	5615 (26%)	245 (23%)	
$45,000 or more	4560 (21%)	190 (18%)	
Insurance type			
Medicare	6200 (30%)	550 (51%)	<0.001
Medicaid	5080 (24%)	135 (13%)	
Private	8065 (39%)	325 (30%)	
Uninsured	1595 (8%)	60 (6%)	
Hospital characteristics			
Hospital region			0.8
Northeast	3690 (17%)	175 (16%)	
Midwest	5300 (24%)	290 (26%)	
South	7830 (36%)	370 (33%)	
West	5055 (23%)	270 (24%)	
Hospital status			
Rural	910 (4%)	25 (2%)	0.3
Urban non-teaching	2880 (13%)	135 (12%)	
Urban teaching	18085 (83%)	945 (86%)	
Vasopressor use	470 (2%)	300 (27%)	<0.001
Age >60 years	7420 (34%)	690 (62%)	<0.001
AKI	5500 (25%)	885 (80%)	<0.001
DIC	105 (1%)	110 (10%)	<0.001
Septic shock	1355 (6%)	695 (63%)	<0.001

ANP, acute necrotizing pancreatitis; SE, standard error; AKI, acute kidney injury; DIC, disseminated intravascular coagulopathy

the determined cutoff value for predicting ANP inpatient mortality over 7- and 30-day periods using the MANP-A scoring system was 2 points using the Liu index, showing sensitivity 78.38%, specificity 92.98%, and sensitivity 76.32%, specificity 88.01%, respectively (Table 3). The ROC curve was used to evaluate the diagnostic efficiency of the MANP-A score. A total of 23,005 patients were included in the derivation cohort. The AUC of the derivation cohort was 0.9195, 95%CI 0.8838-0.9551 (P<0.001) for 7- and 0.8954, 95%CI 0.8723-0.9185 (P<0.001) for 30-day periods (Fig. 1). The validation cohort contained a sample of 38,644 patients. The AUC of the Validation Cohort was 0.9204, 95%CI 0.8937-0.9469 (P<0.001) for 7- and 0.9059, 95%CI 0.8893-0.9223 (P<0.001) for 30-day periods (Fig. 2).

Discussion

Necrosis and multi-organ dysfunction greatly impact inpatient mortality, with severe disease often requiring care

at the Intensive Care Unit (ICU) level [18,19]. ANP can have varying prognoses depending on its severity. No specific score exists for ANP, although the previously described scores are often applied to AP with or without necrosis. Currently, the 4 scoring systems are APACHE-II, Ranson score, BISAP, and MCTSI. Each score has a specific application and its own limitations.

Table 2 Seven- and 30-day inpatient mortality for acute necrotizing pancreatitis hospitalizations in the United States using the mortality in acute necrotizing pancreatitis (MANP) during admission scoring system

MANP score	7-day mortality rate (%)	30-day mortality rate (%)
0	0.29%	0.28%
1	1.78%	2.64%
2	5.81%	9.45%
3	43.05%	55.00%
4	60.11%	63.16%
5	88.99%	99.99%

Table 3 Score-specific sensitives and specificities using the mortality in acute necrotizing pancreatitis scoring system

Score	7-day period (cutoff point=2)		30-day period (cutoff point=2)	
	Sensitivity	Specificity	Sensitivity	Specificity
0	100%	0%	100%	0%
1	95.95%	59.39%	96.84%	52.69%
2	78.38%	92.98%	76.32%	88.01%
3	55.41%	99.46%	53.68%	98.11%
4	16.22%	99.83%	13.16%	99.66%
5	0%	100%	0.53%	100%

In the present study mortality cohort, the population had a mean age of 61.40±1.1 years, with a predominance of white race and male sex (Table 1). This is consistent with previous reports of AP [20]. Several etiologies exist for AP, with the most common being secondary to alcoholic and gallstone pancreatitis [21]. According to previous reports, alcohol use is significantly higher in males than females [22]. The literature is scarce regarding race- and sex-related trends of ANP. In our study, the total mortality of ANP was 5% in the derivation cohort. Depending on severity, previous studies describe similar mortality results from 5-9% [19]. The inpatient mortality can rise as high as 30% in cases of superimposed infection [23].

In the present study, we developed a simple risk scoring system comprised of only 5 variables, based on the clinical picture and biogeographical data. These variables included age ≥60 years, acute renal failure/kidney injury, sepsis with shock, vasopressor use, and disseminated intravascular coagulation. These variables were selected after multivariate Cox regression, adjusting for various multilevel patient comorbidities and hospital level confounders. Using these variables, we estimated percentage mortality at 7- and 30-day intervals. The validity of the predictive model was confirmed using ROC analysis and the Liu index [24].

Mortality was estimated for both 7- and 30-day intervals. The MANP-A scoring system is straightforward to use, as it has a maximum score of only 5 points using dichotomous variables (0 or 1 point). All variables are objective clinical measures, allowing the score to be easily obtained during hospitalization. In contrast to previous scoring systems, such as APACHE II and BISAP, the MANP-A scoring system does not include mental status assessment. It also does not include imaging or subjective measures (radiological assessment that can vary

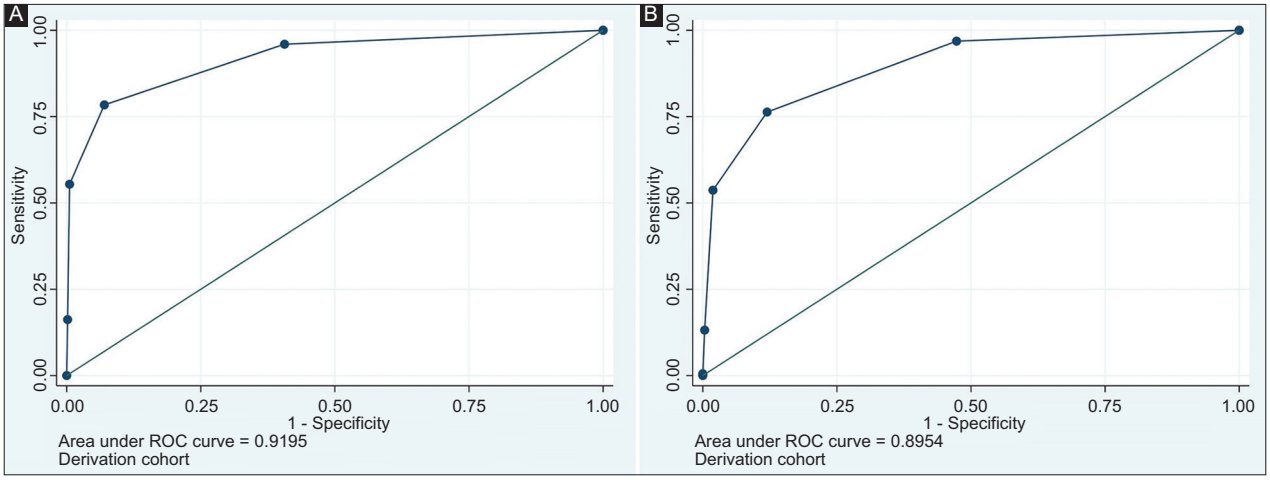

Figure 1 ROC curves for in-hospital mortality over 7- (A) and 30-day (B) periods using the proposed scoring system in the derivation cohort with acute necrotizing pancreatitis
ROC, receiver operating characteristic

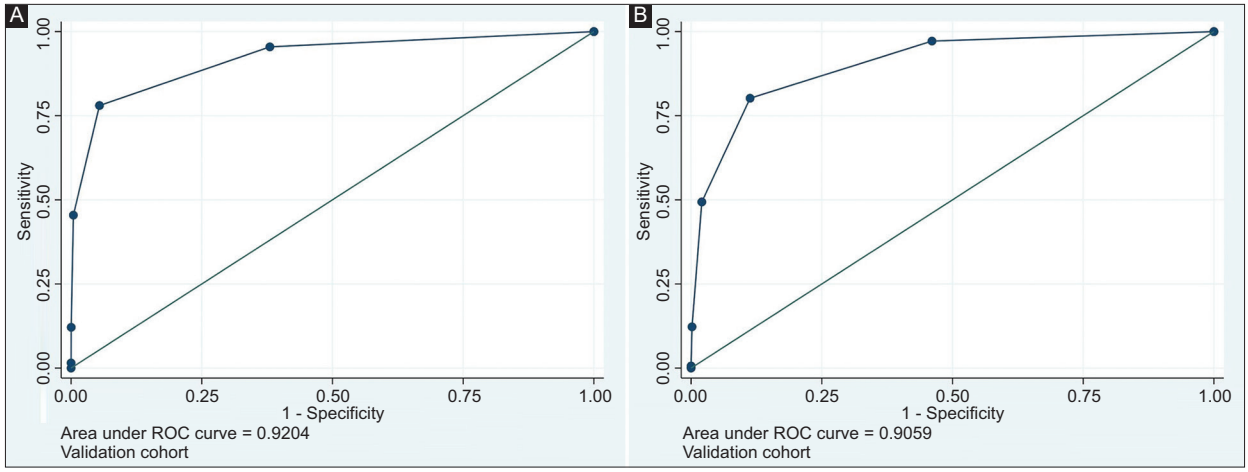

Figure 2 ROC curves for in-hospital mortality over 7- (A) and 30-day (B) periods using the proposed scoring system in the validation cohort with ANP
ROC, receiver operating characteristic; ANP, acute necrotizing pancreatitis

from radiologist to radiologist) to assess inpatient mortality, as the MCTSI system does.

This study has several strengths, with the greatest being the sample size. The study population was obtained from one of the largest inpatient databases available in the US. The weighted counts in the NIS approximate up to 95% of the US population, allowing for generalizable results. Hierarchal regression models allowed for patient and hospital level confounder adjustments, which provided a more accurate and detailed analysis (Supplementary Material). The validation cohort was even larger and had a mix of ICU and general floor patients.

There are several limitations to this study. The database does not report subjective symptoms or AP treatments, nor laboratory values that would be needed to compare our scoring system to other scoring systems. Imaging data, which may offer prognostic value in ANP, were unavailable. The study lacked randomization and blinding, which can impact result interpretation. The scoring system is specific for ANP and not for AP without necrosis, with necrosis confirmation requiring imaging. As the ICD information does not relate to when in the timeline of hospitalization these occurred, it could be that such events only occurred late during hospitalization. Despite these limitations, the large study cohort, unique methodology, and analysis add valuable details to the current literature on ANP.

In conclusion, we report a simple scoring system for predicting inpatient mortality at 7- and 30-day intervals for ANP, based on data from the US population. All variables included in this scoring system can be easily measured during admission. This scoring system would be the first to be specific for ANP. Future research using prospective multicenter studies to compare the MANP-A scoring system to other systems would be beneficial to further support our findings.

Summary Box

What is already known:

- Acute necrotizing pancreatitis (ANP) is a known complication of acute pancreatitis (AP)
- Mild AP is self-limiting; however, ANP leads to significantly higher inpatient mortality rates, up to 30%
- ANP with sepsis has a higher mortality rate than ANP without sepsis

What the new findings are:

- Medicare are the largest payer for ANP hospitalizations, followed by private insurers and Medicaid
- Age ≥60 years, acute renal failure/kidney injury, septic shock, vasopressor use, and disseminated intravascular coagulation significantly increase mortality in ANP hospitalizations
- The mortality in ANP during admission score is a simple mortality scoring system to predict inpatient mortality for ANP hospitalizations

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Supplementary material

Supplementary Table 1 List of ICD-10 codes utilized in the present study

Acute necrotizing pancreatitis	K8502, K8512, K8522, K8532, K8582, K8592, K8501, K8511, K8521, K8531, K8581, K8591
Acute renal failure	N170, N171, N172, N178, N179
Disseminated intravascular coagulation	D65
Septic shock	R6521
Vasopressor use	3E030XZ, 3E033XZ, 3E040XZ, 3E043XZ, 3E050XZ, 3E053XZ, 3E060XZ, 3E063XZ
Pancreatic pseudocyst	K863
Peritonitis	K650
Acute respiratory distress syndrome	J80
Portal vein thrombosis	I81
Paralytic ileus	K560
Hyponatremia	E871
Congestive Heart Failure	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5–I42.9, I43, I50, P29.0
Cardiac Arrhythmia	I44.1–I44.3, I45.6, I45.9, I47–I49, R00.0, R00.1, R00.8, T82.1, Z45.0, Z95.0
Valvular Disease	A52.0, I05–I08, I09.1, I09.8, I34–I39, Q23.0–Q23.3, Z95.2–Z95.4
Pulmonary Circulation Disorders	I26, I27, I28.0, I28.8, I28.9
Peripheral Vascular Disorders	I70, I71, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
Hypertension without Complications	I10
Hypertension with Complications	I11–I13, I15
Paralysis	G04.1, G11.4, G80.1, G80.2, G81, G82, G83.0–G83.4, G83.9
Other Neurological Disorders	G10–G13, G20–G22, G25.4, G25.5, G31.2, G31.8, G31.9, G32, G35–G37, G40, G41, G93.1, G93.4, R47.0, R56
Chronic Pulmonary Disease	I27.8, I27.9, J40–J47, J60–J67, J68.4, J70.1, J70.3
Diabetes without Complications	E10.0, E10.1, E10.9, E11.0, E11.1, E11.9, E12.0, E12.1, E12.9, E13.0, E13.1, E13.9, E14.0, E14.1, E14.9
Diabetes with Complications	E10.2–E10.8, E11.2–E11.8, E12.2–E12.8, E13.2–E13.8, E14.2–E14.8
Hypothyroidism	E00–E03, E89.0
Renal Failure	I12.0, I13.1, N18, N19, N25.0, Z49.0–Z49.2, Z94.0, Z99.2
Liver Disease	B18, I85, I86.4, I98.2, K70, K71.1, K71.3–K71.5, K71.7, K72–K74, K76.0, K76.2–K76.9, Z94.4
Peptic Ulcer Disease excluding Bleeding	K25.7, K25.9, K26.7, K26.9, K27.7, K27.9, K28.7, K28.9
HIV/AIDS	B20–B22, B24
Lymphoma	C81–C85, C88, C96, C90.0, C90.2
Metastatic Cancer	C77–C80

(*Contd...*)

Supplementary Table 1 (*Continued*)

Solid Tumor without Metastasis	C00-C26, C30-C34, C37-C41, C43, C45-C58, C60-C76, C97
Rheumatoid Arthritis/Collagen	L94.0, L94.1, L94.3, M05, M06, M08, M12.0, M12.3, M30, M31.0–M31.3, M32–M35, M45, M46.1, M46.8, M46.9
Coagulopathy	D65–D68, D69.1, D69.3–D69.6
Obesity	E66
Weight Loss	E40–E46, R63.4, R64
Fluid and Electrolyte Disorders	E22.2, E86, E87
Blood Loss Anemia	D50.0
Deficiency Anemia	D50.8, D50.9, D51–D53
Alcohol Abuse	E52, F10, G62.1, I42.6, K29.2, K70.0, K70.3, K70.9, T51, Z50.2, Z71.4, Z72.1
Drug Abuse	F11 E52, F16, F18, F19, Z71.5, Z72.2
Psychoses	F20, F22–F25, F28, F29, F30.2, F31.2, F31.5
Depression	F20.4, F31.3–F31.5, F32, F33, F34.1, F41.2, F43.2

Supplementary Table 2 Univariate cox regression for proposed mortality scoring system

Variables	Hazard Ratio [95%CI]	P-value
Female	1.01 [0.74-1.36]	0.9
Black race vs. white	0.73 [0.44-1.21]	0.23
Hispanic race vs. white	0.58 [0.33-1.01]	0.7
Asian race vs. white	1.32 [0.71-2.46]	0.4
Heart failure	2.01 [1.48-2.95]	<0.001
Cardiac arrythmias	1.78 [1.31-2.42]	<0.001
Valvular disease	1.59 [0.77-3.25]	0.21
Pulmonary embolisms	1.59 [0.96-2.65]	0.07
Peripheral vascular disease	2.24 [1.41-3.54]	<0.001
Hypertension	0.37 [0.27-0.51]	<0.001
COPD	1.14 [0.78-1.66]	0.4
Diabetes Mellitus	0.87 [0.61-1.26]	0.4
Chronic renal failure	2.19 [1.56-3.1]	<0.001
Chronic liver disease	1.58 [1.77-2.13]	<0.001
Peptic ulcer disease excluding bleeding	0.72 [0.24-2.15]	0.5
Coagulopathy	2.34 [1.73-3.15]	<0.001
Obesity	0.97 [0.66-1.43]	0.8
Protein Calorie malnutrition	0.75 [0.56-1.01]	0.06
Fluid and electrolyte disorder	2.49 [1.61-3.85]	<0.001
Iron deficiency Anemia	1.06 [0.59-1.89]	0.8
Alcohol abuse	0.53 [0.37-0.75]	0.001
Age >60	2.99 [2.2-4.10]	0.001

(*Contd*...)

Supplementary Table 2 (*Continued*)

Variables	Hazard Ratio [95%CI]	P-value
ARDS	1.65 [0.79-3.42]	0.1
AKI	4.91 [3.27-7.38]	<0.001
Sepsis with shock	7.31 [5.20 -10.2]	<0.001
Intubation	3.44 [2.42 -4.89]	<0.001
Vasopressor use	5.20 [3.55 -7.61]	<0.001
SIRS	0.59 [0.29 -1.19]	0.1
Pancreatic Pseudocyst	0.53 [0.37 -0.74]	<0.001
Hyponatremia	0.79 [0.57 -1.11]	0.1
Acute Peritonitis	0.38 [0.1 -2.56]	0.3
DIC	4.59 [2.63-8.00]	<0.001
Paralytic Ileus	1.74 [0.85 -3.53]	0.4
Portal venous thrombosis	0.99 [0.61 -1.61]	0.9
Hospital region, Teaching compared to non-teaching	1.09 [0.95-1.25]	0.9
Hospital Bedsize, Large compared to small	1.17 [0.94 -1.47]	0.9

COPD, chronic obstructive pulmonary disease; ARDS, acute respiratory distress syndrome; AKI, acute kidney injury; SIRS, systemic inflammatory response syndrome; DIC, disseminated intravascular coagulation; 95%CI, 95% confidence interval

Supplementary Table 3 Multivariate cox regression for proposed mortality scoring system

Variables	Hazard Ratio [95%CI]	P-value
Heart Failure	1.21 [0.82-1.76]	0.3
Cardiac arrythmias	1.14 [0.82-1.76]	0.4
Peripheral vascular disease	1.62 [0.99-2.50]	0.09
Chronic renal failure	1.43 [0.98-2.07]	0.06
Chronic liver disease	1.60 [0.83-2.21]	0.2
Coagulopathy	1.24 [0.88-1.74]	0.2
Fluid and electrolyte disorders	1.46 [0.95-2.22]	0.07
Age >60	2.75 [2.01-3.79]	<0.001
Acute kidney injury	2.10 [1.34-3.24]	<0.001
Sepsis with shock	3.72 [2.32-5.96]	<0.001
Intubation	0.91 [0.60-1.38]	0.7
Vasopressor	1.97 [1.29-3.03]	<0.001
DIC	1.92 [1.01-2.76]	<0.001
ARDS	1.31 [0.78-2.67]	0.1
Valvular disease	1.72 [0.98-1.93]	0.5
Pulmonary embolisms	1.51 [0.28-3.07]	0.09
Peripheral vascular disease	1.31 [0.78-2.67]	0.2

ARDS, acute respiratory distress syndrome; DIC, disseminated intravascular coagulation; 95%CI, 95% confidence interval