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Identification of Key Blood Biomarkers for In-hospital Risk Assessment in Covid-19 Patients: A Multicenter Cohort Study

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Research Article

Keywords: COVID-19, machine learning, prognosis, intensive care unit, mortality, blood biomarkers, risk stratification

Posted Date: November 23rd, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11447188/v1

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Additional Declarations: No competing interests reported.

Abstract

Background

Early risk stratification of hospitalized COVID-19 patients is essential for resource allocation, yet clinical variables have limited prognostic accuracy. Blood biomarkers have shown prognostic value in COVID-19, but whether a multimarker approach can further improve risk assessment at admission remains unclear. This study aimed to identify a parsimonious panel of blood biomarkers associated with the composite endpoint of intensive care unit (ICU) admission or in-hospital death in hospitalized COVID-19 patients.

Methods

We retrospectively analyzed prospectively collected data from hospitalized COVID-19-positive patients enrolled in the Biobanque Québécoise de la COVID-19 between April 2020 and December 2021. Twenty-eight blood biomarkers reflecting myocardial damage, inflammation, and renal function were measured from admission samples. Feature selection used correlation analysis, Fisher score, random forest importance, and recursive feature elimination. Extreme gradient boosting (XGBoost) models were trained and evaluated across five biomarker and clinical variable combinations using area under the receiver operating characteristic curve (AUC), F1 score, sensitivity, specificity, and Brier score.

Results

Among 1,157 patients, 418 (36.1%) met the composite endpoint. A nine-biomarker panel (creatine kinase, high-sensitivity C-reactive protein, D-dimer, growth differentiation factor-15, human epididymis protein 4, interleukin-6, free thyroxine, triglycerides, vitamin D) achieved an AUC of 0.82 and F1 score of 0.77. Clinical variables alone yielded an AUC of 0.65. Adding clinical variables to the panel marginally improved performance (AUC 0.83). The panel demonstrated stable calibration and robust performance across a broad range of thresholds.

Conclusions

The nine-biomarker panel provides accurate risk stratification of hospitalized COVID-19 patients for the composite endpoint, substantially exceeding clinical variables alone. This approach may facilitate rapid triage in acute care settings.

BACKGROUND

The coronavirus disease 2019 (COVID-19) pandemic placed unprecedented pressure on healthcare systems worldwide, with intensive care unit (ICU) capacity and resource allocation emerging as critical challenges during successive waves of infection [1]. Although most individuals infected with severe

acute respiratory syndrome coronavirus 2 (SARS-CoV-2) experienced mild to moderate symptoms, a substantial proportion of hospitalized patients progressed to severe illness requiring intensive care or resulting in death [2, 3]. Early identification of patients at high risk of clinical deterioration at the time of hospital admission is therefore essential for timely escalation of care and efficient allocation of limited resources.

Several blood biomarkers reflecting inflammation, coagulation, myocardial injury, and organ dysfunction have been individually associated with COVID-19 severity and adverse outcomes, including ICU admission and mortality [4–7]. While individual biomarker associations with severity are well documented, the optimal combination of biomarkers for risk stratification at hospital admission remains poorly defined. Most previous studies have examined biomarkers in isolation or relied on conventional regression-based models with limited ability to capture non-linear relationships and complex interactions among variables. Machine learning algorithms, particularly ensemble methods such as extreme gradient boosting (XGBoost), have shown promise in leveraging multi-dimensional clinical and laboratory data for outcome prediction in COVID-19 [8, 9].

The present study aimed to develop and internally evaluate a parsimonious multimarker model for the composite outcome of ICU admission or in-hospital death among patients hospitalized with COVID-19 and enrolled in the Biobanque Québécoise de la COVID-19 (BQC-19).

METHODS

Study population

We retrospectively analyzed data prospectively collected between April 2020 and December 2021 from 1157 patients enrolled in the BQC-19, a provincial infrastructure involving 11 healthcare facilities of the Health and Social Services Network of Québec (Canada) [10]. This province-wide, multicenter initiative enabled the collection of biosamples and clinical data since the beginning of the pandemic [10]. Demographic and clinical information was obtained at the time of the first COVID-19 diagnosis, and a blood sample was drawn on the day of the initial visit or at the earliest available time if the window was missed.

COVID-19 Case/Control Outcome and Study Population

Positive COVID-19 diagnostic (COVID-19+) was confirmed if a positive result of real-time reverse transcriptase–polymerase chain reaction (RT-PCR) assay of nasal and pharyngeal swabs was obtained. The grading score for COVID-19 severity was based on the World Health Organization (WHO) Working Group on the Clinical Characterization and Management of COVID-19 infection [11]. In brief, the WHO clinical progression scale ranges from 0 (not infected) to 10 (death) by including several parameters such as: the viral burden (quantitative PCR or cycle threshold), patient progression through the health-care system (hospitalization, oxygen therapy, intubation, mechanical ventilation) and survival [11]. This

study aimed at examining the association between baseline clinical characteristics and blood biomarkers of hospitalized COVID-19 + patients with admission in ICU and/or in-hospital death. Patients who i) were not diagnosed with COVID-19+; ii) who had been diagnosed with COVID-19 + but had not been hospitalized or iii) with missing outcome data, were excluded. This study was approved by the institutional review board of each center (coordinating committee: Research Ethics Board of the Centre hospitalier de l'Université de Montréal [CHUM], #MP-02-2020-8929, 19.389), and all participants signed a written informed consent at the time of inclusion.

Blood Biomarkers

Biomarker analyses were conducted in a core laboratory using enzyme-linked immunosorbent assay (ELISA) and electrochemiluminescence immunoassay (ECLIA) kits approved for clinical use and commercialized by Roche Diagnostics (Laval, Canada). The blood biomarkers included: i) myocardial damage and cardiac stress: creatine kinase (CK), creatine kinase myocardial band (CK-MB), growth differentiation factor-15 (GDF-15), high-sensitivity cardiac troponin T (hs-cTnT), N-terminal pro-B-type natriuretic peptide (NT-proBNP), human epididymis protein 4 (HE4) and cancer antigen 125 (CA-125); ii) inflammation and immune response: interleukin-6 (IL-6), high-sensitivity C-reactive protein (hs-CRP), ferritin, soluble fms-like tyrosine kinase-1 (sFlt-1), procalcitonin (PCT), alkaline phosphatase (ALP), alanine aminotransferase (ALT), alpha-1 antitrypsin (AAT), and anti-SARS-CoV-2 spike antibody (ACOV2S); iii) renal function and metabolism: creatinine, cystatin C, D-dimer, phosphate, potassium, urea, calcium, triglycerides, free thyroxine (free T4), vitamin B12, low-density lipoprotein cholesterol (LDL cholesterol), and vitamin D.

Study Endpoint

The primary study endpoint was a composite of ICU admission and in-hospital mortality. In-hospital mortality was defined as any death occurring during the patient's hospitalization. Data on ICU admission and in-hospital mortality were obtained through review of the medical records.

Statistical Analysis

Models and Data Processing

Initial selection of clinical variables and blood biomarkers was based on prior clinical relevance to the composite endpoint, and previously published studies [4–7]. Categorical variables including sex and comorbidities were one-hot encoded, and numerical variables (age and biomarkers) were standardized using StandardScaler. Four patients (0.3%) had a missing value for one of two biomarkers (CA-125, n = 1; creatinine, n = 3) and were excluded, yielding 1,157 patients for analysis. Imputation strategies (XGBoost-based and median imputation) were also evaluated and yielded similar results; complete-case analysis was therefore retained. The biomarker model was refined with a multistep feature selection strategy

combining correlation analysis, univariate screening, random forest importance, and recursive feature elimination with cross-validation.

The dataset was randomly split into a training set (70%) and a test set (30%). The training set was used for model comparison, hyperparameter tuning, and final model fitting; the test set was reserved for performance evaluation. Supervised algorithms tested included random forest, support vector machine, gradient boosting, and LightGBM, with XGBoost retained for its prognostic performance and robustness. Hyperparameters and class weights were optimized to enhance prediction performance.

Repeated stratified K-fold cross-validation (5 splits, 3 repeats) was performed on the training set as an internal diagnostic during model development; all performance metrics reported in this study were computed on the held-out test set. Model performance was assessed using area under the receiver operating characteristic (ROC) curve (AUC), F1 score, sensitivity, specificity, and Brier score. F1 score was computed using macro averaging across both outcome classes, whereas sensitivity and specificity refer to the positive class. Multiple models of variables were considered to compare clinical strategies when dealing with establishing real-world priority when providing care to at-risk patients. These models included clinical variables only, blood biomarkers only or best performing blood biomarkers after feature selection: (i) a **Clinical model** including age, sex, and 16 comorbidities (history of hypertension, diabetes, obesity, dementia, coronary artery disease, atrial fibrillation or flutter, heart failure, prior myocardial infarction, pulmonary hypertension, prior stroke or transient ischemic attack (TIA), asthma, chronic kidney disease, dialysis, cancer, malnutrition, and human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS); (ii) a **Nine-biomarker panel** including the nine top-ranked biomarkers (CK, hs-CRP, D-dimer, GDF-15, HE4, IL-6, free T4, triglycerides, vitamin D); (iii) an **All blood biomarkers model** including all 28 measured blood biomarkers (CK, CK-MB, GDF-15, hs-cTnT, NT-proBNP, HE4, CA-125, IL-6, hs-CRP, ferritin, sFlt-1, PCT, ALP, ALT, AAT, ACOV2S, creatinine, cystatin C, D-dimer, phosphate, potassium, urea, calcium, triglycerides, free T4, vitamin B12, LDL cholesterol, and vitamin D); (iv) a **Clinical + nine-biomarker panel** combining the variables from subsets (i) and (ii); and (v) a **Clinical + all blood biomarkers model** combining the variables from subsets (i) and (iii).

Final model performance on the composite endpoint was evaluated for each model on the held-out test set (n = 348) using the metrics described above. Feature importance was assessed using the built-in XGBoost tool. For model calibration, predicted probabilities were grouped into 10 equally sized bins using a quantile-based strategy. For each bin, the mean predicted probability and the corresponding observed event rate in the test dataset were calculated. These values were then used to generate calibration curves. Graphs were generated using Matplotlib (version 3.8.0) and Seaborn (version 0.13.2). Data processing, model training and evaluation, feature selection, and class imbalance steps were performed on Python version 3.9.18.

Use of Large Language Models

The authors used an AI-based large language model to assist with language editing of the manuscript. The AI tool was not used to generate, analyze, or interpret data, nor to produce code. The authors reviewed and verified all AI-assisted text and take full responsibility for the integrity, accuracy, and interpretation of the work. No AI tool is listed as an author.

RESULTS

Baseline Characteristics and Short-Term Outcomes

Baseline characteristics of the study population are described in Table 1. The mean age was 64 ± 17 years, and 42.8% of patients were male. Comorbidities such as hypertension and diabetes were common. The mean hospital stay was 19 ± 31 days, 364 (31.5%) patients were admitted in ICU, 147 (12.7%) died during hospitalization and 418 (36.1%) met the composite endpoint of ICU admission and in-hospital death. Blood biomarker levels according to the composite endpoint are presented in **Additional file 1: Table S1.**

Table 1
Baseline Clinical Characteristics of the Study Population

Age, years	**COVID-19 + Hospitalized patients (n = 1,157)**
	64 ± 17
Female, n (%)	662 (57.2%)
BMI, kg/m²	28.8 ± 7.3
Hypertension, n (%)	612 (52.9%)
Diabetes, n (%)	376 (32.5%)
Obesity, n (%)	165 (14.3%)
Coronary artery disease, n (%)	181 (15.6%)
AF or flutter, n (%)	145 (12.5%)
Heart failure, n (%)	110 (9.5%)
Prior myocardial infarction, n (%)	64 (5.5%)
Pulmonary hypertension, n (%)	13 (1.1%)
Prior stroke or TIA, n (%)	100 (8.6%)
COPD, n (%)	145 (12.5%)
Asthma, n (%)	145 (12.5%)
Chronic kidney disease, n (%)	180 (15.6%)
Dialysis, n (%)	27 (2.3%)
Malignant neoplasm, n (%)	165 (14.3%)
Psychiatric disease, n (%)	160 (13.8%)
Rheumatologic disease, n (%)	141 (12.2%)
Dementia, n (%)	135 (11.7%)
Immunosuppressed state, n (%)	124 (10.7%)
Chronic neurological disorder, n (%)	119 (10.3%)
Liver disease, n (%)	57 (4.9%)

Legends. Continuous data are expressed as mean ± SD or median [25th–75th percentile]. Categorical data are expressed as number (percent). AF, atrial fibrillation; AIDS, acquired immunodeficiency syndrome; BMI, body mass index; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; ICU, intensive care unit; TIA, transient ischemic attack.

Age, years	COVID-19 + Hospitalized patients (n = 1,157)
	64 ± 17
Malnutrition, n (%)	26 (2.2%)
HIV or AIDS, n (%)	9 (0.8%)

Legends. Continuous data are expressed as mean ± SD or median [25th–75th percentile]. Categorical data are expressed as number (percent). AF, atrial fibrillation; AIDS, acquired immunodeficiency syndrome; BMI, body mass index; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; ICU, intensive care unit; TIA, transient ischemic attack.

Selection of Blood Biomarkers

The feature selection analyses identified several overlapping subsets of blood biomarkers as most associated with ICU admission or death **(**Fig. 1**).** The correlation matrix showed strong correlation for Cystatin C with creatinine (r = 0.83), HE4 (r = 0.78), and urea (r = 0.76), while moderate correlation between potassium and phosphate (r = 0.64), hs-CRP and AAT (r = 0.64), HE4 and urea (r = 0.66), CK and CK-MB (r = 0.66), and HE4 and creatinine (r = 0.67) was observed (Fig. 1A). Feature importance rankings based on the Fisher score and Random Forest analysis (Fig. 1B) highlighted IL-6 and urea as important variables while other blood biomarkers such as HE4 and D-dimer differ in their importance. Recursive feature elimination over five iterations (Fig. 1C) repeatedly highlighted a group of biomarkers: CK, creatinine, hs-CRP, D-dimer, GDF-15, HE4, IL-6, free T4, triglycerides, urea, and vitamin D. Both subsets included CK, hs-CRP, D-dimer, GDF-15, IL-6, free T4, triglycerides, and vitamin D, one favored creatinine and urea, while the other emphasizes HE4. The subset including HE4 was chosen as the optimized nine-biomarker panel.

Optimal Risk Assessment Model

Feature selection analysis was conducted to explore various models to identify the most relevant data for optimal risk assessment during triage. The tested models demonstrated similar discriminative performance during the exploratory phase when applied to the Clinical + nine-biomarker panel **(Additional file 1: Figure S1)**. XGBoost and LightGBM showed comparable AUCs, and XGBoost was selected for subsequent risk assessment based on its overall performance and implementation practicality. The performance of the XGBoost model across different variables subsets is presented in Table 2. The use of clinical variables alone resulted in suboptimal performance across all metrics, with a lower AUC of 0.65 and a Brier score of 0.23, indicating moderate calibration. The nine-biomarker panel provided a balanced trade-off with an AUC of 0.82, an F1 score of 0.77, sensitivity of 0.71, specificity of 0.83, and a reasonable Brier score of 0.16. Additionally, while the all blood biomarkers model demonstrated marginally superior performance, the nine-biomarker panel emerged as a more feasible and more reliable subset of variables in a clinical setting. Incorporating clinical variables into the nine-biomarker panel further improved model performance with a higher F1 score (0.77) and sensitivity (0.72), while the clinical + all blood biomarkers model showed superior AUC (0.84), specificity (0.84), and

Brier score (0.15). However, the enhanced performances of the latter combinations come at the cost of greater data acquisition difficulty.

Table 2
Prognostic Performance of XGBoost Models Using Clinical and Blood Biomarker Models.

Models	AUC	F1 Score	Sensitivity	Specificity	Brier Score
Clinical	0.648	0.595	0.641	0.576	0.234
Nine-biomarker panel	0.825	0.773	0.710	0.834	0.163
All blood biomarkers	0.838	0.763	0.695	0.829	0.157
Clinical + nine-biomarker panel	0.826	0.774	0.725	0.825	0.164
Clinical + all blood biomarkers	0.845	0.769	0.695	0.839	0.154
Legends. AUC: area under the receiver operating characteristic curve.					
A					

Among the tested models, three were selected for further evaluation in the context of clinical implementation: clinical, nine-biomarker panel, and the clinical + all blood biomarkers model. The prognostic performance of these three models is summarized in Fig. 2, while their calibration is shown in **Additional file 1: Figure S2**. Both the nine-biomarker panel and the clinical + all blood biomarkers model demonstrated acceptable calibration, with the latter exhibiting more consistent alignment between predicted probabilities and observed outcomes. Variables importance was largely consistent across the three models, as illustrated in **Additional file 1: Figure S3**. Threshold selection is important for considering which patients must be admitted at triage. The decision threshold defines the predicted probability above which a patient is considered positive (i.e., to be admitted). As shown in **Additional file 1: Figure S4**, the clinical model showed marked discordance between sensitivity and specificity across thresholds, with performance peaking around 0.37 (maximum F1 score) and deteriorating rapidly when deviating from this value. In contrast, the nine-biomarker panel and the clinical + all blood biomarkers model maintain more stable sensitivity and specificity across a broader range of thresholds, indicating better calibration and allowing threshold selection to be tailored to clinical priorities (higher sensitivity to minimize missed high-risk patients or higher specificity to limit unnecessary escalation of care).

DISCUSSION

In this multicenter study, we developed and internally evaluated machine-learning models for the composite outcome of ICU admission or in-hospital death among patients hospitalized with COVID-19. The main findings are: 1) A parsimonious nine-biomarker panel achieved strong performance (AUC 0.82) to predict adverse in-hospital outcomes, which substantially exceeded that of clinical variables alone (AUC 0.65); 2) The addition of clinical variables to biomarkers yielded only marginal incremental benefit;

and 3) The nine-biomarker panel demonstrated stable calibration and robust performance across a broad range of decision thresholds, supporting its potential utility as a triage tool.

Biomarkers versus Clinical Variables for Risk Assessment

A key finding of this study is that blood biomarkers alone provided substantially superior prognostic performance compared with standard clinical variables. The clinical model (age, sex, 16 comorbidities) achieved an AUC of 0.65 with poor calibration (Brier score 0.23), whereas the nine-biomarker panel reached an AUC of 0.82 with better calibration (Brier score 0.16). This has practical implications, because in acute care settings reliable clinical history is often difficult to obtain, whereas blood biomarkers can be measured objectively and rapidly from a single admission sample, enabling standardized risk stratification.

Combining clinical variables with the full biomarker model yielded the highest AUC (0.84), but the gain over the nine-biomarker panel alone was modest (ΔAUC = 0.02) with substantially greater effort of data acquisition. Similarly, adding clinical variables to the nine-biomarker panel (AUC 0.83) did not meaningfully improve performance over biomarkers alone (AUC 0.82). These results suggest that in emergency and acute care contexts where rapid triage is essential, a blood biomarker panel may offer the best compromise between prognostic accuracy and feasibility.

Prognostic Value of the Blood Biomarker in COVID-19 Patients

The nine biomarkers retained in the panel cover multiple pathophysiological axes relevant to COVID-19 severity. IL-6 and hs-CRP reflect the systemic inflammatory response that characterizes severe SARS-CoV-2 infection and have been consistently identified as variables of adverse outcomes in meta-analyses [12, 13]. D-dimer captures the coagulopathy and microvascular thrombosis frequently observed in severe COVID-19 [14]. GDF-15, a member of the transforming growth factor-β superfamily is upregulated in response to tissue injury, oxidative stress, hypoxemia, and has demonstrated prognostic performance superior to that of conventional biomarkers in hospitalized COVID-19 patients [7, 15]. HE4, traditionally known as a biomarker of ovarian cancer, is increasingly recognized as a marker of pulmonary epithelial damage and fibrosis [16], elevated levels at ICU admission have been shown to strongly predict mortality in COVID-19 [6]. CK reflects skeletal and myocardial muscle injury, which is common in severe COVID-19 and may be linked to both direct viral cytopathic effects and systemic inflammation. Free T4 may reflect euthyroid sick syndrome, a condition associated with critical illness severity and poorer outcomes [17]. Low vitamin D levels have been epidemiologically associated with increased susceptibility to respiratory infections and more severe COVID-19, potentially through modulation of innate and adaptive immune responses [18]. Finally, alterations in triglyceride metabolism have been observed in the context of acute systemic inflammation and may reflect the metabolic disruption associated with critical illness.

Threshold Selection and Clinical Applicability

The clinical model exhibited poor robustness to threshold variation, with rapid deterioration of sensitivity or specificity outside a narrow optimal range. In contrast, the nine-biomarker panel and the clinical + all blood biomarkers model maintained stable performance across a broader range of thresholds. This property is particularly relevant in clinical practice, where the optimal threshold may differ depending on institutional capacity, pandemic phase, and local priorities: settings with limited ICU capacity may favor a lower threshold to maximize sensitivity, whereas resource-constrained environments may prioritize specificity to avoid unnecessary escalation of care.

Comparison with Prior Models

Several machine-learning prediction models for COVID-19 severity have been developed, with ensemble methods generally demonstrating superior performance [8, 9]. Our findings are consistent with these reports, as XGBoost outperformed other algorithms during the model selection phase. The reported AUC of 0.825 for the nine-biomarker XGBoost model is within the range of prior COVID-19 prediction studies, although direct comparisons are limited by differences in populations, outcomes, predictors, and validation procedures. The strength of the present approach lies in the systematic feature selection process that converged on a parsimonious and clinically actionable nine-biomarker panel, rather than requiring the full spectrum of available laboratory data or clinical data.

Limitations

Several limitations warrant consideration. First, the study used a random train-test split for internal evaluation and lacked external validation. However, the BQC-19 represents one of the largest and most comprehensive provincial COVID-19 biobanks, encompassing 11 healthcare facilities with diverse patient populations, which enhances the generalizability of the findings. Second, blood samples were drawn at the time of the initial visit, and serial biomarker measurements were not available, the temporal trajectory of biomarker levels may provide additional prognostic information. Third, the study was conducted during a specific period of the pandemic (April 2020 to December 2021), and the prognostic performance of the model may differ in the context of emerging variants and evolving therapeutic protocols. Fourth, the composite outcome combines ICU admission and in-hospital death without a fixed time horizon and may vary with local practice. Fifth, the clinical comparator included age, sex, and comorbidities but not acute vital signs, oxygen requirements, or routine laboratory data. Finally, although XGBoost offers strong prognostic accuracy, its limited interpretability compared with traditional regression models may hinder clinical adoption, future work integrating explainability methods may be warranted.

CONCLUSIONS

In this historical multicenter cohort, a nine-biomarker panel measured at hospital admission provided strong prognostic value for ICU admission or in-hospital death in patients hospitalized because of COVID-19 infection. Blood biomarkers substantially outperformed clinical variables for risk stratification, while the addition of clinical variables conferred only marginal incremental benefit. The nine-biomarker

panel demonstrated robust calibration and stable performance across a wide range of decision thresholds. These findings support the nine-biomarker panel as a promising tool for triage strategy that may facilitate rapid and objective risk assessment in acute care settings during respiratory pandemic surges. Future studies should validate the biomarker panel in independent and contemporary cohorts, compare it with acute clinical data and routine laboratory tests, and assess calibration and clinical utility before implementation.

Abbreviations

AAT
alpha-1 antitrypsin
ACOV2S
anti-SARS-CoV-2 spike antibody
AF
atrial fibrillation
AIDS
acquired immunodeficiency syndrome
ALP
alkaline phosphatase
ALT
alanine aminotransferase
AUC
area under the receiver operating characteristic curve
BMI
body mass index
BQC-19
Biobanque Québécoise de la COVID-19
CA-125
cancer antigen 125
CK
creatine kinase
CK-MB
creatine kinase myocardial band
COPD
chronic obstructive pulmonary disease
COVID-19
coronavirus disease 2019
ECLIA
electrochemiluminescence immunoassay
ELISA

enzyme-linked immunosorbent assay
GDF-15
growth differentiation factor-15
HE4
human epididymis protein 4
HIV
human immunodeficiency virus
hs-CRP
high-sensitivity C-reactive protein
hs-cTnT
high-sensitivity cardiac troponin T
ICU
intensive care unit
IL-6
interleukin-6
LDL
low-density lipoprotein
NT-proBNP
N-terminal pro-B-type natriuretic peptide
PCR
polymerase chain reaction
PCT
procalcitonin
ROC
receiver operating characteristic
RT-PCR
reverse transcriptase-polymerase chain reaction
SARS-CoV-2
severe acute respiratory syndrome coronavirus 2
SD
standard deviation
sFlt-1
soluble fms-like tyrosine kinase-1
T4
thyroxine
TIA
transient ischemic attack
WHO
World Health Organization
XGBoost

extreme gradient boosting

Declarations

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The BQC-19 protocol was approved by the Research Ethics Board of the Centre hospitalier de l'Université de Montréal (CHUM) (#MP-02-2020-8929, 19.389), acting as the coordinating ethics committee, and by the institutional review board of each participating center. Access to BQC-19 data for the present study was granted by the BQC-19 independent Data and Sample Access Committee. Written informed consent was obtained from all participants or from their legally authorized representative at the time of inclusion in the BQC-19.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from the Biobanque Québécoise de la COVID-19 (BQC-19), but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the BQC-19.

COMPETING INTERESTS

P.P. holds the Canada Research Chair in Valvular Heart Diseases and has core laboratory contracts with Edwards Lifesciences and Medtronic for echocardiography CoreLab analyses with no personal compensation. S.H., L.-J.R., B.A., M.L., A.D., N.C. declare that they have no competing interests.

FUNDING

This work was made possible through the data and biospecimens shared by the Biobanque Québécoise de la COVID-19 (BQC-19), which is funded by the Fonds de recherche du Québec - Santé (FRQS), Génome Québec, the Public Health Agency of Canada, and, since March 2022, the ministère de la Santé et des Services sociaux du Québec. The funders had no role in the design of the study, the collection, analysis and interpretation of the data, or the writing of the manuscript.

AUTHORS' CONTRIBUTIONS

P.P., S.H., and N.C. conceived and designed the study. L.-J.R. developed and implemented the machine-learning analyses. S.H. and L.-J.R. interpreted the data and drafted the manuscript. B.A., M.L., and A.D. critically reviewed and revised the manuscript for important intellectual content. P.P. supervised the

study and obtained the data access. All authors read and approved the final version and agree to be accountable for all aspects of the work.

ACKNOWLEDGEMENTS

This work was made possible through the sharing of data and biospecimens by the Quebec COVID-19 Biobank (BQC-19), funded by the Fonds de recherche du Québec - Santé (FRQS), Genome Québec, the Public Health Agency of Canada, and the Ministère de la Santé et des Services sociaux du Québec. We sincerely thank all BQC-19 participants for their invaluable contribution.

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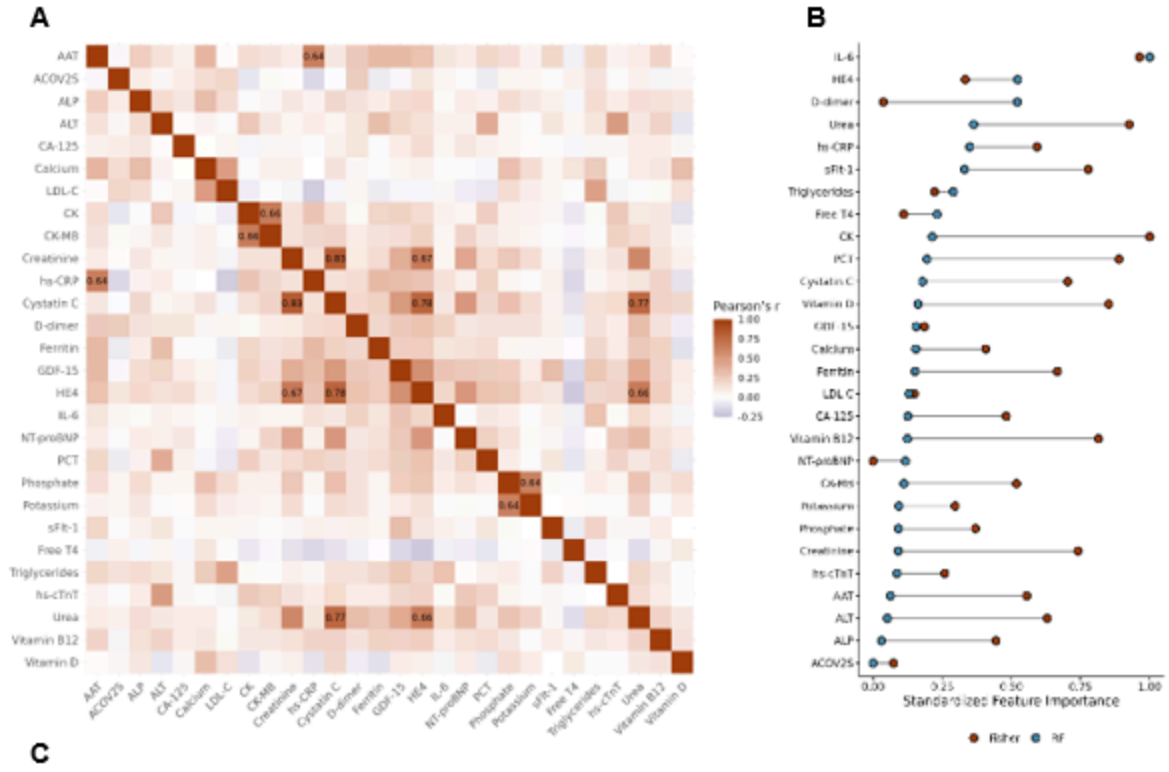
Figures



C

Recursive feature elimination						
	Iteration 1	Iteration 2	Iteration 3	Iteration 4		Iteration 5
Selected features	CK	CK	CK	ALT	IL-6	CK
	Creatinine	Creatinine	Creatinine	CA-125	PCT	Creatinine
	hs-CRP	hs-CRP	hs-CRP	Calcium	sFlT-1	hs-CRP
	D-dimer	D-dimer	D-dimer	CK	Free T4	D-dimer
	GDF-15	GDF-15	GDF-15	CK-MB	Triglycerides	GDF-15
	HE4	HE4	HE4	Creatinine	Urea	HE4
	IL-6	IL-6	IL-6	hs-CRP	Vitamine B12	IL-6
	Free T4	Free T4	Free T4	Cystatin C	Vitamin D	Free T4
	Triglycerides	Triglycerides	Triglycerides	D-dimer		Triglycerides
	Urea	Urea	Urea	GDF-15		Urea
	Vitamin D	Vitamin D	Vitamin D	HE4		Vitamin D
ROC AUC	0.636	0.634	0.642	0.624		0.646

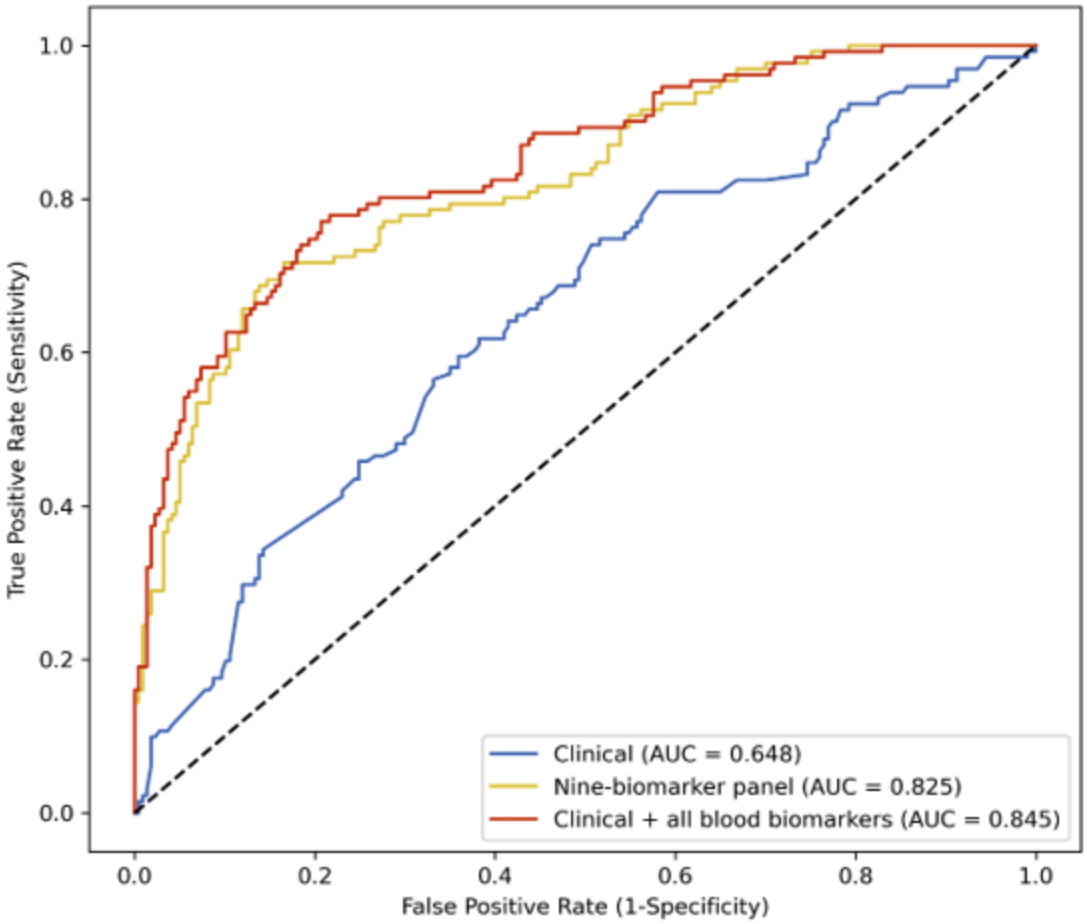
Legends. A) Pearson correlation matrix showing pairwise correlations between blood biomarkers. Correlation coefficients greater than 0.6 are highlighted with their corresponding values. **B)** Feature importance of all blood biomarkers based on Fisher score **(red)** and Random Forest **(blue)**, where higher value indicates greater importance. **C)** Recursive feature elimination performed over five iterations with cross-validation. For each iteration, the area under the receiver operating characteristic curve (AUC) is reported for the selected subset of features.

Figure 1

Identification and Selection of Blood Biomarkers Associated with the Composite Endpoint of ICU Admission or Death.

(A) Pearson correlation matrix showing pairwise correlations between blood biomarkers. Correlation coefficients greater than 0.6 are highlighted with their corresponding values. **(B)** Feature importance of all blood biomarkers based on Fisher score **(red)** and Random Forest **(blue)**, where higher values indicate greater importance. **(C)** Recursive feature elimination performed over 5 iterations with cross-validation. For each iteration, the area under the receiver operating characteristic curve (AUC) is reported for the selected subset of features.

Legends: AUC, area under the receiver operating characteristic curve; ICU, intensive care unit.



Legends. AUC: area under the receiver operating characteristic curve.

Figure 2

Discriminative Performance Comparison of Three Models Using XGBoost.

Receiver operating characteristic curves comparing the discriminative performance of 3 models for the composite endpoint of in-hospital death or intensive care unit admission. Legends: XGBoost, extreme gradient boosting.

Supplementary Files

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- Additionalfile1RespRes.docx