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Integrated Hematological, Biochemical and Radiological Markers Associated with Disease Severity and Mortality in Patients with Acute Respiratory Diseases: A Cross-Sectional Study

Ossaid Ibrahim Quneis[1], Nabeel Al-Omari[2], Ahmad I. Quneis[3], Tarek Mohamed M. Mansour[4], Qise Semrin Mustafa Alawamleh[5], Yasser Abd El Aal Ahmed Abdellah[6], Mohamed Ahmed Soliman[7]

[1]Yarmouk University, Faculty of Medicine, Amman, Jordan., ossaidquneis1@gmail.com, ORCID: 0009-0008-8804-0424
[2]Clinical Science Department, Faculty of Medicine, Yarmouk University, Irbid, Jordan., Nabeelo.omari@gmail.com
[3]Department of Medicine, School of Medicine, Belgorod State University, Belgorod, Russia., quneisahmad@yahoo.com, ORCID: 0009-0007-5636-8962
[4]Assistant Professor of Radio Diagnosis, Al-Azhar University, Assiut, Egypt. Drtarekrad@gmail.com, ORCID: 0000-0001-7074-9939
[5]Department of General Medicine, Institute of Medical Education, Yaroslav-the-Wise Novgorod State University, Veliky Novgorod, Russia., Qaisawamleh7@gmail.com, ORCID: 0009-0005-4772-6022
[6]Assistant Professor of Radio Diagnosis and Interventional Radiology, Faculty of Medicine, Al-Azhar University, Assiut, Egypt., dryasserradiologist@gmail.com, ORCID: 0009-0006-1763-903X
[7]Department of Radiology, Faculty of Medicine, Beni-Suef University, Beni-Suef, Egypt., d.msoliman2015@gmail.com, ORCID: 0009-0006-0975-5292

ABSTRACT:

Background: Early recognition of deterioration in acute respiratory disease requires rapidly available and biologically interpretable information. This study evaluated hematological and biochemical markers, together with structured chest computed tomography (CT) status, in relation to disease severity and mortality.

Methods: A secondary analytical cross-sectional analysis used the iCTCF resource. Severity analysis included 894 laboratory-confirmed COVID-19 pneumonia cases (620 mild/regular and 274 severe/critical), while mortality analysis included 719 patients with known outcomes (662 cured and 57 deceased). Group differences were assessed using nonparametric or categorical tests with Benjamini-Hochberg correction. Biomarker-specific logistic models adjusted for age, sex, underlying disease and hospital. Repeated five-fold cross-validation evaluated clinical, hematological, biochemical and integrated logistic models.

Results: Severe/critical cases were older, more often male and more frequently had underlying disease. Higher neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), lactate dehydrogenase (LDH), blood urea nitrogen and interleukin-6, together with lower lymphocyte count and albumin, characterized worse outcomes. Mortality associations were strongest for LDH (OR 3.76 per 1-SD increase; 95% CI 2.29-6.17), CRP

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(OR 3.33; 95% CI 1.46-7.62) and NLR (OR 2.85; 95% CI 2.11-3.85). Mean cross-validated ROC-AUC increased from 0.743 to 0.802 for severe/critical disease and from 0.819 to 0.888 for mortality when moving from clinical-only to integrated models.

Conclusion: Multidomain biomarker information improved discrimination beyond clinical variables alone. NLR, LDH, lymphocyte count and albumin were particularly informative. The structured CT variable should be interpreted as radiological evidence status rather than a quantitative CT severity score, and external validation is required before clinical implementation.

1. INTRODUCTION

Acute respiratory infections may quickly progress to acute respiratory failure due to the potential of local lung injury, and secondary organ dysfunction and immune dysfunction. Thus, severity is now considered a multi-faceted construct as opposed to a single laboratory abnormality or imaging finding (Elson et al., 2025). In clinical practice, it is common for clinicians to combine the findings of physiological measurements with those of blood-cell indices, biochemical tests and chest imaging since each of these domains represents a different aspect of the disease mechanism. Clinically relevant consideration of their complementary value is transparent, particularly if decisions need to be made prior to the complete course of the disease.

Routine hematology is worth pursuing for risk stratification as it is accessible, readily available and sensitive to SIS. Neutrophilia, lymphopenia and altered platelet profile have been consistently associated with severe COVID-19 and the neutrophil-to-lymphocyte ratio (NLR) with severe disease and mortality (Alnor et al., 2020; Henry et al., 2020a; Li et al., 2021; Simadibrata et al., 2021). These findings suggest testing to see if haematological signals provide additional information to that of demographic and clinical characteristics.

Biochemical markers represent complementary inflammatory pathways, tissue injury pathways and organ-dysfunction pathways. There has been previous evidence that CRP, procalcitonin, LDH, albumin and renal or hepatic indices are related to poor outcomes in COVID-19, and that IL-6 can give an additional insight into the inflammatory status when measured (Coomes & Haghbayan, 2020; Henry et al., 2020b; Malik et al., 2021; Soetedjo et al., 2021). Their combined assessment is more clinically relevant than focusing on one of the laboratory abnormalities. Chest CT directly shows the pulmonary involvement and quantitative CT severity scores have shown to be useful in the discrimination of severe disease and mortality in COVID-19 meta-analysis (Prakash et al., 2023). But the radiological variables should be accurately depicted. The tabular iCTCF data here include evidence of CT as positive, negative or unknown – there is no patient-level numerical CT severity score. For this study, therefore, the status of CT is considered as a structured radiological indicator and the burden of the lesions is not assumed from the tabular field. The iCTCF resource is ideal for integrated secondary analysis as it provides clinical details, routine haematology, biochemical, immune measurements, CT data and adjudicated morbidity and mortality data for each patient (Ning et al., 2020). While the original publication showed the benefit of multimodal deep learning for outcome prediction, an interpretable epidemiological analysis can provide a different type of answer to a different question: which routinely available markers are still associated with severe or fatal outcomes after adjustment for major patient characteristics, and what is the increase in discrimination achieved when the complementary domains are combined? The aim of the present study was therefore to find biomarkers in the haematology, biochemical and structured radiology data that were linked to severe/critical disease and death, and to compare the discriminative power of clinical-only, domain-specific and integrated models. An integrated model was hypothesized to improve on clinical information alone as higher NLR, CRP, LDH and markers of organ dysfunction, lower lymphocyte count and lower albumin were hypothesized to be associated with worse outcomes.

2. LITERATURE REVIEW

Although respiratory disease risk stratification has been traditionally based on clinical severity scores and physiological observation, there is potential for including laboratory biomarkers that provide mechanistic information, and which may be available at a similar early stage of care. Biomarkers like PCT and CRP have been moderately useful in the prognosis of C-AP, but systematic review evidence suggests that none of these biomarkers consistently supplants existing clinical scores (Viasus et al., 2016). This is in favor of complementary (not substitutional) use of biomarkers. More recent ARI surveillance efforts also highlight the importance of integrating the symptom, sign, investigation and outcome data in describing severity of the different respiratory syndromes (Elson et al., 2025). In the haematological literature there is a relative uniformity of opinion. In pooled

studies, Alnor et al. (2020) found an elevated white-cell and neutrophil count as well as a decreased lymphocyte, platelet and hemoglobin concentration in severe COVID-19. Henry et al. (2020a) came to a similar conclusion and found inflammatory, liver, renal and immune abnormalities were found in sever and fatal illness. NLR has got special attention as neutrophilia and lymphopenia may coexist in the case of severe systemic inflammation. Simadibrata et al. (2021) conducted a meta-analysis of 38 reports that found significantly higher admission NLR in severe cases and non-survivors, and Li et al. (2021) found an association using adjusted effect estimates which could not be attributed to simple demographic differences. NLR, therefore, provides a clinically intuitive summary of the inflammatory cell profile, but with appropriate threshold differing across populations and use of NLR as a risk marker rather than as a diagnostic cut-off. Biochemical markers offer second layer of prognostic information. Malik et al. (2021) performed a synthesis of 32 studies and over 10,000 confirmed cases, and identified poor prognosis with high CRP, PCT, LDH, AST and creatinine and lymphopenia and thrombocytopenia. A raised level of LDH could indicate diffuse tissue injury or hypoxic and inflammatory cell damage, and was shown by Henry et al (2020b) to be associated with a significantly increased risk of severe disease and death. There is another route, namely that of albumin. Hypoalbuminemia may be related to systemic inflammation, capillary leak, decreased synthesis and catabolic load and in a diagnostic meta-analysis of 19 studies were strongly associated with severe or fatal COVID-19 (Soetedjo et al., 2021). IL-6 is closer to inflammatory signaling, and pooled evidence indicates that there is an increase in the concentration in complicated disease, but there is a significant amount of heterogeneity and selectivity in the cytokine testing, which makes it difficult to directly compare (Coomes & Haghbayan, 2020). The severity seen on the x-ray is also of prognostic importance, but the degree of detail on the x-ray is important. Quantitative CT severity scores are able to capture the extent of parenchymal involvement and have pooled summary AUCs of ~0.91 for severe disease and ~0.84 for mortality in a systematic review and meta-analysis (Prakash et al., 2023). In contrast, a binary CT-positive indicator is only able to answer the question of whether there is any radiological evidence compatible with pneumonia or not. It can not measure burden, nor distribution or temporal evolution. This separation from images is particularly relevant in the iCTCF resource as there is a wealth of image data but the accompanying tabular data used for the current epidemiological analysis only provides evidence of CT status. It therefore is not determining whether or not individual biomarkers have been presented that is important, but the complementary domains when used in the same patients with an interpretable and reproducible framework. The previous iCTCF study used a deep-learning architecture of 130 clinical features and CT images, and demonstrated good predictive performance (Ning et al., 2020). This current work builds on this open resource by focusing specifically on effect estimates, uncertainty, missingness and incremental discrimination. This is an attempt to separate out strong, clinically meaningful relationships from age-comorbidity relationships that might be due to selective testing and/or how severity is defined.

3. METHODOLOGY

3.1 Study Design and Data Source

This study adopted an analytical cross-sectional secondary-data design of integrative CT images and clinical features for COVID-19 (iCTCF) as described by Ning et al. (2020). This is a source database of 1,521 individuals from Union Hospital and Liyuan Hospital in Wuhan, China with attached clinical features, lab measurements, chest CT data and SARS-CoV-2 status. Since the measures of the clinical features and the first available CT examination were obtained after hospital admission, the present analyses use the measure of the clinical-feature set and the CT examination of that time only, not longitudinal trajectories (Ning et al., 2020). Since this is a final hospital outcome, the analytical question was not a causal or time-to-event analysis, but rather the association between the index admission profile and documented outcome. Thus, odds ratios are viewed as association measures, rather than causal effect estimates. Reporting was done using the STROBE guidelines for observational studies (von Elm et al., 2007).

3.2 Study Population and Outcomes

There were 894 laboratory confirmed cases in the source population with an adjudicated morbidity category of 24 mild, 596 regular, 202 severe and 72 critically ill. The grouping for the primary severity outcome was as per the source publication: mild/regular cases were considered as non-severe (n = 620) while severe/critically ill cases were considered as severe/critical (n = 274). Patients, who were transferred to others without a definite final outcome were excluded leaving 719 patients, 662 cured and 57 dead. The analytic cohorts are summarized in figure 1. The mortality endpoint was coded as "deceased" or "cured" (mortal status). Mortality associations were also adjusted for the binary severe/critical category with a sensitivity analysis to assess which biomarker signals remained after adjusting for the contemporaneous clinical severity classification.

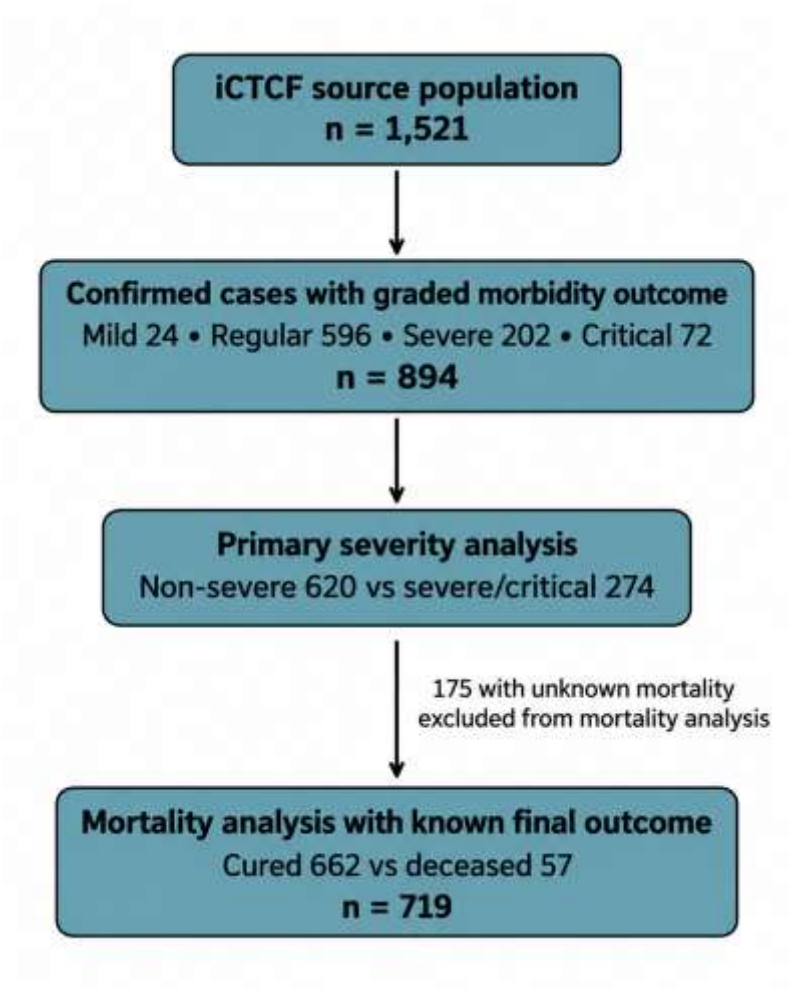

Figure 1. Flow of participants into the disease-severity and mortality analyses.

3.3 Exposures and Covariates

Hematological parameters measured were white blood cell count (WBC), absolute neutrophil count, absolute lymphocyte count, platelet count, hemoglobin and derived inflammatory parameters. NLR was measured as absolute neutrophils / absolute lymphocytes; the platelet-to-lymphocyte ratio (PLR) and the systemic immune-inflammation index were descriptively investigated. Biochemical and inflammatory measurements were taken, such as CRP, PCT, erythrocyte sedimentation rate, LDH, albumin, AST, alanine aminotransferase, blood urea nitrogen (BUN), creatinine, glucose, serum amyloid A and IL-6. Biological relevance, previous evidence and data availability were used a priori to select candidate markers for the adjusted models and not only univariable statistical significance.

Core adjustment variables included age, sex, hospital (or not) and underlying disease recorded or none. If the underlying disease was any other response than 'No' the underlying disease was coded as present. Structured radiological variable was the source CT evidence field (positive, negative or unavailable). A quantitative radiological burden was not created or imputed because the tabular data set didn't include a quantitative CT severity score.

3.4 Data Quality and Missingness

Patient identifiers were deduplicated, categorical patient labels were harmonized and ratios of categorical data were only calculated if the base numbers were known. No imputation was made for an outcome value. There were significant differences in missingness by domain: age and demographic data were essentially complete; routine hematological data were missing in ~17% of the severity cohort and ~10% of the mortality cohort; several biochemical data were missing in ~40–65% of observations. This is because it is based on the clinical workflows of the sources and is inefficient and potentially selective to

have a single full clinical model with all biomarkers. For this reason, in descriptive comparisons, the observations in the possession of the institutions were used. The association models were marker-specific and each marker was included with the same core of markers. To avoid information leakage, missing values for numerical predictors were median imputed within each training fold and those for categorical predictors were imputed with the most frequent value within each training fold for predictive cross validation.

3.5 Statistical Analysis

Many laboratory distributions were skewed and so continuous variables were summarized using medians and interquartile ranges. The Mann-Whitney U test and chi-square or Fisher's exact test were used for two-group comparisons for continuous and categorical variables, respectively. Multibiomarker screening tables were corrected for false-discovery-rate (FDR) and a $q < .05$ was deemed statistically significant. Binomial generalized linear models were used to estimate adjusted associations with severe/critical disease and death. All biomarkers were modelled individually with age, sex, underlying disease and hospital. Markers with strong right skewness were log-transformed prior to analysis ($\log(1+x)$); reported ORs therefore refer to a 1 SD increment in the log transformed biomarker or the original biomarker (for continuous biomarkers). Albumin, lymphocyte count and platelet count remained on their original scale prior to standardization. The severe/critical indicator was also added to the mortality sensitivity models. CT status was excluded from the severity association model because all of the severe/critical patients with a recorded CT result were CT positive, and were thus structurally separated, so there may be issues of incorporation; it was left as a categorical prediction variable in the exploratory discrimination model. Regularized logistic regression was used for predictive discrimination in four feature sets: clinical variables alone; clinical + hematology; clinical + biochemistry; and integrated (clinical, hematological, biochemical and CT status). Pre-processing was done on each of the training folds. Each of the 5-fold stratified cross-validation was repeated 30 times. The main discrimination index was the area under the receiver-operating-characteristic curve (ROC-AUC), whilst the precision-recall AUC and Brier score were also computed. Results are presented as mean of repeated cross-validations, with the empirical 2.5th-97.5th percentile range for ROC-AUC. Analyses were conducted in Python 3.13.5 using pandas 2.2.3, SciPy 1.17.0, statsmodels 0.14.6 and scikit-learn 1.8.0.

3.6 Ethics

The source investigators reported approval for collection, use and retrospective analysis of CT images, clinical features and SARS-CoV-2 RT-PCR results from the institutional ethics committees of Union Hospital and Liyuan Hospital (IRB ID [2020] IEC [A001]); informed consent was waived because of the COVID-19 emergency (Ning et al., 2020). The present study used an anonymized publicly available secondary dataset and involved no new patient contact.

4. RESULTS

4.1 Cohort Characteristics and Radiological Status

The severity analysis included 894 confirmed cases. Severe/critical patients were older than non-severe patients (median 65 years [IQR 55-72] vs 54 [37-65], $p < .001$), were more often male (52.6% vs 42.7%, $p = .007$) and more often had at least one underlying disease (58.4% vs 35.8%, $p < .001$). Median body temperature was also modestly higher in the severe/critical group (38.4°C vs 38.0°C, $p < .001$). Table 1 summarizes these characteristics.

Table 1. Baseline characteristics by disease-severity group

Characteristic	Non-severe (n=620)	Severe/critical (n=274)	P value
Age, years, median (IQR)	54 (37-65)	65 (55-72)	< .001
Male sex, n (%)	265 (42.7)	144 (52.6)	.007
Any underlying disease, n (%)	222 (35.8)	160 (58.4)	< .001
Body temperature, °C, median (IQR)	38.0 (36.8-38.6)	38.4 (37.8-38.9)	< .001

Characteristic	Non-severe (n=620)	Severe/critical (n=274)	P value
Union Hospital, n (%)	485 (78.2)	227 (82.8)	.126
CT positive among known CT, n/N (%)	542/564 (96.1)	205/205 (100.0)	.002

Note. IQR = interquartile range; CT = computed tomography. CT percentages use only patients with a recorded positive/negative CT result.

Among patients with known mortality status, non-survivors were substantially older than cured patients (median 71 [64-79] vs 57 [41-67] years, $p < .001$), more frequently male (66.7% vs 44.3%, $p = .001$) and more frequently had underlying disease (75.4% vs 40.5%, $p < .001$). In a clinical-only adjusted model, each 10-year increase in age was associated with severe/critical disease (OR 1.54, 95% CI 1.38-1.72) and mortality (OR 2.01, 95% CI 1.56-2.58). Male sex and underlying disease also remained associated with both outcomes, whereas hospital did not.

The structured CT field had limited variation among severe disease. Of the 769 patients with a recorded positive/negative CT result, all 205 severe/critical cases were CT-positive, compared with 542 of 564 non-severe cases. This yielded a significant unadjusted distributional difference but prevented a stable adjusted odds ratio. For mortality, only 19 deceased patients had a known CT result and all were positive; 575 of 593 cured patients with known CT status were also positive. Accordingly, the tabular CT evidence indicator did not provide a meaningful standalone mortality contrast. The much richer image-level CT information available in the full iCTCF archive was outside the scope of this tabular analysis.

To provide visual radiological context for the CT component, Figure 2 links to representative HUST-19 chest CT examples published in a peer-reviewed open-access study that used the same HUST-19 imaging resource as the present iCTCF analysis (Mehboob et al., 2022; Ning et al., 2020). The HUST-19 panel contains a COVID-positive CT slice and a COVID-negative CT slice. Because the current epidemiological analysis retained only the structured positive/negative/unavailable CT field and did not preserve patient-level image identifiers, these images are presented as representative source-resource examples and must not be interpreted as the exact individuals contributing to any specific odds ratio or outcome estimate.

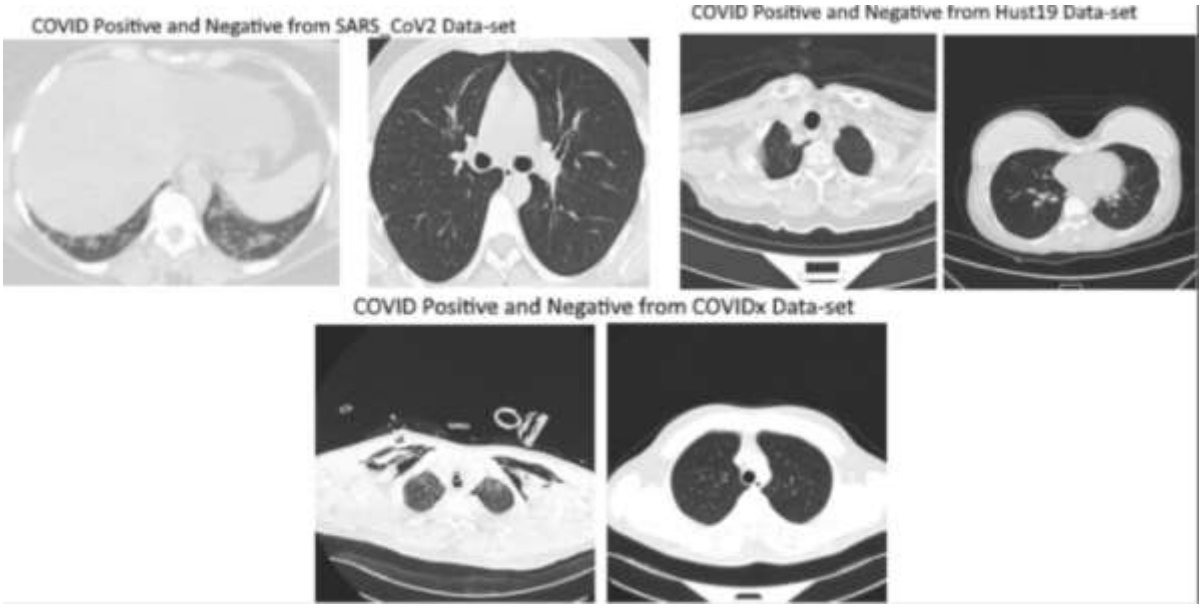

Figure 2. Representative chest CT examples from the HUST-19 imaging resource, showing COVID-positive and COVID-negative CT appearances. Source: adapted from Mehboob et al. (2022), Figure 4, which includes HUST-19 images; HUST-19/iCTCF source resource described by Ning et al. (2020). The linked article is licensed CC BY 4.0; the original HUST-19 resource is available for academic use under CC BY-NC 4.0. These images provide radiological context and are not linked to individual outcome records in the present tabular analysis.

Because the tabular release of the source resource distributes chest CT to secondary users as a categorical evidence field rather than as patient-level images or a numerical severity score, no image-level data were accessed, segmented or analysed in the present study. To allow readers to relate the categorical CT variable used here to the underlying parenchymal abnormalities it indexes, the radiological spectrum of pulmonary involvement in COVID-19 pneumonia is illustrated in Figure 3 using previously published images from an independent cohort.

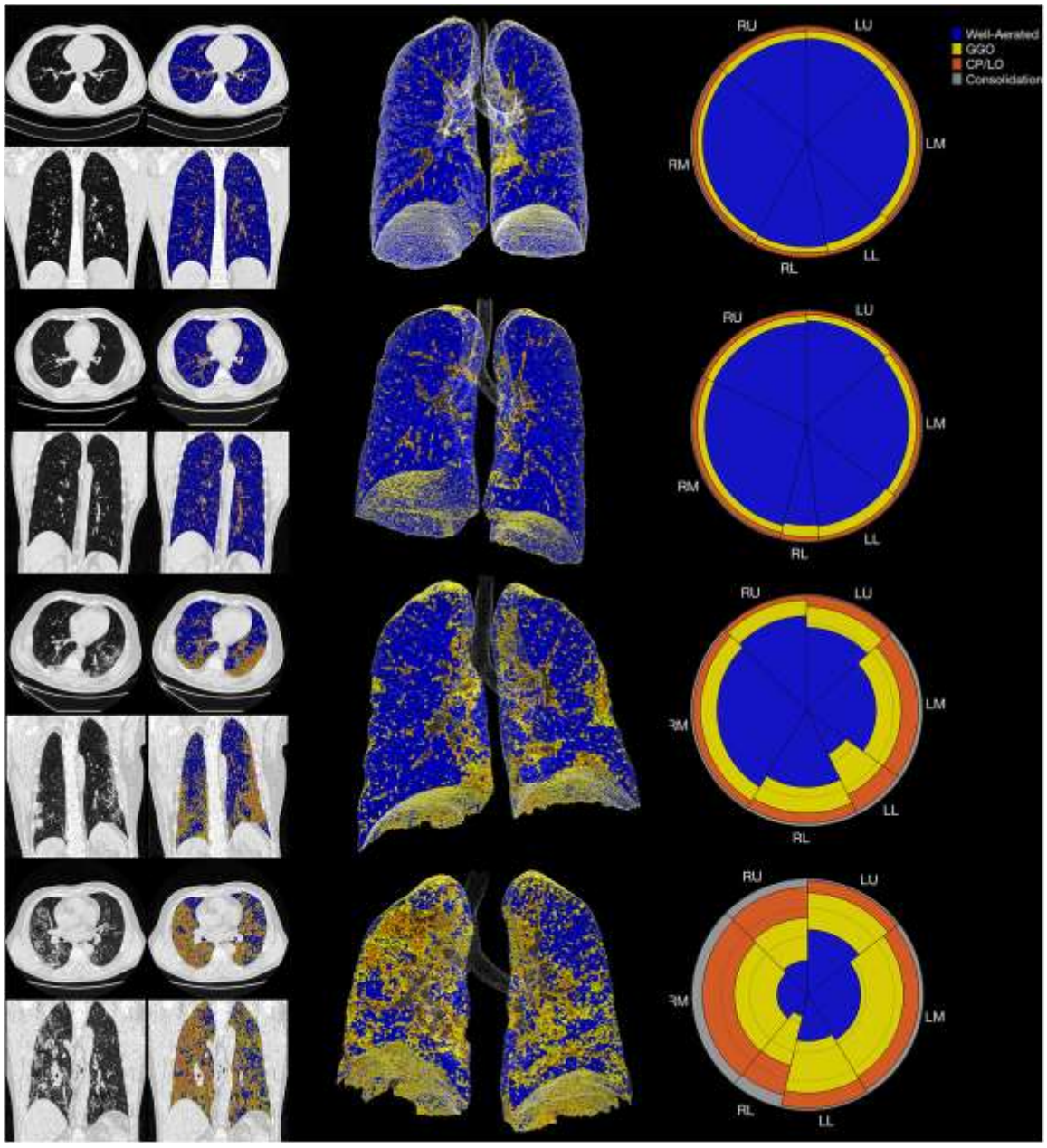

Figure 3. Representative chest computed tomography appearances across the spectrum of pulmonary involvement in COVID-19 pneumonia. For each case, axial and coronal slices are shown in native form and with computer-aided classification overlay (left column), together with the corresponding three-dimensional reconstruction (centre) and a regional summary glyph (right); colour coding denotes well-aerated parenchyma (blue), ground-glass opacity (yellow), crazy paving and linear opacities (orange) and consolidation (grey). Rows represent, from top to bottom, a control subject and patients with mild, moderate and severe pulmonary involvement. Images are reproduced for illustrative purposes only from Carvalho et al. (2020), Frontiers in Medicine, 7, 577609, under a Creative Commons Attribution 4.0 International (CC BY 4.0) licence. These images are not derived from the present study cohort and were not used in any analysis reported here.

4.2 Hematological and Biochemical Profiles

Clear biomarker gradients were observed across severity. Severe/critical patients had higher WBC, NLR, CRP, LDH, AST, BUN, creatinine and IL-6 and lower lymphocyte, platelet and albumin values than non-severe patients. The largest unadjusted separation was seen for NLR, lymphocyte count and albumin. NLR increased from a median of 2.29 (IQR 1.63-4.04) in non-severe disease to 5.36 (2.58-12.12) in severe/critical disease. Albumin decreased from 38.1 (33.6-41.7) to 31.5 (26.5-35.9), while LDH increased from 209 (171-272) to 294 (221-455.5). All three comparisons remained significant after FDR correction. Table 2 presents the main severity comparisons.

Table 2. Selected hematological and biochemical markers by severity

Marker	Non-severe, median (IQR)	Severe/critical, median (IQR)	FDR q
WBC	5.05 (3.97-6.58)	6.04 (4.38-8.35)	< .001
LY	1.28 (0.94-1.68)	0.85 (0.57-1.23)	< .001
PLT	205.00 (159.00-263.75)	185.00 (140.00-241.00)	.002
NLR	2.29 (1.63-4.04)	5.36 (2.58-12.12)	< .001
CRP	9.17 (3.14-27.73)	44.23 (9.79-88.84)	< .001
PCT	0.13 (0.13-0.13)	0.13 (0.13-0.21)	.006
LDH	209.00 (171.00-272.00)	294.00 (221.00-455.50)	< .001
ALB	38.10 (33.60-41.70)	31.50 (26.52-35.88)	< .001
AST	24.40 (19.00-33.00)	34.00 (25.15-49.50)	< .001
BUN	3.94 (3.05-5.04)	5.35 (3.82-7.80)	< .001
CREA	63.20 (55.67-77.35)	71.20 (58.50-86.00)	< .001
IL-6	6.28 (4.11-17.49)	16.05 (6.00-35.73)	< .001

Note. Available-case analysis; sample size therefore differs by biomarker. NLR = neutrophil-to-lymphocyte ratio; CRP = C-reactive protein; PCT = procalcitonin; LDH = lactate dehydrogenase; ALB = albumin; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CREA = creatinine; IL-6 = interleukin-6.

The mortality contrasts were larger for several markers. Median NLR was 10.50 (5.30-18.65) among deceased patients versus 2.54 (1.72-4.60) among cured patients; LDH was 451 (318.5-581) versus 227 (177-301.5), and albumin was 28.1 (23.9-31.8) versus 36.65 (31.28-41.03). Deceased patients also had higher WBC, CRP, PCT, BUN, creatinine and IL-6 and lower lymphocyte and platelet counts. Most of these differences remained significant after FDR correction (Table 3).

Table 3. Selected hematological and biochemical markers by mortality status

Marker	Cured, median (IQR)	Deceased, median (IQR)	FDR q
WBC	5.17 (4.08-6.78)	8.94 (5.50-10.97)	< .001
LY	1.20 (0.88-1.60)	0.68 (0.45-1.01)	< .001
PLT	205.00 (156.50-264.00)	146.50 (117.50-220.25)	< .001
NLR	2.54 (1.72-4.60)	10.50 (5.30-18.65)	< .001
CRP	10.60 (3.14-39.46)	81.20 (37.70-114.10)	< .001
PCT	0.13 (0.13-0.13)	0.29 (0.15-0.94)	< .001

Marker	Cured, median (IQR)	Deceased, median (IQR)	FDR q
LDH	227.00 (177.00-301.50)	451.00 (318.50-581.00)	< .001
ALB	36.65 (31.27-41.02)	28.10 (23.90-31.80)	< .001
AST	26.00 (19.40-38.00)	33.00 (27.00-56.35)	< .001
BUN	4.12 (3.25-5.47)	7.05 (4.82-11.05)	< .001
CREA	65.25 (56.65-79.83)	80.05 (61.05-92.83)	.002
IL-6	6.51 (4.14-17.71)	53.36 (18.88-186.68)	< .001

Note. Available-case analysis; sample size differs by biomarker. FDR q values are Benjamini-Hochberg adjusted.

Mortality was strongly concentrated in the highest clinical severity categories. There were no deaths among mild or regular cases with known final outcome, whereas mortality was 8.8% among severe cases and 76.4% among critically ill cases. Figure 4 displays this gradient, which also motivated the sensitivity models that adjusted biomarker-mortality associations for severity category.

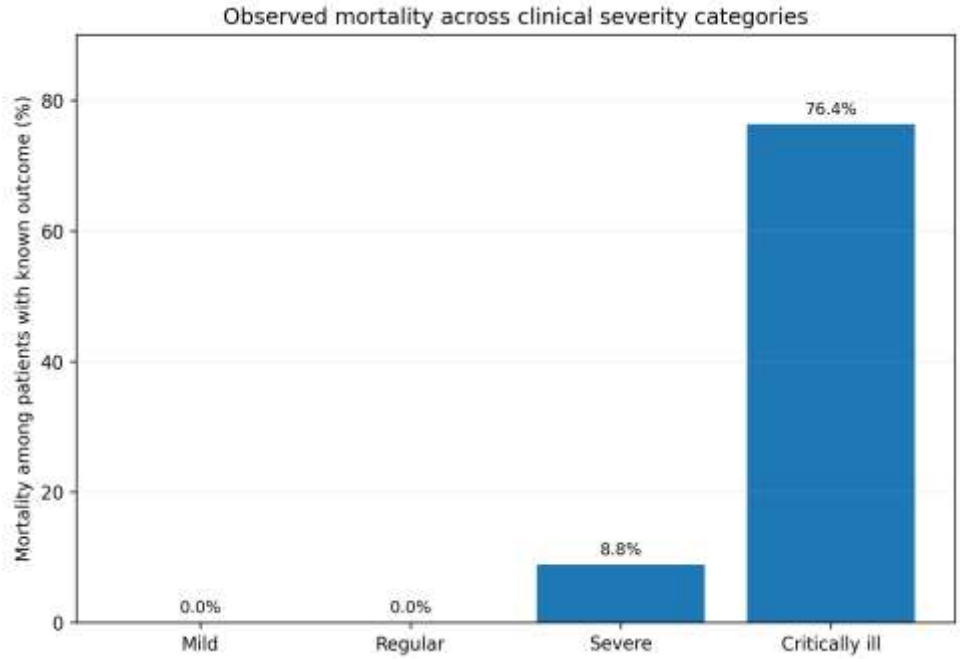

Figure 4. Observed mortality percentage within each morbidity category among patients with a known final outcome.

4.3 Adjusted Biomarker Associations

After adjustment for age, sex, underlying disease and hospital, the main laboratory associations with severe/critical disease remained directionally consistent (Table 4; Figure 5). A one-standard-deviation increase in NLR was associated with more than twice the odds of severe/critical disease (OR 2.38, 95% CI 1.96-2.89), as were higher PCT (OR 2.22, 1.38-3.56), LDH (OR 2.21, 1.73-2.84) and CRP (OR 2.15, 1.63-2.83). Higher BUN and AST also remained associated with severity. In contrast, higher lymphocyte count (OR 0.37, 0.28-0.48) and albumin (OR 0.46, 0.36-0.59) were protective-direction associations, and higher platelet count showed a smaller inverse association. All prespecified severity markers shown in Table 4 retained q < .05.

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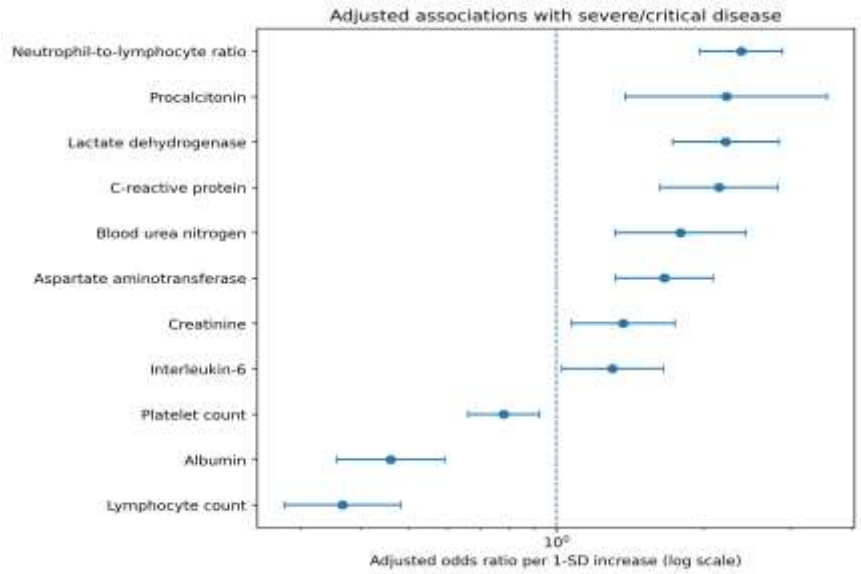

Figure 5. Adjusted odds ratios for severe/critical disease. Each biomarker was modeled separately with age, sex, underlying disease and hospital; continuous biomarkers are shown per 1-SD increase.

For mortality, LDH showed the largest adjusted association among well-estimated markers (OR 3.76, 95% CI 2.29-6.17), followed by CRP (OR 3.33, 1.46-7.62) and NLR (OR 2.85, 2.11-3.85). IL-6 and BUN were also positively associated with mortality, whereas lymphocyte count, platelet count and albumin were inversely associated. PCT had a wide confidence interval because only nine deaths had an available PCT measurement and did not remain significant in the adjusted model. AST and creatinine were also not independently significant after FDR correction. When the mortality models were further adjusted for severe/critical status, NLR (OR 1.99, 95% CI 1.44-2.75; q < .001), LDH (OR 2.48, 1.49-4.12; q = .002) and lymphocyte count (OR 0.42, 0.25-0.72; q = .006) retained the clearest associations, indicating that these signals were not explained entirely by the categorical severity label.

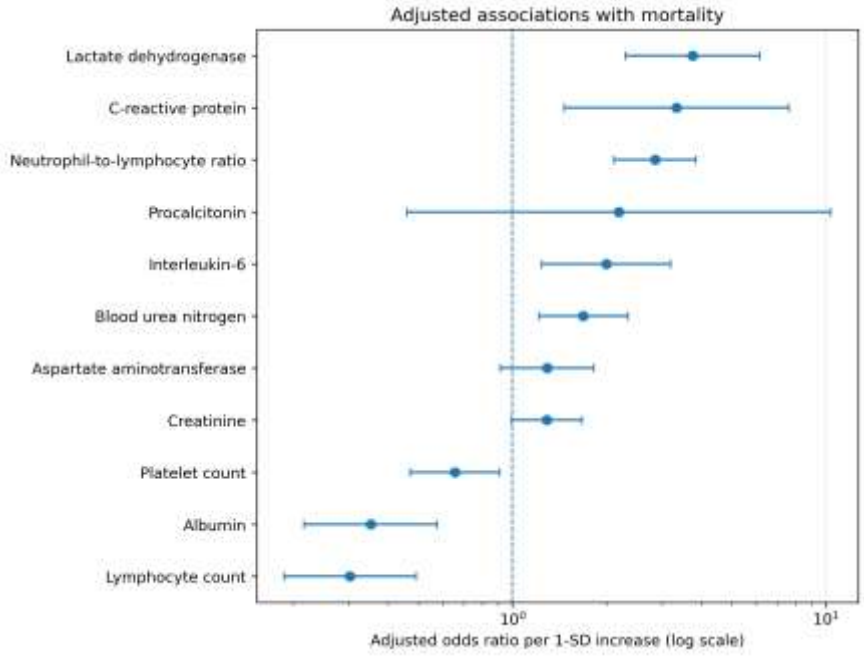

Figure 6. Adjusted odds ratios for mortality. Each biomarker was modeled separately with age, sex, underlying disease and hospital; continuous biomarkers are shown per 1-SD increase.

For ease of comparison across outcomes, the principal adjusted estimates for both disease severity and mortality are consolidated in Table 4.

Table 4. Adjusted biomarker associations with severe/critical disease and mortality

Marker	Severity OR (95% CI)	q	Mortality OR (95% CI)	q
NLR	2.38 (1.96-2.89)	< .001	2.85 (2.11-3.85)	< .001
LY	0.37 (0.28-0.48)	< .001	0.30 (0.19-0.49)	< .001
PLT	0.78 (0.66-0.92)	.005	0.66 (0.47-0.91)	.017
CRP	2.15 (1.63-2.83)	< .001	3.33 (1.46-7.62)	.007
PCT	2.22 (1.38-3.56)	.001	2.18 (0.46-10.37)	.326
LDH	2.21 (1.73-2.84)	< .001	3.76 (2.29-6.17)	< .001
ALB	0.46 (0.36-0.59)	< .001	0.35 (0.22-0.58)	< .001
AST	1.66 (1.32-2.09)	< .001	1.29 (0.91-1.82)	.162
BUN	1.79 (1.32-2.44)	< .001	1.68 (1.21-2.34)	.004
CREA	1.37 (1.07-1.74)	.013	1.29 (0.99-1.67)	.070
IL-6	1.30 (1.03-1.65)	.030	1.99 (1.24-3.20)	.007

Note. Each model adjusted for age, sex, any underlying disease and hospital. ORs are per 1-SD increase; strongly skewed biomarkers were log(1+x) transformed before standardization. q = Benjamini-Hochberg FDR-adjusted p value.

4.4 Multidomain Discrimination

The repeated cross-validation analysis showed that laboratory information improved discrimination beyond the clinical-only model. For severe/critical disease, the clinical model had a mean ROC-AUC of 0.743; adding hematological markers increased the mean AUC to 0.791, adding biochemical markers to 0.779, and the integrated model to 0.802. The same pattern was more pronounced for mortality: mean AUC increased from 0.819 for clinical information alone to 0.880 with hematology, 0.862 with biochemistry and 0.888 in the integrated model. Precision-recall performance and Brier scores improved in the same direction, particularly for mortality, where class imbalance makes precision-recall performance informative. Table 5 provides the repeated-cross-validation results, and Figures 7 and 8 show representative out-of-fold ROC curves.

Table 5. Repeated five-fold cross-validated model performance

Model	Severity ROC-AUC mean (empirical 95% range)	Severity PR-AUC	Mortality ROC-AUC mean (empirical 95% range)	Mortality PR-AUC
Clinical	0.743 (0.739-0.746)	0.542	0.819 (0.810-0.828)	0.239
Clinical + hematology	0.791 (0.788-0.795)	0.653	0.880 (0.872-0.889)	0.419
Clinical + biochemistry	0.779 (0.775-0.782)	0.621	0.862 (0.850-0.870)	0.391
Integrated	0.802 (0.799-0.805)	0.672	0.888 (0.875-0.896)	0.440

Note. Empirical ranges are the 2.5th-97.5th percentiles of AUC values across 30 repeated five-fold cross-validations and are not formal confidence intervals. PR-AUC = area under the precision-recall curve. Brier scores are reported in the accompanying Results text.

The numerical performance summary in Table 5 is complemented by the receiver operating characteristic curves shown in Figures 7 and 8, which illustrate the relative separation achieved by the clinical, hematology, biochemical, and integrated models.

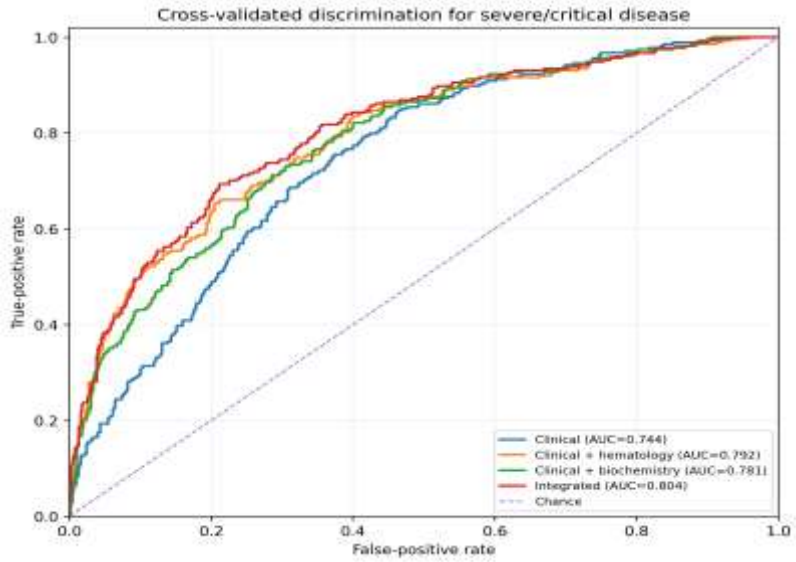

Figure 7. Representative five-fold out-of-fold ROC curves for severe/critical disease. Mean repeated-cross-validation AUCs are reported in Table 5.

Using the same validation framework, the corresponding mortality ROC curves are presented next so that discrimination for the two outcomes can be compared directly.

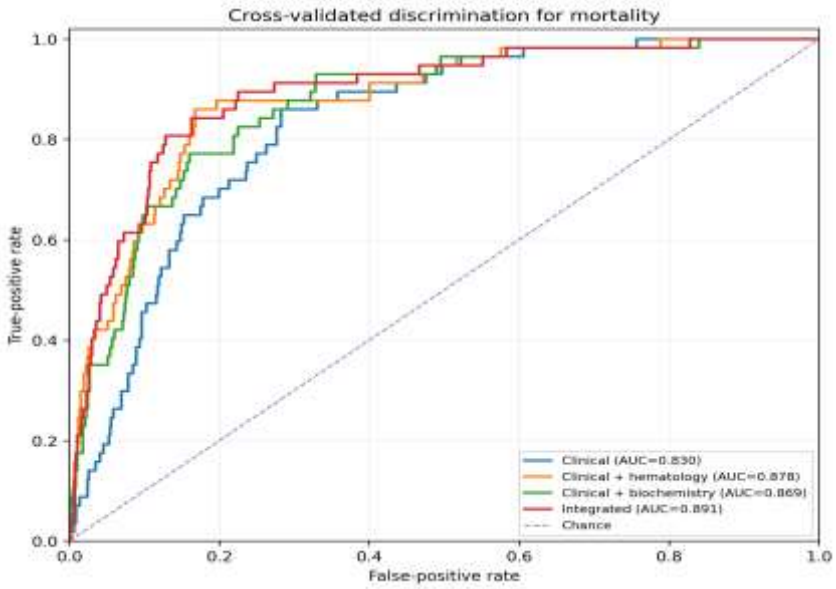

Figure 8. Representative five-fold out-of-fold ROC curves for mortality. Mean repeated-cross-validation AUCs are reported in Table 5.

5. DISCUSSION

A consistent multi-domain pattern was found in this analysis and was related to poorer outcomes for respiratory diseases in the iCTCF cohort. Severe/critical disease and mortality were defined as an inflammatory and tissue-injury profile (increased NLR, CRP, LDH, decreased lymphocytes, decreased albumin, renal, hepatic and cytokine perturbation). These relationships remained to varying extents after the adjustment for age, sex, underlying disease and hospital. The predictive analysis confirmed the findings of the main analysis but from another perspective: laboratory domains added additional discrimination, over and above

clinical characteristics and the combined model of all domains demonstrated the best overall performance. The results together suggest that there is clinical sense to multidomain assessment and that this is largely driven by a small number of interpretable routine markers.

One of the most consistent of these findings was NLR. No matter the case, the severe/critical disease and deceased patients showed more than double and nearly quadruple Median NLR than the cured patients, respectively. The odds ratios were 2.38 for the severe/critical disease and 2.85 for mortality per one-standard-deviation increase, and the relationship with mortality persisted after further adjustment for severity category. This is a good approximation to literature published. The overall results indicated that there was significant heterogeneity across reports, and severe cases and non-survivors were found to have significantly higher levels of admission NLR in 38 reports (Simadibrata et al., 2021) and in adjusted estimates (Li et al., 2021). Biological rationale is also plausible; neutrophilia may be a sign of innate immune activation and stress; lymphopenia may be due to redistribution of immunity cells and/or consumption or a viral-induced immune dysfunction. The current findings provide further evidence of the use of NLR as a continuous risk marker based on a routine blood count and not a single cut-off.

However, the absolute value of lymphocytes continued to be useful, especially in regard to mortality. Levels of lymphocytes were significantly related to much reduced odds of severe/critical disease and death, and this was true when models for mortality were adjusted for the severity category. This is consistent with two systematic reviews which found lymphopenia to be one of the most consistent laboratory abnormalities of severe COVID-19 (Alnor et al., 2020; Henry et al., 2020a). This strong NLR effect in the sensitivity analysis, in addition to an independent lymphocyte effect, indicates that the cellular immune profile in this context represents clinically relevant data, which is not fully captured by age or comorbidity.

LDH was the best biochemical predictor of death in the primary adjusted analysis. Factors indicating higher tumor burden, such as the median LDH, were about doubled for the deceased patients compared to the cured patients and each standard deviation increment was associated with a 3.76-fold incremental adjusted odds of death. Interestingly, this association of LDH was retained following further adjustment for severe/critical status. A pooled analysis by Henry et al. (2020b) also showed a strong association of elevated LDH with severe disease and death, albeit of a higher magnitude as it included dichotomized LDH (elevated or not) and a mix of study populations. We have gone with a more conservative continuous adjusted estimate which indicates the same direction. Though nonspecific, this could be clinically helpful in severe respiratory disease as it reflects generalized tissue injury, as opposed to only one pathway in a given organ.

The inflammatory part of the risk profile was corroborated by CRP, PCT and IL-6, but highlighted the need for completeness of data. After adjustment CRP was strongly associated with both severe disease and death, similar to the meta-analysis performed by Malik et al. (2021). Elevated IL-6 levels have been noted in complicated COVID-19 (Coomes and Haghbayan, 2020) and in the primary models, IL-6 was also associated with both outcomes. But routine haematology testing was much more complete than cytokine and inflammatory testing, with only 13 deaths having a CRP value and nine having a PCT value in the adjusted mortality analyses. The very broad PCT confidence interval and the lack of statistical significance should thus not be interpreted as evidence of the lack of prognostic relevance of PCT but as imprecision. There is some evidence for informative missingness as selective laboratory ordering could be a plausible reason – clinicians could be more likely to request these tests in patients perceived to be more unwell.

There was a strong inverse correlation between mortality and severity and albumin. Soetedjo et al. (2021) have conducted a meta-analysis, where hypoalbuminemia was linked to severe disease and mortality in 19 studies. Inflammatory redistribution, increased vascular permeability, and alteration of synthesis, fluid balance and nutritional/catabolic effects may all cause a decrease in albumin. As these mechanisms are not SARS-CoV-2 specific, albumin is also a promising target for respiratory-disease research. In the current sensitivity model which further adjusted the mortality associations by clinical severity, the effect of the albumin estimate was reduced and was no longer significant at FDR level. This indicates that one of its mortality association may have some overlap with the global severity state and not be a standalone indicator of mortality.

There was a more mixed pattern seen with renal and hepatic indices. In the primary adjusted model, BUN was independently associated with severe/critical disease and mortality while AST was independently associated with severe/critical disease only. AST and Creatinine were less powerful for mortality when adjusted and FDR corrected. Although Malik et al. (2021) found correlations between higher creatinine or AST levels and poor outcomes in the studies included in the COVID-19 literature, the results from the present study suggest that the incremental value of these may be limited after adjustment for other case-

mix characteristics and age. This is important from a clinical point of view because a biomarker may be different between survivors and non-survivors but have limited independent value once adjusted for.

Modelling results support integration and indicate the biggest gains from integration. In the severe/critical disease, the mean ROC-AUC was 0.743, 0.791 and 0.802 with the hematology, with the fully integrated model, respectively. In the case of mortality, the AUC for hematology went from 0.819 to 0.880, while the integrated model attained 0.888. The incremental improvement was then the greatest with the use of routine blood-count data, and particularly the NLR, with the biochemical and CT data giving a smaller resulting increment. This is of clinical interest as routine hematology is less costly and was less likely to be missing. The mortality AUC is also quite comparable to the 0.856 mortality AUC from the original HUST-19 study (Ning et al., 2020); however, the results should not be considered a head-to-head comparison since the algorithms, features, and validation procedures used were different.

Care needs to be taken in interpreting the radiological findings. In earlier meta-analysis quantitative CT severity scores have demonstrated good prognostic discrimination (Prakash et al., 2023), but this structured variable is only positive/negative/unavailable CT evidence. Almost all confirmed cases (with known CT status) had a positive result and all severe/critical cases (with known CT status) were positive. This leads to little variation and to a separation of the structures, and an conventional adjusted odds ratio is therefore not suitable. Furthermore, imaging characteristics helped in characterization of clinical setting, which may be able to be incorporated between the radiology and severity label. Therefore, the conclusion of the present study is by no means that radiology is unimportant, but rather that a binary field for evidence of a CT is not a fine enough granularity to be used to quantify the radiological contribution. A future analysis of the archived CT images could be a more stringent test of the radiological component, to derive lesion burden or validated CT severity scores.

There are multiple strengths that support the findings. A relatively large adjudicated 4-level severity open patient level resource, with hospital outcome and multiple biological domains was utilized. The selection of markers was clinically driven and multiple testing was controlled in the screening analysis, adjusted association was reported with confidence interval and data leakage was reduced in the predictive analysis by using preprocessing within repeated cross validation. Further discrimination of biomarkers that track general severity from those that have a residual association with death after accounting for severity was found in the sensitivity model that adjusted mortality associations for severity.

The restrictions are important, too. First, this is a retrospective secondary analysis of patients hospitalised in Wuhan in the first wave of the pandemic, treatment algorithms and viral variants and immunity in the population will have changed since then. Second, the empirical cohort consists of laboratory confirmed COVID-19 pneumonia (one phenotype of acute respiratory disease), and extrapolation to other acute respiratory infections (ARIs) such as influenza or respiratory syncytial virus (RSV), bacterial pneumonia or mixed ARIs requires external validation. Third, in the mortality analysis, 175 confirmed cases were transferred and their outcome was unknown, which can have an impact on the analysis. Fourth, there were significant amounts of missing data in the laboratory markers for several biochemical and immune markers, hindering precision and the development of a stable all-biomarker association model. Fifth, comorbidity was reported as any versus none as the free-text field was heterogeneous and this does not capture disease-specific risk as well as a validated comorbidity index. Finally, the cross sectional association approach does not provide temporal causality and analyses do not take treatments after the index measurement into account. Lastly, the discrimination outcomes are estimates from internal cross validation, so they need to be validated externally prior to clinical application. Finally, because only the categorical CT evidence field was released, radiological burden could not be quantified in this cohort; the illustrative images in Figure 3 are drawn from an independent published cohort and carry no analytical weight, and studies with access to patient-level imaging would be required to integrate quantitative CT severity scores with the haematological and biochemical domains examined here.

However, there is clinical coherence in the pattern, and it is not something that is taken outside the clinical field. Even if one cut-off point does not identify all high-risk patients, then a combination of age, comorbidity and routine inflammatory/tissue-injury markers may help to stratify patients earlier. Signals associated with mortality were especially strong for NLR and LDH, which were not confounded by severity and showed an inverse signal for albumin and lymphocyte count. Most of these markers are also useful: They are available in hospital labs and not restricted to special cytokine testing or to the use of image-derived features.

6. CONCLUSION

A reproducible multidomain profile comprising demographic risk and haematological inflammation and biochemical evidence of tissue/organ stress, was associated with severe/critical disease and mortality at the patient-level in the iCTCF cohort. Levels of NLR, LDH, CRP, BUN and IL-6 rose with worse outcomes, whilst the levels of lymphocyte and albumin fell. After further adjustment for clinical severity, the associations of NLR, LDH and lymphocyte count were the most significant. When hematological and biochemical information was added, the discrimination was significantly better than with clinical characteristics alone with mean ROC-AUCs of 0.802 for severe/critical disease and 0.888 for mortality. The defined CT field did not allow for the quantification of radiological burden and should not be considered as a CT severity score. The results corroborate a multidomain approach to risk-stratify that can be easily interpreted, and highlight the need for external validation of these findings in modern and non-COVID acute respiratory disease cohorts prior to implementation in the clinical setting.

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