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Abstract

Background: The burden of paralytic ileus (PI) in the intensive care unit (ICU) remains high, and the Charlson Comorbidity Index (CCI) is strongly associated with the prognosis of several acute and chronic diseases. However, there is no literature on the clinical value of CCI as a prognostic assessment tool for critically ill patients with PI in the ICU.

Objective: The aim of this study was to investigate the relationship between CCI and clinical prognosis in critically ill patients with PI.

Methods: In this study, data from the Critical Care Medical Information Marketplace IV 2.2 database were used to determine the optimal cutoff value of CCI for predicting mortality in patients with PI using receiver operating characteristic (ROC) curves, and the relationship between CCI and mortality was evaluated using Cox regression and restricted cubic spline analysis. A machine learning (ML) prediction model was then constructed to predict hospital mortality by combining CCI and other clinical characteristics.

Results: The study included 863 patients with PI (median age 65.4 years [interquartile range 54.6-75.5 years], 66.6% male). The ROC curve identified an optimal cut-off value of 4.5 for CCI. Multivariate Cox regression analysis showed that compared to the lowest CCI quartile, patients with elevated CCI levels were more likely to have elevated hospital (Q4: HR 2.447, 95% CI 1.210-4.951), 28-day (Q4: HR 3.891, 95% CI 1.956-7.740) and 90-day (Q4: HR 3.994, 95% CI 2.224-7.173) all-cause mortality were significantly associated with elevated CCI levels; however, the association with ICU mortality (Q4: HR 1.892, 95% CI 0.653-5.480) was weak. Among the 11 ML models, the LightGBM model performed best, with internal validation results showing an area under the curve of 0.811, a G-mean of 0.670, and an F1 score of 0.895.

Conclusions: The CCI is an important predictor of hospital, 28-day, and 90-day all-cause mortality in critically ill patients with PI, and the optimal threshold is 4.5. ML models including the CCI show high accuracy in predicting hospital mortality, and the CCI occupies an important position in the model. This suggests that the CCI helps to identify high-risk patients, supports clinical decision making, and improves prognosis. Clinical Trial: NO

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Original Manuscript

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Abstract

Background

The burden of paralytic ileus (PI) in the intensive care unit (ICU) remains high, and the Charlson Comorbidity Index (CCI) is strongly associated with the prognosis of several acute and chronic diseases. However, there is no literature on the clinical value of CCI as a prognostic assessment tool for critically ill patients with PI in the ICU. The aim of this study was to investigate the relationship between CCI and clinical prognosis in critically ill patients with PI.

Methods

In this study, data from the Critical Care Medical Information Marketplace IV 2.2 database were used to determine the optimal cutoff value of CCI for predicting mortality in patients with PI using receiver operating characteristic (ROC) curves, and the relationship between CCI and mortality was evaluated using Cox regression and restricted cubic spline analysis. A machine learning (ML) prediction model was then constructed to predict hospital mortality by combining CCI and other clinical characteristics.

Results

The study included 863 patients with PI (median age 65.4 years [interquartile range 54.6-75.5 years], 66.6% male). The ROC curve identified an optimal cut-off value of 4.5 for CCI. Multivariate Cox regression analysis showed that compared to the lowest CCI quartile, patients with elevated CCI levels were more likely to have elevated hospital (Q4: HR 2.447, 95% CI 1.210-4.951), 28-day (Q4: HR 3.891, 95% CI 1.956-7.740) and 90-day (Q4: HR 3.994, 95% CI 2.224-7.173) all-cause mortality were significantly associated with elevated CCI levels; however, the association with ICU mortality (Q4: HR 1.892, 95% CI 0.653-5.480) was weak. Among the 11 ML models, the LightGBM model performed best, with internal validation results showing an area under the curve of 0.811, a G-mean of 0.670, and an F1 score of 0.895.

Conclusion

The CCI is an important predictor of hospital, 28-day, and 90-day all-cause mortality in critically ill patients with PI, and the optimal threshold is 4.5. ML models including the CCI show high accuracy in predicting hospital mortality, and the CCI occupies an important position in the model. This suggests that the CCI helps to identify high-risk patients, supports clinical decision making, and improves prognosis.

Keywords: Charlson Comorbidity Index, Paralytic ileus, MIMIC-IV database, all-cause mortality, machine learning

Introduction

Paralytic ileus (PI) is a common functional intestinal obstruction due to decreased or loss of intestinal motility, with etiologic factors including electrolyte imbalance, severe infection, substance abuse, and abdominal surgery^{1, 2}. The global incidence is approximately 1-5 cases per 100,000 people, with a higher incidence in women but a higher mortality rate in men³. The overall mortality rate for PI is 5-6%, but this increases to 10-20% in the intensive care unit (ICU) patients^{1, 4}. Patients with PI are often associated with chronic diseases or comorbidities such as diabetes, neurological diseases, systemic sclerosis, and malignant cancer, and the cumulative burden of these underlying diseases may have a significant impact on mortality⁵⁻⁸. Given the high morbidity and mortality associated with PI, it is important to accurately identify high-risk patients and assess their prognostic risk.

The Charlson Comorbidity Index (CCI) is a comprehensive index that calculates a patient's expected years of survival by scoring the patient's common underlying diseases (e.g., diabetes, malignant cancer, connective tissue disorders, etc.) and their impact on the overall prognosis, and thus predicting the patient's risk of death^{9, 10}. This index has been widely used in the prognostic assessment of many diseases, and has significant prognostic value especially in elderly patients, critically ill patients and cancer patients¹¹⁻¹⁴. In addition, the CCI has also been widely validated in chronic granulocytic leukemia¹⁵, in the assessment of postoperative complications¹⁶, and in the prediction of fracture risk¹⁷. Despite the important prognostic value of CCI in a variety of clinical scenarios, its role in specific high-risk populations has not been fully investigated. In particular, in critically ill patients with PI, the assessment of mortality risk is more challenging because of the complex underlying diseases that often accompany them, and studies on the prognostic predictive value of CCI in such patients are scarce.

In recent years, with the rapid development of big data and machine learning (ML) technologies, mortality prediction models based on electronic health record data and clinical characteristics have gradually become a hot research topic. ML models are able to discover the complex relationship between potential patient characteristics and mortality risk by processing a large amount of unstructured and high-dimensional data, and have stronger predictive ability than traditional statistical methods, which can realize the accurate assessment of mortality risk in critically ill patients¹⁸⁻²⁰. Therefore, the primary objective of this study was to evaluate the relationship between CCI and all-cause mortality at hospital, ICU, 28-day, and 90-day in patients with PI in the ICU. The exploratory objective was to assess the feasibility of CCI in constructing ML models for predicting all-cause mortality in hospitals with PI patients.

Methods

Study participants

This is a retrospective cohort study. The Massachusetts Institute of Technology (MIT) and Beth Israel Deaconess Medical Center (BIDMC) collaborated to develop the Medical Information Marketplace in Critical Care (MIMIC-IV) electronic database (version 2.2), which was used for this study²¹. The database contains information on more than 50,000 patients who received ICU care at BIDMC between 2008 and 2019. The database provides a wide range of clinical data and has been used extensively in critical care medicine research²²⁻²⁴. Detailed information about the database, including access instructions, is available at <https://physionet.org/content/mimiciv/2.2/>. The Institutional Review Board (IRB) of BIDMC waived informed consent and allowed sharing of research resources because all data were de-identified. Therefore, this study did not require additional informed consent (2001-P-001699/14; No. 0403000206). In order to comply with the regulations, the author, Feng Hui, obtained a Cooperative Institutional Training Initiative (CITI) license (certification number: 61863057) and the necessary permission to use the MIMIC-IV database. All procedures involving human participants in this study adhered to the ethical standards of the Institutional and National Research Councils as well as the 1964 Declaration of Helsinki and its subsequent amendments or equivalent ethical standards.

Adult patients who were first admitted to hospital with a diagnosis of PI according to the International Classification of Diseases (ICD-9: 427.31, ICD-10: I48.X) were included in this study. Individual patient consent was not required due to anonymised nature of patient health information in this database. Exclusion criteria included: (1) patients who stayed in the ICU for <6 h; (2) multiple ICU admissions for which only data from the first admission were extracted; and (3) patients who lacked information on CCI. Finally, a total of 863 patients were included in this study and divided into four groups according to the quartiles of CCI (**Fig. 1**).

Fig. 1 Flow of included patients through the trial

Patient characteristics

Data collection involved the use of Structured Query Language (SQL) and PostgreSQL (version 16.3.7) to extract baseline patient characteristics. The following data were obtained: (1) Demographic information: sex, age, race. (2) Comorbidities identified according to ICD-9 or ICD-10: congestive heart failure (CHF), renal disease, malignant cancer, sepsis, diabetes, hypertension. (3) Mean vital signs: respiratory rate, mean blood pressure (MBP), heart rate (HR), oxygen. (4) Laboratory parameters include white blood cell (WBC), red blood cell distribution width (RDW), platelets (PTL), hemoglobin (Hb), anion gap, blood urea nitrogen, creatinine, total calcium (Ca), chloride (Cl), sodium (Na), potassium (K). (5) Scores: Simplified Acute Physiology Score II (SAPSII), Oxford Acute Severity of Illness Score (OASIS), Acute Physiology Score III (APSIII), Sequential Organ Failure Assessment Score (SOFA) and CCI. (6) Therapeutic agents: ondansetron and neostigmine. All laboratory variables were obtained from the first 24 hours after the patient's admission to the ICU. Follow-up began on the date of ICU admission and ended on the date of death. Variables with more than 10% missing values were excluded to mitigate potential bias²⁵. The proportions of missing values for variables are shown in **Supplementary Fig. S1A**, and variables

with less than 10% missing values were interpolated using the Random Forest interpolation method implemented in the missForest package of the R software²⁶. In the ML section, the PI patients were divided into a 70% training cohort and a 30% test cohort.

Clinical outcome

The primary outcome of this study was all-cause hospital mortality, and secondary outcomes were ICU mortality and mortality at 28 and 90 days after ICU admission. In addition, the primary objective of the ML modeling was all-cause hospital mortality.

Statistical analysis

The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Continuous variables that followed a normal distribution were analyzed using the t-test or ANOVA, and those that were not normally distributed were analyzed using the Mann-Whitney U-test or the Kruskal-Wallis test. Categorical variables were compared by the chi-square test. The CCI was categorized into four quartiles, Kaplan-Meier survival analysis was used to assess differences in mortality between groups, and Log-rank tests were used to compare differences between groups. The optimal cut-off value for CCI was determined by receiver operating characteristic (ROC) curve analysis using Youden index maximisation method. Variance inflation factor (VIF) was used to assess multicollinearity between variables, and variables with a VIF greater than 5 were removed (**Supplementary Fig. S1B**).

Cox regression analysis was used to assess the association between CCI and hospital mortality, ICU mortality, as well as 28- and 90-day mortality, with model 1 including only CCI and model 2 including age and sex as correction variables. Model 3 included the following variables on the basis of clinical expertise, previous literature⁴, the ML algorithm and the results of the feature importance selection of the LASSO algorithm: sex, age, CHF, renal disease, malignant cancer, sepsis, diabetes, hypertension, RR, SpO₂, WBC, RDW, platelet, anion gap, BUN, creatinine, SAPSII, OASIS, APACHE II, SOFA. In addition, restricted cubic spline(RCS) analyses were performed in order to explore the potential non-linear relationship between CCI levels and hospital, ICU, and 28- and 90-day all-cause mortality rates. the CCI was used as a continuous or ordinal variable entered into the model (the first quartile of CCI served as the reference group). P values for trends were calculated using interquartile ranges. Further stratified analyses were performed according to sex, age (≤ 65 and > 65 years), CHF, malignant cancer, sepsis, and diabetes to determine the consistency of the prognostic value of CCI for the primary outcome. Likelihood ratio tests were used to examine the interaction between CCI and the variables used for stratification. A two-sided $P < 0.05$ was considered statistically significant.

To test the robustness of the results of the primary analysis, several sensitivity analyses were performed. First, patients who died within 3 days of ICU admission were excluded to assess whether these patients had a significant impact on the primary outcome. Second, patients were grouped according to the optimal cut-off value of the CCI to test the stability of the main results by different CCI groupings. Finally, a stratified analysis of SOFA scores was performed: patients were divided into three groups based on their 24-hour SOFA scores after ICU admission: low (first 1/3 quartile), intermediate (1st/3rd to 2nd/3rd quartile), and high (last 1/3 quartile). This grouping method helps to further validate the effect of different SOFA score groups on the relationship between CCI and

mortality.

In addition, an ML model was constructed to predict all-cause hospital mortality in PIs using a binary classification approach. The correlation between all variables was first assessed using a Pearson correlation test, with a threshold correlation coefficient (r) > 0.5 indicating a moderate correlation. Variables with correlation coefficients above this threshold were excluded to mitigate potential problems of multicollinearity, which could mask the independent effects of key predictor variables, destabilise model parameter estimates and affect the reliability of feature importance rankings. The entire cohort was then divided into a training cohort and an internal validation cohort in a 7:3 ratio. Continuous variables were then standardised, categorical variables were uniquely coded, and lasso regression and three ML algorithms with default parameters were used to rank the importance of features in the training cohort. For model building, we selected the top 10 most important features identified by lasso regression and each of the three ML methods, and created a combined set of features based on their importance ranking for subsequent model building. The selected features were again tested for Pearson correlation and additional variance inflation factors to avoid multicollinearity between features. The ten features were then incorporated into 11 common medical ML algorithms (e.g. LightGBM, Random Forest, Extreme Gradient Boosting model). A random search approach was used for hyperparameter tuning in R using the trainControl function. This approach is powerful and efficient, and is particularly suited to exploring large hyperparameter spaces because it works by randomly sampling different combinations of parameters rather than exhaustively testing all combinations. The optimal hyperparameters identified by this process are shown in **Supplementary Table S1**. Subsequently, in the internal validation queue, ROC curves were plotted for the ML model, SOFA and SAPS II and their performance was compared based on different metrics (area under the curve [AUC], accuracy, specificity, F1 score, G-mean, precision and recall). Finally, for the best performing ML models, Shapley Additive Properties (SHAP) were used to visualise the importance of features in the model and to generate partial dependence graphs to illustrate the relationship between specific features and outcomes. Finally, an easy-to-use online prediction platform was built based on the best performing ML models to improve clinical accessibility.

All statistical analyses were performed by using SPSS 23.0 (IBM SPSS Statistics, Armonk, NY, USA), R software (version 4.3.2, USA) and Python (version 3.11.1, USA).

Results

Baseline characteristics

After screening the data of PI patients in the MIMIC IV database, 863 patients who met the inclusion criteria were included in this study. **Table 1** shows the baseline characteristics of critically ill PI patients stratified by CCI quartiles. Patients were divided into four groups based on their CCI level on admission [quartiles (Q)1: 0-3; Q2: 3-5; Q3: 5-7; Q4: 7-14]. The median CCI values for each quartile in each group were 2 (quartile: 1-3), 4.5 (quartile: 4-5), 6 (quartile: 6-7) and 9 (quartile: 8-10), respectively. The median age of the enrolled patients was 65.4 years (interquartile range: 54.6-75.5 years), of which 575 (66.6%) were male. The median CCI for all participants was 5 (interquartile range: 3-7). Compared to the lower group, patients in the highest CCI quartile generally had higher age, RDW, anion gap, BUN, creatinine, SAPSII, OASIS, APSIII, SOFA, and lower MBP,

heart rate, and haemoglobin, higher CHF, renal disease, malignant cancer, diabetes prevalence, lower hypertension prevalence. Hospital mortality, ICU mortality, 28-day mortality, and 90-day mortality were 18.2%, 8.81%, 19.8%, and 27%, respectively. As the Q4 group was better associated with all-cause mortality, the differences between Q4 and Q1-3 were further compared. The analysis showed that different grouping methods gave similar results (**Supplementary Table S2**).

Table 1 Characteristics and outcomes of participants categorised by CCI

Table 2 shows the differences in baseline characteristics between survivors and non-survivors during hospitalisation. Patients in the non-survivor group were more likely to have higher RR, heart rate, RDW, anion gap, BUN, creatinine, SAPSII, OASIS, APSIII, SOFA, CCI, higher prevalence of CHF, sepsis, lower prevalence of hypertension, lower SpO₂, platelets, haemoglobin, calcium, lower ondansetron and neostigmine use. CCI values were significantly higher in the non-survivors than in the survivors (6 vs 5, $P < 0.001$). Figure S1 shows the distribution of CCIs stratified by mortality status for inpatient deaths, ICU deaths, 28-day deaths, and 90-day deaths (**Supplementary Fig. S2**).

Table 2 Baseline characteristics of the survivor and non-survivor groups

Primary outcomes

Kaplan-Meier survival analyses showed that patients with higher CCI scores had a significantly higher risk of hospital, 28-day and 90-day all-cause mortality (**Fig. 2**). ROC curve analyses assessed the clinical efficacy of the CCI (**Supplementary Fig. S3**) and showed that the AUCs of the CCIs were all greater than 0.5, which to some extent discriminated patients who died in hospital, ICU, 28-day and 90-day from those who did not (AUC for hospital deaths: 0.631, OR: 1.17, 95% CI: 1.10 - 1.24, $P < 0.001$; AUC for ICU deaths: 0.58, OR: 1.10, 95% CI: 1.02 - 1.20, $P = 0.016$; 28-day deaths (AUC: 0.678, OR: 1.24, 95% CI: 1.17 - 1.32, $P < 0.001$; 90-day ICU death AUC: 0.687, OR: 1.27, 95% CI: 1.20 - 1.34, $P < 0.001$). The optimal CCI cut-off for hospital, ICU, 28-day and 90-day death was 4.5.

Fig. 2 Kaplan-Meier survival analysis curves for all-cause mortality. footnote CCI quartiles: Q1 (0-3), Q2 (3) Kaplan-Meier curves for cumulative mortality: Q1 (0-3), Q2 (3-5), Q3 (5-7), Q4 (7-14). Kaplan-Meier curves showing cumulative probability of all-cause mortality by group at hospital (a), ICU (b), 28 days (c) and 90 days (d)

Cox regression analysis was used to assess the association between CCI and in-hospital mortality. The results showed that when CCI was a continuous variable, CCI was a significant risk factor in the unadjusted model [HR, 1.159 (95% CI 1.099-1.222) $P < 0.001$], the partially adjusted model [HR, 1.158 (95% CI 1.088-1.233) $P < 0.001$] and the fully adjusted model [HR, 1.204 (95% CI 1.099-1.319) $P < 0.001$]. When CCI was the ordinal variable, patients in higher quartiles of CCI were significantly associated with a higher risk of in-hospital death compared with subjects in the lowest quartile in all three established Cox regression analysis models: unadjusted model [HR, 3.124 (95% CI 1.945-5.017) $P < 0.001$], partially adjusted model [HR, 2.950 (95% CI 1.708-5.097) $P < 0.001$], and fully adjusted model [HR, 2.447 (95% CI 1.210-4.951) $P = 0.013$] and showed an increasing trend with increasing CCI (**Table 3; Figure 3a**). Similar results were observed in multivariate Cox regression analyses for 28-day mortality (**Table 3; Fig 3**) and 90-day mortality (**Supplementary Table S3; Fig 3**), but less favourable results were observed in multivariate Cox regression analyses

for CCI and ICU mortality (**Supplementary Table S3; Fig 3**). In addition, the use of an RCS regression model showed a linear increase in the risk of hospital, ICU, 28-day and 90-day mortality with increasing CCI (non-linear P values of 0.725, 0.872, 0.635 and 0.288, respectively) (**Fig. 3**).

Fig. 3: HRs (CIs) and restricted cubic spline curves for all-cause mortality from CCI after adjustment for confounders

All models were adjusted for multiple confounders, including sex, age, CHF, renal disease, sepsis, hypertension, diabetes, white blood cell count, red blood cell distribution width, anion gap, creatinine, and CCI. The bar graph shows the HRs for all-cause mortality between different CCI quartiles with the CIs for each group. The bar graph shows the HRs for all-cause mortality between different CCI quartiles, with the CIs for each group. The first quartile of CCI is the reference group to which the other quartiles are compared. The central thick solid line represents the estimated HR after adjustment, the shaded area represents the CIs, and the horizontal dashed line represents the HR of 1.0. The vertical dashed line corresponds to the CCI value where the HR is 1.0. (A) Hospital mortality: The vertical dashed line corresponds to a CCI value of 3.65. (B) ICU mortality: The vertical dashed line corresponds to a CCI value of 2.68. (C) 28-day mortality: The vertical dashed line corresponds to a CCI value of 1.0. (C) 28-day mortality: The vertical dashed line corresponds to a CCI value of 2.68. (C) 28-day mortality: The vertical dashed line corresponds to a CCI value of 4.47. (D) 90-day mortality: The vertical dashed line corresponds to a CCI value of 4.39. HR: hazard ratio; CI: confidence interval HR: hazard ratio; CI: confidence interval; ICU: intensive care unit; CCI: Charlson comorbidity index

Subgroup analysis

Subgroup analyses by sex, age, CHF, malignancy, sepsis and diabetes showed no interaction (all interactions $P > 0.05$), i.e. the association between CCI and the risk of all-cause hospital mortality did not change with changes in the stratification variables of sex, age, CHF, malignant cancer, sepsis and diabetes levels (**Fig. 4**).

Fig. 4 Forest plots of hazard ratios for all-cause mortality in different subgroups. (A) Hospital mortality. (B) ICU mortality. (C) 28-day mortality. (D) 90-day mortality. HR, hazard ratio; CI, confidence interval; ICU, intensive care unit; CHF, congestive heart failure

Sensitivity analysis

Supplementary Table S4 shows that the association between CCI and mortality outcomes in patients with PI remained stable and similar after excluding patients who died within 3 days of ICU admission.

Supplementary Table S5 shows that the sample was divided into groups of ≤ 4.5 and > 4.5 based on the optimal cut-off value for CCI. The results show that regardless of the grouping method used, the conclusions obtained are consistent with the results of the main analysis.

A further sensitivity analysis of the SOFA score for the three groups was performed. The analysis showed that for the different subgroups of SOFA scores, consistent associations were observed between CCI in the higher quartiles and mortality from PIs, supporting the stability of the findings (**Supplementary Table S6**).

Feature pre-selection for ML Models

Baseline characteristics of patients in the training and test cohorts are shown in **Supplementary Table S7**. (**Supplementary Fig. S4**) Heatmaps of all variables for which correlations are provided. Because BUN and creatinine ($r = 0.69$), SAPSII and APSIII ($r = 0.69$) or OASIS ($r = 0.68$), OASIS and APSIII ($r = 0.62$), age and CCI ($r = 0.59$) and chloride and sodium ($r = 0.66$), BUN, SAPSII, OASIS, age and chloride were excluded in the next step. In the training queue, the three ML algorithms with default parameters and the LASSO algorithm preselected the 10 features used to construct the model (**Supplementary Fig. S5**), with CCI ranking in the top ten in each algorithm. Importantly, there is no strong correlation or multicollinearity between the selected features (**Supplementary Fig. S6**).

ML model construction and evaluation

The best hyperparameters were determined after inputting the selected features into the 11 ML models. Then, **Fig. 5A** is the confusion matrix of the LightGBM model, and the ROC curves (**Fig. 5B**) and other metrics (**Fig. 5C**) were evaluated among all the ML models. LightGBM was considered the best model, outperforming other ML models including Random Forest and Extreme Gradient Boosting model. This is because the internal validation results show that it has the highest AUC (0.811), F1 score (0.895) and G-mean (0.670) and outperforms both the traditional SOFA score and the APS III score (**Table 4**).

Visualization of feature importance

The corresponding SHAP values for each feature in the internal validation cohort of the LightGBM model were calculated and ranked (**Fig. 5D** and **Fig. 5E**), and CCI ranked third in significance compared to the other predictor variables. The bias dependence plot (**Fig. 5F**) showed that increased CCI was associated with an increased risk of hospital death in patients with PI.

Fig. 5 Machine learning model construction and evaluation and feature importance visualisation. Confusion matrix of the LightGBM model (A); ROC curves of 11 machine learning models (B); various evaluation metrics of 11 machine learning models (C); feature importance plot of the LightGBM model (D); SHAP plot of the CCI feature (E); bias dependence plot of the CCI (F). RR, respiratory rate; SOFA, Sequential Organ Failure Assessment; CCI, Charlson Comorbidity Index; APS III, Acute Physiology Score III; SPO2, peripheral capillary oxygen saturation; RDW, red blood cell distribution width; AUC, area under the curve; SHAP, Shapley Additive Explanations; XGBoost, Extreme Gradient Boosting; AdaBoost, Adaptive Boosting; SVM, Support Vector Machine; MLP, Multilayer Perceptron; NN, Neural Network; KNN, k-Nearest Neighbours; GBM, Gradient Boosting Machine; GP, Gaussian Process; LR, Logistic Regression; RF, Random Forest; LightGBM, Light Gradient Boosting Machine

Web-based forecasting platform

To improve the usability of the LightGBM model, it has been embedded in a user-friendly website for external users and practitioners to validate or make predictions. The website is "<http://182.92.81.83:8000/>". For example, **Supplementary Fig. S7A** illustrates the case of a 48-year-old PI patient with the characteristics shown. The final output probability of hospital all-cause

mortality is 0.68, indicating a high risk status. This website also allows you to view and download this patient's SHAP Force Plot, as shown in **Supplementary Fig. S7B**.

Discussion

This study analysed the relationship between CCI and clinical outcomes in a US cohort of critically ill PI patients, with the following key findings: (i) Higher levels of CCI were significantly associated with hospital, 28-day and 90-day all-cause mortality in PI patients. Even after correction for confounders, CCI remained strongly correlated with these mortality indicators, with a trend towards a linear relationship. Our study suggests that the critical value of 4.5 for CCI levels provides a potential reference for mortality risk stratification, helping clinicians to identify high-risk patients who require closer monitoring. (ii) A LightGBM model was developed combining CCI and other clinical variables beyond the traditional critical illness score, and the results showed that CCI had a higher weight and contribution in the model. Overall, this study highlights the critical role of CCI in risk stratification of mortality in critically ill PI patients, helping to optimise clinical management strategies.

CCI affects the prognosis of patients with PI through several interrelated biological mechanisms. First, CCI reflects a patient's chronic disease burden, including conditions such as diabetes, neurological disorders and malignant cancer, all of which increase all-cause mortality^{5, 6, 8}. Chronic disease states are associated with persistent low-grade systemic inflammation, which can lead to endothelial dysfunction, oxidative stress and vasoactive imbalances, which in turn exacerbate gut microcirculatory disturbances²⁷⁻²⁹. In addition, patients with high CCI often have suppressed immune function, as evidenced by decreased monocyte HLA-DR expression, T-cell dysfunction and prolonged immune paralysis, making them more susceptible to infectious complications^{30, 31}. The development of infection and sepsis can further exacerbate intestinal dysbiosis³², leading to a vicious cycle of gut flora translocation and toxin release³³. Dysbiosis may also affect the function of the enteric nervous system through abnormalities in short-chain fatty acid metabolism, thereby prolonging the course of PI³⁴⁻³⁶. In addition, patients with a higher CCI usually have a poor nutritional status, as evidenced by hypoproteinemia, muscle wasting and inadequate metabolic reserve³⁷⁻³⁹. These factors may lead to reduced contractile function of the intestinal smooth muscle, delaying recovery of bowel function in PI and increasing the risk of death^{40, 41}. Taken together, CCI affects several key pathophysiological aspects of patients with PI, including chronic inflammation, immunosuppression, impaired intestinal barrier function and malnutrition. The interaction of these mechanisms may explain why CCI is an important predictor of mortality in patients with PI and emphasises the need for early detection and targeted intervention.

This study found that higher CCI was significantly associated with hospital, 28-day and 90-day all-cause mortality in patients with PI, highlighting the importance of CCI in predicting the prognosis of critically ill patients. Patients with PI are often accompanied by a variety of comorbidities, such as diabetes mellitus and malignant cancer^{5, 8}, and CCI, as a standardized measure of comorbidity burden, is effective in reflecting the systemic health status of the patient and in revealing the potential impact of comorbidities^{9, 10}. An international multicenter and subgroup bias assessment study showed that the risk of death in elderly critically ill patients increased with elevated CCI, emphasizing the profound prognostic impact of comorbidity accumulation¹¹. In addition, this study

also found that the critical value of CCI was 4.5 for hospital death, 28-day death, and 90-day death, a finding that further supports the important role of CCI in the prognostic assessment of patients with PI. There is no literature on the clinical value of CCI as a prognostic assessment tool for patients with PI, and this study is the first to explore and present this important finding. Compared with a single physiological parameter or laboratory index, CCI can provide more comprehensive information to the clinic by comprehensively assessing multidimensional health status, which may help in fine risk stratification and individualized treatment.

However, Cox regression analyses showed that patients with elevated CCI scores were associated with suboptimal ICU all-cause mortality outcomes after adjustment for confounders, while Kaplan-Meier survival analyses also showed that higher CCI scores were not significantly associated with ICU mortality in patients with PI. This may be related to the fact that patients in the ICU typically receive more comprehensive and intensive care, including mechanical ventilation, hemodynamic support and renal replacement therapy, which may reduce the impact of certain chronic conditions, such as comorbidities represented by CCI, on mortality⁴²⁻⁴⁴. In addition, the risk of death in the ICU is not only determined by the burden of chronic disease, but may also be influenced by many acute pathologic conditions. For example, acute clinical factors such as the patient's organ failure, the intensity of the inflammatory response, and the severity of infection may play a more critical role in ICU prognosis. A prospective cohort study found that inflammatory markers were associated with delirium and coma in critically ill patients⁴⁵. Another multicenter prospective and retrospective study found that inflammatory markers and organ dysfunction may influence 90-day mortality in acute respiratory distress syndrome⁴⁶. Thus, although the CCI has significant prognostic value as a tool to assess chronic disease burden in conventionally hospitalized patients, its predictive effect in ICU patients may be overshadowed by other acute clinical variables. In addition, the limited sample size and low ICU mortality rate in this study may have influenced the statistical results. Future studies should increase the sample size and include other clinical indicators (e.g., inflammatory markers, organ function scores, etc.) to further validate the association between CCI and ICU mortality.

RCS regression analysis in this study showed that the level of CCI was significantly and linearly related to hospital mortality, ICU mortality, and 28- and 90-day mortality. Specifically, the threshold for hospital mortality was 3.65, the threshold for ICU mortality was 2.68, and the thresholds for 28-day and 90-day mortality were 4.47 and 4.39, respectively. These results suggest that lower CCI values (e.g., thresholds for hospital and ICU mortality) indicate that the acute course of illness may be the primary risk factor for death, whereas higher thresholds reflect the importance of chronic disease burden in long-term prognosis. Chronic diseases, such as diabetes and malignant cancer, may have little impact on patient survival in the short term, but over time they progressively affect the patient's immune system, organ function, and overall health^{47, 48}, and may increase the risk of patient death in acute conditions, such as PI. Thus, the impact of chronic disease burden on prognosis was more pronounced during the 28- and 90-day observation periods, and long-term patient survival was closely linked to effective management of comorbidities. The results highlight the need to closely monitor and adjust patients' CCI levels in clinical practice to optimize their short- and long-term prognosis.

Subgroup analyses showed no significant differences between subgroups (sex, age, CHF, malignant

cancer, sepsis and diabetes) in the effect of CCI on hospital, ICU, 28-day and 90-day mortality. CCI levels have been shown to be strongly associated with poor prognosis in patients with CHF and malignant cancer^{49, 50}. Gadre SK et al. concluded that CCI ≥ 2 is a high risk factor for readmission after sepsis hospitalization and may serve as an important indicator of poor prognosis in sepsis⁵¹. These findings highlight the potential of CCI in a wide range of patient populations. Notably, in the sensitivity analysis of this study, the association between CCI and mortality outcomes in patients with PI remained stable and similar after excluding patients who died within 3 days of ICU admission. In addition, based on the optimal cutoff value (4.5) for CCI grouping, the results obtained were consistent with the results of the primary analysis, further validating the reliability of CCI for predicting mortality. Finally, three-group sensitivity analyses on SOFA scores were performed, and consistent associations between CCI and mortality were observed in the higher quartiles, supporting the stability and consistency of the findings. These sensitivity analyses demonstrate the strong robustness of CCI in predicting mortality in patients with PI under different subgroups and assumptions.

This study successfully developed and validated a ML model incorporating ICC for predicting hospital mortality in patients with PI. Ten features were selected by a combination of LASSO and other ML algorithms, of which CCI ranked high in all algorithms, indicating the importance of CCI in predicting hospital mortality. This is similar to previous studies, many of which have demonstrated the importance of CCI in predicting mortality in a variety of patient populations, particularly critically ill patients^{11, 49, 50}. This result is also consistent with the results of our previous Cox regression analysis. The performance of the ML model, SOFA⁵² and APSIII score⁵³ was evaluated by several metrics such as confusion matrix, ROC curve and F1 score. It was found that the LightGBM algorithm outperformed other ML models, traditional SOFA and APSIII scoring systems, achieving an AUC of 0.811 and an F1 score of 0.895, demonstrating its excellent predictive ability. These results are consistent with a growing body of literature showing that LightGBM has significant advantages in clinical prediction tasks, e.g., Chen Y et al. concluded that LightGBM models outperform ML models such as Random Forest and Support Vector Machines in predicting mortality in critically ill AF patients²⁰. Feature importance analysis further highlighted the critical role of CCI in predicting mortality. SHAP value analysis, an interpretable ML technique, revealed that increasing CCI was associated with a higher risk of death in patients with PI, a finding consistent with the known relationship between comorbidities and patient prognosis^{11, 54}. The biased dependency plot also confirmed that increasing CCI values were associated with an increased risk of all-cause hospital mortality, further confirming its clinical relevance. Interpretable ML provides a more transparent model decision process and helps clinicians better understand the impact of features on predicted outcomes^{55, 56}. Razo et al⁵⁷ constructed a predictive model using deep learning and obtained an AUC of 0.887. However, because the predictive goal of this model is different from that of our study, it is not possible to directly compare the performance of the two models.

Strengths and limitations

This study has several important strengths. First, it is the first validation that elevated CCI is a significant independent risk factor for short- and long-term mortality in a US cohort of critically ill patients with PI. Second, this study innovatively incorporates CCI into ML models for predicting PI-related prognosis, thus complementing applied research on CCI in the prognostic assessment of PI.

Finally, a web platform based on the LightGBM model was developed to provide clinicians with a convenient tool for real-time prognostic assessment.

However, this study has some limitations. First, although higher CCI was significantly associated with hospital, 28-day, and 90-day all-cause mortality in patients with PI, as a composite scoring tool, CCI still did not cover all clinical factors that may affect prognosis, such as BNP level, etiology of PI, individual patient differences, nutritional status, and cause of death. These factors not included in the analysis may have a significant impact on the risk of death, thus introducing a potential confounding bias. Second, given the retrospective design of this study, we could only identify associations between variables and not infer causality. Although there was a significant association between CCI and all-cause mortality, this does not mean that CCI was the direct cause of death. Third, CCI is mainly based on patients' past medical history and does not take into account dynamic changes during the course of the disease, which may lead to limitations in capturing the complexity of the disease and the comprehensiveness of prognostic assessment. Fourth, although the ML-based LightGBM model performed well in internal validation, the lack of external validation data limits its application to other independent populations. Fifth, given the multiple disease states and comorbidities of PI patients, the model may be overly dependent on certain specific variables, ignoring complex interactions that may affect prognosis. Although multiple characteristics were included, the interactions between disease progression and comorbidities may not have been adequately considered. Future studies should improve the modeling of interactions between variables and dynamic factors to improve the accuracy of prognosis prediction. Sixth, although mortality was used as the primary endpoint in this study, considering the complexity of the prognosis of patients with PI, a single mortality indicator may not be able to comprehensively assess the health status and quality of life of patients. Therefore, future studies should explore more dimensional prognostic indicators, such as functional recovery, quality of life, and long-term survival, to provide a more comprehensive prognostic assessment. In conclusion, although CCI and machine learning-based models show promise in predicting mortality in critically ill PI patients, their limitations need to be fully recognized in practical applications and combined with external validation data and dynamic clinical information to improve their clinical utility and accuracy.

Conclusion

This study demonstrated that higher CCI levels were strongly associated with hospital, 28-day and 90-day all-cause mortality in PI patients and were valuable in mortality risk stratification. Monitoring CCI levels in patients with PI in the ICU may be useful for early identification of high-risk patients and optimization of treatment strategies.

Conflicts of Interest

The authors confirm that there are no conflicts of interest associated with this publication.

Data Availability Statement

All data pertinent to this study can be accessed by reaching out to the corresponding author via email at qsy6312@163.com.

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Author Contributions:

H.F. and H.P. contributed to the conception and design of the study.

QS.Y. provided financial support.

YY.Y. and Y.S. offered administrative support.

FH.Z. and Z.W. provided study materials.

WS.J. was responsible for data collection and assembly.

Z.Z. performed data analysis and interpretation.

H.F. drafted the manuscript.

All authors critically revised the manuscript for important intellectual content and approved the final version of the manuscript.

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Ethics approval and consent to participate: This study was a retrospective observational cohort study using the publicly available MIMIC-IV database (version 2.2), which contains de-identified patient data. The Institutional Review Board (IRB) of Beth Israel Deaconess Medical Center (BIDMC) waived the requirement for informed consent, as all data in the MIMIC-IV database are de-identified. The use of the database for this research was approved by the IRB of BIDMC. To comply with relevant regulations, the author Hui Feng obtained a Collaborative Institutional Training Initiative (CITI) certification (certification number: 61863057) and the necessary permissions to access and use the MIMIC-IV database.

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Table 1 Characteristics and outcomes of participants categorized by CCI ^a

Categories	Overall (N=863)	Q1(N=268)	Q2(N=236)	Q3(N=169)	Q4(N=190)	P- value
Sex: Male, n%	575 (66.6)	176 (65.7)	160 (67.8)	109 (64.5)	130 (68.4)	0.831
Age (years)	65.4 (54.6-75.5)	52.8 (42-59.3)	67.4 (58-76.5)	71.4 (62.4-80.3)	73.6 (66.7-81.7)	<0.001
Race , n%						0.642
White	576 (66.7)	175 (65.3)	153 (64.8)	115 (68.0)	133 (70.0)	
Others	287 (33.3)	93 (34.7)	83 (35.2)	54 (32.0)	57 (30.0)	
Comorbidities, n(%)						
CHF	220 (25.5)	17 (6.34)	53 (22.5)	68 (40.2)	82 (43.2)	<0.001
Renal disease	194 (22.5)	4 (1.49)	26 (11.0)	59 (34.9)	105 (55.3)	<0.001
Malignant cancer	161 (18.7)	14 (5.22)	28 (11.9)	33 (19.5)	86 (45.3)	<0.001
Sepsis	282 (32.7)	76 (28.4)	70 (29.7)	65 (38.5)	71 (37.4)	0.052
Diabetes	226 (26.2)	34 (12.7)	55 (23.3)	45 (26.6)	92 (48.4)	<0.001
Hypertension	355 (41.1)	97 (36.2)	133 (56.4)	74 (43.8)	51 (26.8)	<0.001
Vital signs						
RR(bpm)	18.8 (16.4-21.9)	19.0 (16.6-21.9)	19.1 (16.1-21.7)	19.1 (16.6-23.0)	18.3 (16.4-21.9)	0.604
MBP(mmHg)	73.9 (68.6-81.8)	77.4 (71.3-84.7)	73.9 (68.5-82.2)	73.3 (68.5-79.0)	72.2 (66.5-78.1)	<0.001
Heart rate(bpm)	89.2 (79.2-103)	93.0 (81.3-106)	88.1 (79.1-101)	88.6 (77.8-102)	86.4 (76.5-99.0)	0.001
SpO ² (%)	97.0 (95.5-98.4)	97.2 (95.8-98.5)	96.7 (95.1-98.2)	96.8 (95.2-98.3)	97.3 (95.7-98.4)	0.090
Laboratory						
WBC (K/uL)	12.8 (9.15-18.0)	13.2 (9.20-18.2)	12.4 (8.90-18.2)	13.4 (9.20-19.7)	12.0 (8.98-15.7)	0.280
RDW (%)	15.0 (13.9-16.6)	14.5 (13.6-15.7)	15.1 (13.8-16.5)	15.6 (14.1-17.0)	15.4 (14.4-17.1)	<0.001
Platelet(K/ μ L)	176 (113-235)	190 (126-241)	158 (99.5-225)	171 (119-233)	175 (119-234)	0.149
Hemoglobin(g/dL)	9.60 (8.40-11.0)	10.0 (8.60-11.5)	9.50 (8.20-11.0)	9.70 (8.30-11.0)	9.20 (8.10-10.4)	0.001
Anion gap(mmol/L)	14.0 (12.0-17.0)	14.0 (11.0-16.0)	14.0 (11.0-16.0)	14.0 (13.0-17.0)	15.0 (12.0-17.0)	0.001
BUN (mg/dL)	21.0 (14.0-34.0)	15.0 (11.0-23.0)	22.0 (15.0-34.1)	26.0 (18.0-38.0)	30.0 (18.2-40.8)	<0.001
Creatinine (mg/dL)	1.10 (0.80-1.60)	0.90 (0.60-1.20)	1.10 (0.80-1.50)	1.20 (0.90-1.63)	1.45 (1.00-1.81)	<0.001
Calcium (mg/dL)	8.10 (7.70-8.60)	8.00 (7.60-8.50)	8.10 (7.72-8.60)	8.20 (7.80-8.60)	8.12 (7.70-8.60)	0.081

Baseline characteristics of the Survivors and Non-survivors groups ^a

Categories	Overall(N=863)	Survivor (N=706)	Non-survivor (N=157)	P- value
Sex: Male, n%	575 (66.6)	469 (66.4)	106 (67.5)	0.867
Age (years)	65.4 (54.6-75.5)	65.3 (54.1-75.4)	66.1 (56.0-75.9)	0.293
Race , n%				1.000
White	576 (66.7)	471 (66.7)	105 (66.9)	
Others	287 (33.3)	235 (33.3)	52 (33.1)	
Comorbidities, n(%)				
CHF	220 (25.5)	169 (23.9)	51 (32.5)	0.034
Renal disease	194 (22.5)	149 (21.1)	45 (28.7)	0.052
Malignant cancer	161 (18.7)	123 (17.4)	38 (24.2)	0.063
Sepsis	282 (32.7)	187 (26.5)	95 (60.5)	<0.001
Diabetes	226 (26.2)	188 (26.6)	38 (24.2)	0.600
Hypertension	355 (41.1)	308 (43.6)	47 (29.9)	0.002
Vital signs				
RR(bpm)	18.8 (16.4-21.9)	18.4 (16.3-21.4)	20.5 (17.6-23.9)	<0.001
MBP(mmHg)	73.9 (68.6-81.8)	74.6 (69.4-82.4)	71.4 (66.4-77.5)	<0.001
Heart rate(bpm)	89.2 (79.2-103)	88.6 (78.6-102)	92.5 (80.9-105)	0.025
SpO ² (%)	97.0 (95.5-98.4)	97.2 (95.7-98.4)	96.2 (94.8-98.1)	<0.001
Laboratory tests				
WBC (K/uL)	12.8 (9.15-18.0)	12.6 (9.20-17.7)	14.0 (8.90-19.7)	0.098
RDW (%)	15.0 (13.9-16.6)	14.9 (13.8-16.3)	16.4 (14.5-17.6)	<0.001
Platelet(K/ μ L)	176 (113-235)	180 (121-237)	147 (67.0-227)	0.001
Hemoglobin(g/dL)	9.60 (8.40-11.0)	9.70 (8.40-11.1)	9.11 (8.20-11.0)	0.043
Anion gap(mmol/L)	14.0 (12.0-17.0)	14.0 (12.0-16.0)	15.0 (13.0-18.0)	<0.001
BUN (mg/dL)	21.0 (14.0-34.0)	20.0 (14.0-31.0)	31.0 (18.0-41.9)	<0.001
Creatinine (mg/dL)	1.10 (0.80-1.60)	1.00 (0.80-1.50)	1.30 (0.90-1.80)	<0.001
Calcium (mg/dL)	8.10 (7.70-8.60)	8.11 (7.70-8.60)	8.00 (7.50-8.50)	0.042
Chloride(mEq/L)	105 (101-109)	105 (101-109)	104 (99.0-109)	0.162

Sodium(mEq/L)	138 (135-141)	138 (136-141)	138 (134-141)	0.135
Potassium (mEq/L)	4.20 (3.80-4.50)	4.10 (3.73-4.50)	4.20 (3.80-4.70)	0.226
Severe Score				
SAPSII	37.0 (30.0-47.0)	35.0 (28.0-43.0)	47.0 (37.0-56.0)	<0.001
OASIS	33.0 (27.0-39.5)	32.0 (27.0-39.0)	36.0 (30.0-44.0)	<0.001
SIRS	3.00 (2.00-3.00)	3.00 (2.00-3.00)	3.00 (2.00-4.00)	0.182
APSIHI	47.0 (35.0-63.5)	44.0 (33.0-58.0)	68.0 (50.0-77.4)	<0.001
SOFA	2.00 (1.00-5.00)	2.00 (1.00-4.00)	4.00 (2.00-6.27)	<0.001
CCI	5.00 (3.00-7.00)	5.00 (3.00-7.00)	6.00 (4.00-8.00)	<0.001
Medication, n(%)				
Ondansetron	475 (55.0)	413 (58.5)	62 (39.5)	<0.001
Neostigmine	101 (11.7)	96 (13.6)	5 (3.18)	<0.001

^a Continuous data is presented as median (interquartile range), whereas categorical data are presented as frequency (percentage)

Abbreviations: CHF, Congestive heart failure; RR, Respiratory Rate; MBP, Mean Blood Pressure; SpO₂, Saturation of Peripheral Oxygen; WBC, white blood cell; RDW, Red Cell Distribution Width; BUN, blood urea nitrogen; SAPSII, simplified acute physiological score II; OASIS, oxford acute severity of illness score; SIRS, Systemic Inflammatory Response Syndrome; APS III, Acute Physiology Score III; SOFA, sequential organ failure assessment; CCI, Charlson comorbidity index; ICU, intensive care unit.

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Table 3 Cox proportional hazard ratios (HR) for all-cause mortality of Hospital and 28-day

Categories	Model 1			Model 2			Model 3		
	HR (95% CI)	P-value	P for trend	HR (95% CI)	P-value	P for trend	HR (95% CI)	P-value	P for trend
Hospital mortality									
Continuous ariable	1.159□1.099-1.222□	<0.001		1.158□1.088-1.233□	<0.001		1.204□1.099-1.319□	<0.001	
Per unit Quartile			<0.001			<0.001			0.013
Q1 (N=190)	Ref						Ref		
Q2 (N=162)	1.936□1.196-3.135□	0.007		1.868□1.119-3.117□	0.017		1.442□0.832-2.499□	0.192	
Q3(N=159)	2.091□1.254-3.487□	0.004		2.003□1.140-3.518□	0.016		1.643□0.857-3.149□	0.135	
Q4(N=170)	3.124□1.945-5.017□	<0.001		2.950□1.708-5.097□	<0.001		2.447□1.210–4.951□	0.013	
28-days mortality									
Continuous ariable	1.202□1.143-1.264□	<0.001		1.237□1.166-1.311□	<0.001		1.255□1.154-1.366□	<0.001	
Per unit Quartile ^a			<0.001			<0.001			<0.001
Q1 (N=190)	Ref						Ref		
Q2 (N=162)	2.315□1.398-3.833□	0.001		2.683□1.567-4.594□	<0.001		1.849□1.054-3.245□	0.032	
Q3(N=159)	3.035□1.817-5.069□	<0.001		3.660□2.087-6.427□	<0.001		2.375□1.256-4.493□	0.008	
Q4(N=170)	4.563□2.833-7.349□	<0.001		5.668□3.267-9.833□	<0.001		3.891□1.956-7.740□	<0.001	

Model 1: unadjusted.
Model 2: adjusted for sex, age.
Model 3: adjusted for sex, age, CHF, renal disease, malignant cancer, sepsis, diabetes, hypertension, RR, SpO², WBC, RDW, platelet, anion gap, BUN, creatinine, SAPSII, OASIS, APSIII, SOFA.
a CCI: Q1 (0–3), Q2 (3–5), Q3 (5–7), Q4 (7–14)

Abbreviations: confidence interval; ICU, intensive care unit; CHF, Congestive heart failure; RR, Respiratory Rate; SpO², Saturation of Peripheral Oxygen; WBC, white blood cell; RDW, Red Cell Distribution Width; BUN, blood urea nitrogen; SAPSII, simplified acute physiological score II; OASIS, oxford acute severity of illness score; APSIII, Acute Physiology Score III; SOFA, sequential organ failure assessment; CCI, Charlson comorbidity index.

Model	Accuracy	Recall	Precision	F1	Specificity	Gmean	AUC
SVM	0.824	0.234	0.524	0.324	0.953	0.472	0.751
NN	0.831	0.191	0.600	0.290	0.972	0.431	0.808
MLP	0.793	0.277	0.394	0.325	0.907	0.501	0.745
GP	0.828	0.149	0.583	0.237	0.977	0.381	0.807
GBM	0.808	0.404	0.463	0.432	0.897	0.602	0.771
LR	0.839	0.340	0.593	0.432	0.949	0.568	0.806
AdaBoost	0.774	0.319	0.357	0.337	0.874	0.528	0.771
XGBoost	0.824	0.213	0.526	0.303	0.958	0.451	0.799
RF	0.824	0.255	0.522	0.343	0.949	0.492	0.774
KNN	0.816	0.191	0.474	0.273	0.953	0.427	0.778
LightGBM	0.824	0.875	0.916	0.895	0.514	0.670	0.811
APSIH	0.787	0.966	0.806	0.879	0.059	0.238	0.742
SOFA	0.802	0.99	0.807	0.889	0.039	0.197	0.646

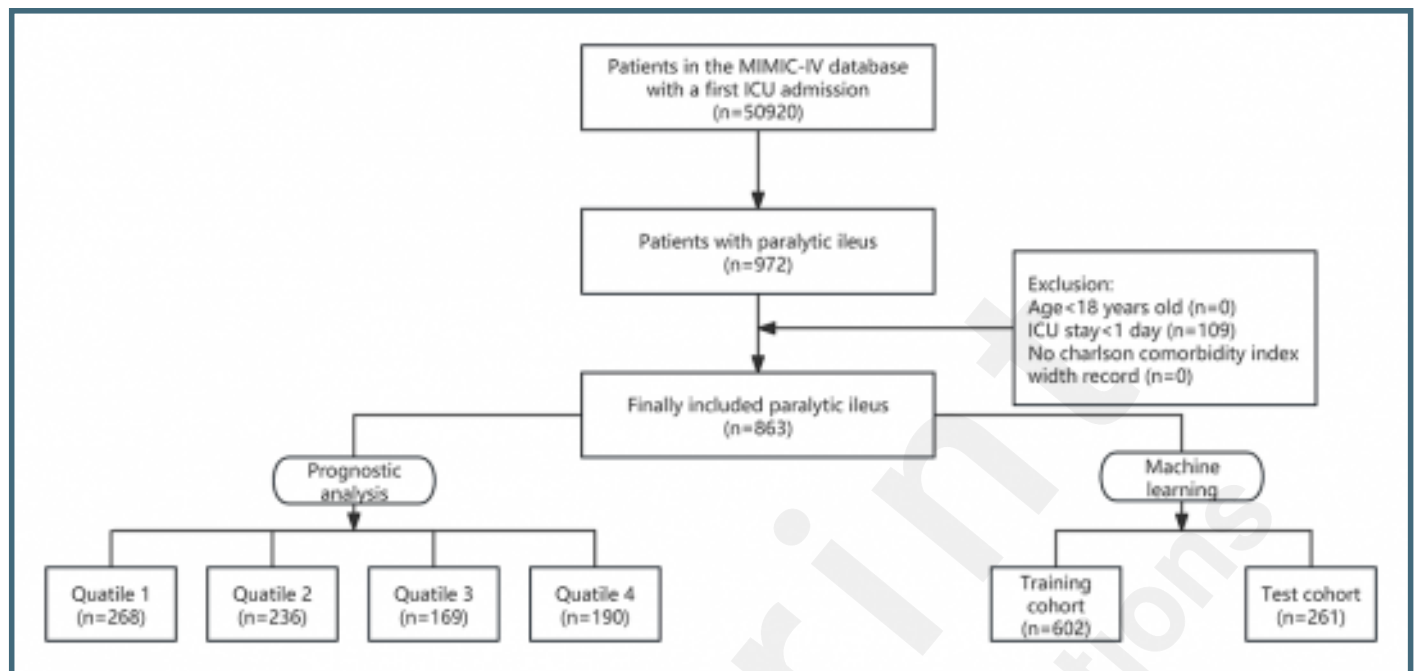
Abbreviations: SVM, Support Vector Machine; NN, Neural Network; MLP, Multi-Layer Perceptron; GP, Gaussian Process; GBM, Gradient Boosting Machine; LR, Logistic Regression; AdaBoost, Adaptive Boosting; XGBoost, Extreme Gradient Boosting; RF, Random Forest; KNN, K-Nearest Neighbors; LightGBM, Light Gradient Boosting Machine; APSIH, Acute Physiological Score III; SOFA, Sequential Organ Failure Assessment.

Table 4 Performance Evaluation of Machine Learning Models for Predicting Clinical Outcomes

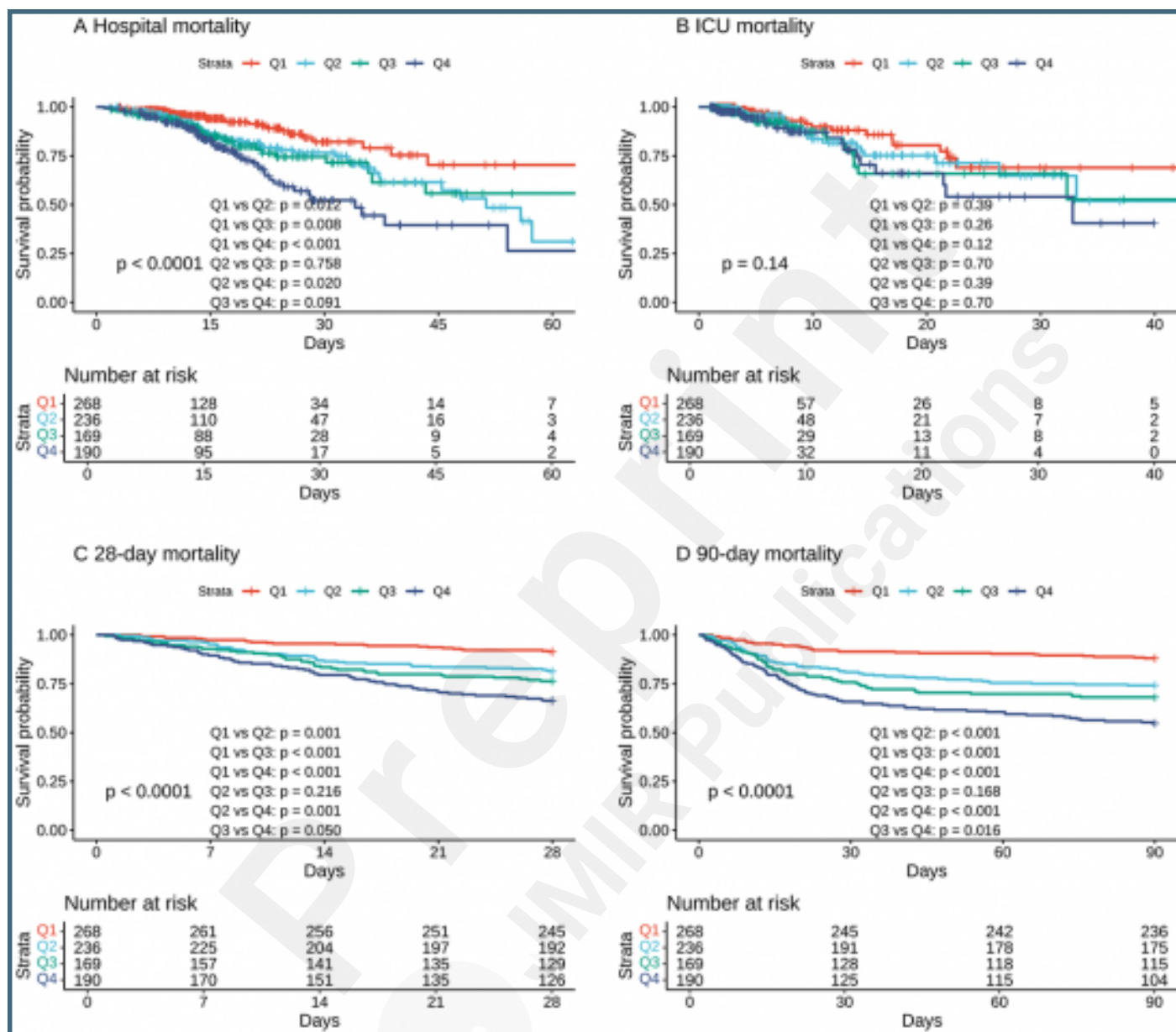
Supplementary Files

Figures

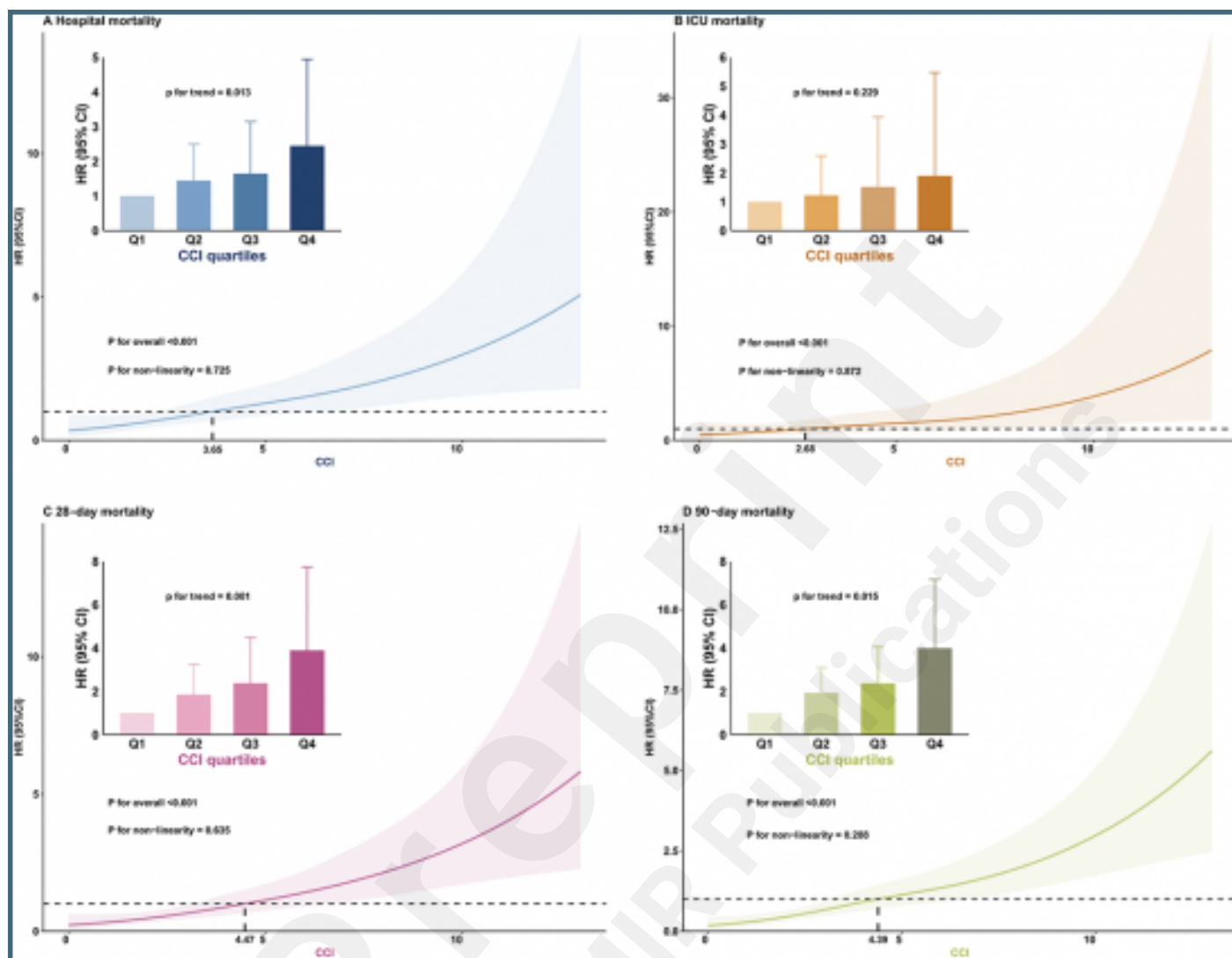
Flow of included patients through the trial.



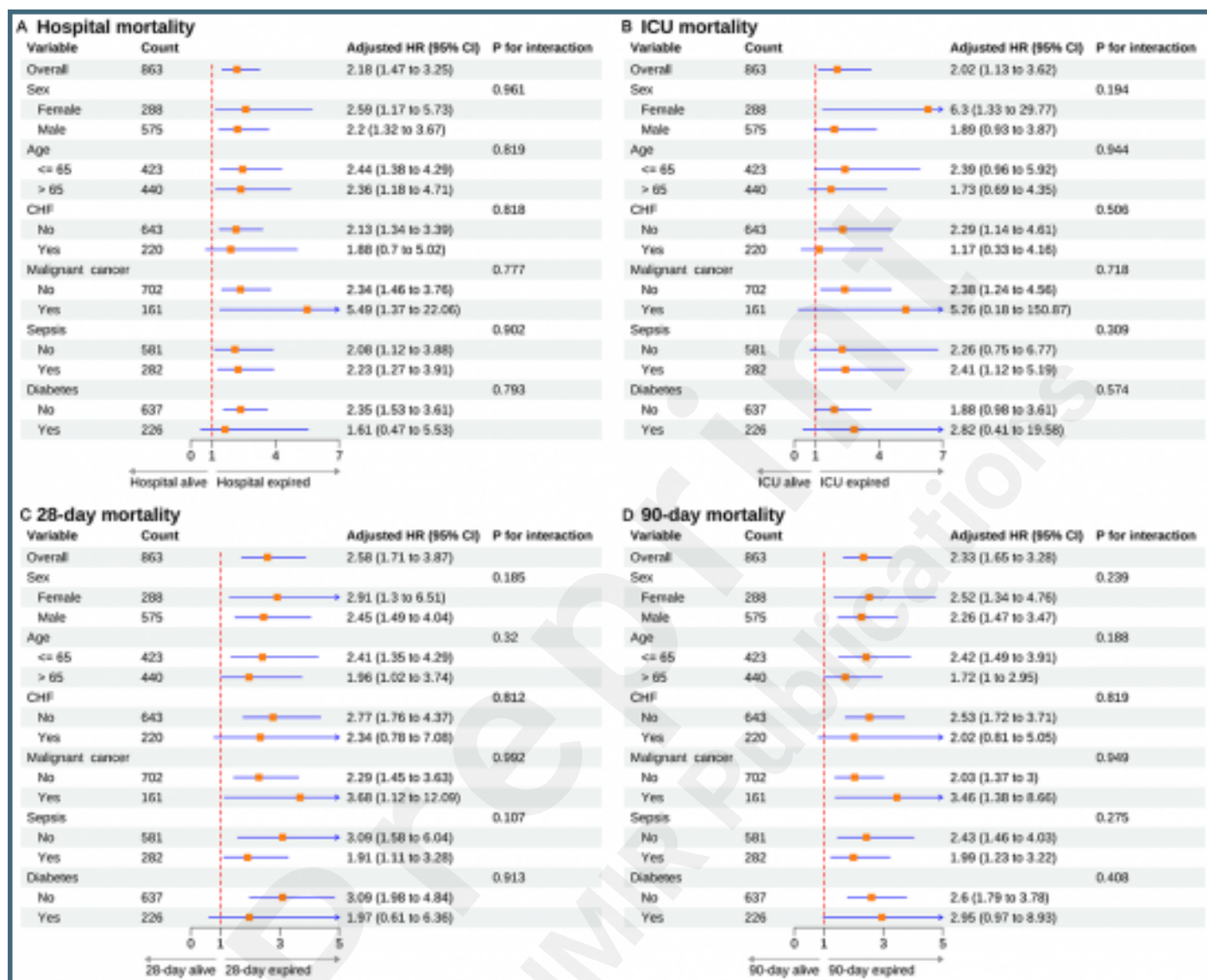
Kaplan-Meier survival analysis curves for all-cause mortality. footnote CCI quartiles: Q1 (0-3), Q2 (3) Kaplan-Meier curves for cumulative mortality: Q1 (0-3), Q2 (3-5), Q3 (5-7), Q4 (7-14). Kaplan-Meier curves showing cumulative probability of all-cause mortality by group at hospital (a), ICU (b), 28 days (c) and 90 days (d).



HRs (CIs) and restricted cubic spline curves for all-cause mortality from CCI after adjustment for confounders.

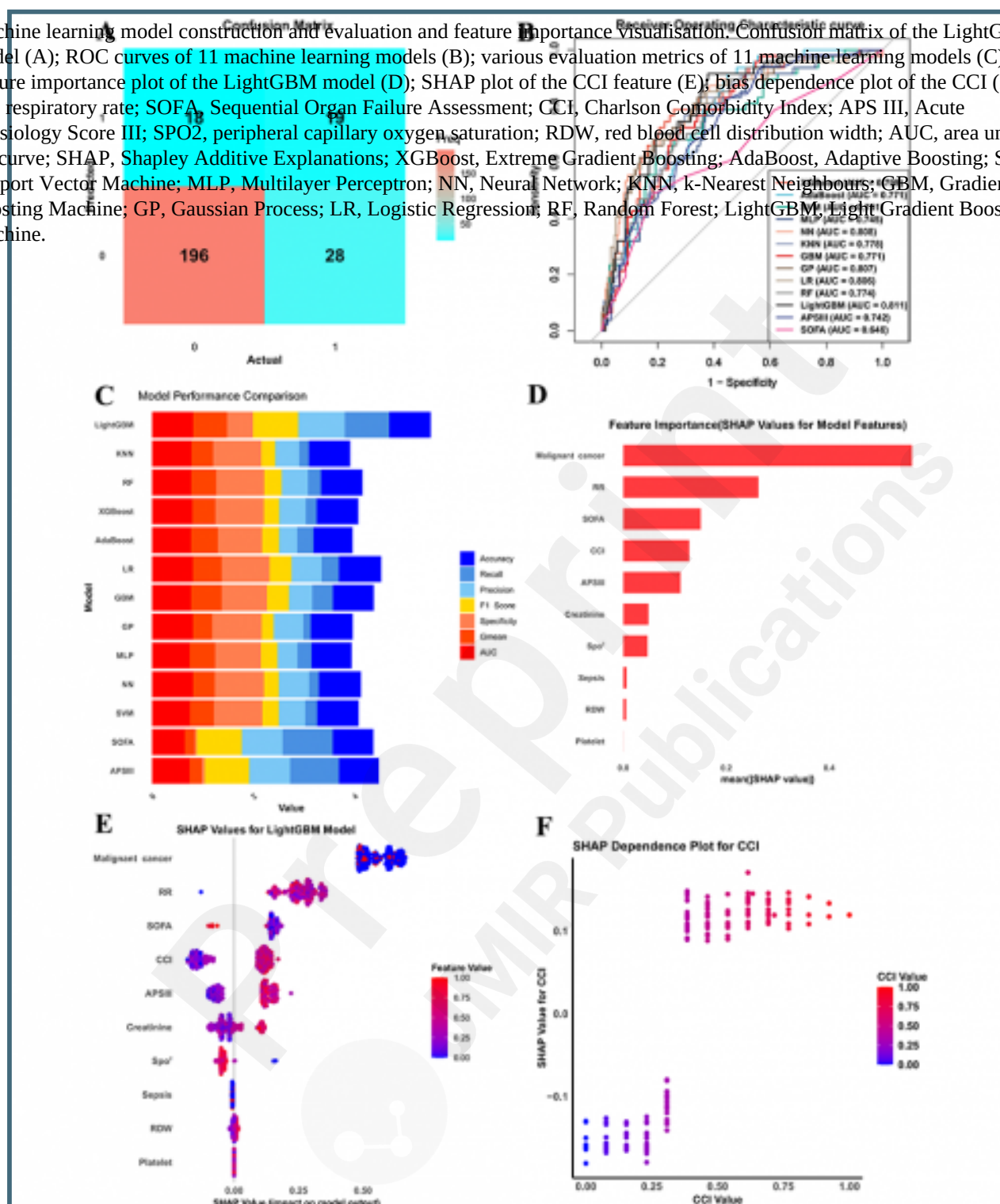


Forest plots of hazard ratios for all-cause mortality in different subgroups. (A) Hospital mortality. (B) ICU mortality. (C) 28-day mortality. (D) 90-day mortality. HR, hazard ratio; CI, confidence interval; ICU, intensive care unit; CHF, congestive heart failure.



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Machine learning model construction and evaluation and feature importance visualisation. Confusion matrix of the LightGBM model (A); ROC curves of 11 machine learning models (B); various evaluation metrics of 11 machine learning models (C); feature importance plot of the LightGBM model (D); SHAP plot of the CCI feature (E); bias dependence plot of the CCI (F). RR, respiratory rate; SOFA, Sequential Organ Failure Assessment; CCI, Charlson Comorbidity Index; APS III, Acute Physiology Score III; SPO2, peripheral capillary oxygen saturation; RDW, red blood cell distribution width; AUC, area under the curve; SHAP, Shapley Additive Explanations; XGBoost, Extreme Gradient Boosting; AdaBoost, Adaptive Boosting; SVM, Support Vector Machine; MLP, Multilayer Perceptron; NN, Neural Network; KNN, k-Nearest Neighbours; GBM, Gradient Boosting Machine; GP, Gaussian Process; LR, Logistic Regression; RF, Random Forest; LightGBM, Light Gradient Boosting Machine.



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