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Tomographic features of lung damage associate with D-Dimer levels and further clinical outcome in patients with acute respiratory distress syndrome due to COVID-19

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Abstract

Background Rapid progression of symptoms and development of Acute Respiratory Distress Syndrome (ARDS) frequently occurred during COVID-19 pandemic, while CT-Scan was useful to assess severity of lung damage, with classic patterns like early Ground Glass Opacity and/or late consolidation. Likewise, lung injury has been related to activation of the coagulation-fibrinolysis systems and pro-inflammatory mediators; where D-Dimer acquires prognostic relevance. The present study aimed to evaluate whether the extent of lung involvement and pattern of lung injury, as determined by chest CT-scan, are related with D-Dimer; and further impact clinical prognosis in patients with ARDS due to COVID-19.

Methods Longitudinal, prospective, observational, multi-center study. Patients diagnosed with ARDS due to COVID-19, without previous lung damage, clotting disorder and/or anticoagulants use, who were attended at the Intensive Care Unit and Internal Medicine Department from March to June 2020. Tomographic extent of lung involvement was analyzed by image software, as well as damage patterns, assessed by experienced radiologists. Endpoints included relation of lung injury with coagulopathy markers like D-Dimer, and prognostic outcome including mortality, mechanical ventilation and hospitalization time.

Results One-hundred and four patients mean aged 55 years old, 66% males, main comorbidities obesity, hypertension and diabetes mellitus. Larger lung damage was associated with older age, male gender and higher pro-inflammatory mediators like leukocytes and ferritin; whilst consolidation pattern was related to higher Body Mass Index. Higher values of D-Dimer were related either to a larger extent of lung involvement or late consolidation pattern. In addition, the extent of lung involvement was related with longer hospital stay, higher requirement of

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mechanical ventilation (HR 0.12, $p < 0.01$) and mortality rate (HR 0.13, $p < 0.01$); whereas late consolidation was mainly associated with requirement of mechanical ventilation (HR 0.23, $p < 0.01$).

Conclusion Tomographic extent of lung involvement and the pattern of lung injury are related with coagulopathy severity markers like D-Dimer, and own prognostic clinical ability in ARDS.

Keywords Acute respiratory syndrome, D-Dimer, CT-scan, COVID-19, Lung injury, Ground glass opacity, Consolidation

Introduction

According to the World Health Organization, COVID-19 pandemic caused the death of more than 3 million people worldwide. Up to June 2021, there had been 174 million confirmed cases across the world. The Americas having the most cases, with almost 69 million infected, followed by Europe with 54 million, and South-East Asia with 33 million people [1].

Early phase of respiratory infection is characterized by SARS-CoV-2 virus entry into pneumocytes, followed by rapid development of Acute Respiratory Distress Syndrome (ARDS) and progressive multiple organ failure leading to death [2, 3].

Chest CT-Scan represents a very useful tool during assessment of severity of lung injury due to SARS-CoV-2 infection [4]. In this regard, tomographic patterns like Ground Glass Opacity have been associated with interstitial thickening [5], while parenchymal consolidation has been related to alveolar filling by pathological tissues or fluids [6–8]. Furthermore, it has been suggested that the tomographic extent of lung involvement and the pattern of lung injury own prognostic ability [9, 10].

Lung damage in ARDS, despite COVID-19-related or not, is associated with an inflammatory response that can activate the coagulation-fibrinolysis systems and pro-inflammatory mediators, leading to pulmonary microvascular damage. Then, fibrin deposition in the alveoli, resulting from the coagulation cascade, contributes to impaired gas exchange and hampered respiratory function [11]. Plasma D-Dimer values reflect processes of fibrin formation and breakdown; therefore, D-Dimer has been considered a biomarker for the severity of coagulopathy in ARDS, particularly useful as prognostic marker of mortality and complications during COVID-19-related ARDS, indicating the need for more aggressive interventions [11–15]. In addition, other processes like inflammation, exudate and/or fibrogenic progression may underlie tomographic findings of lung damage [16]. Despite previous potential implications, it is unclear whether tomographic patterns like the extent of lung involvement (only ground-glass pattern) and further development of patterns of lung injury, including parenchymal consolidation; are related with the severity of coagulopathy severity, as evaluated by D-Dimer; as well as whether such tomographic findings own further clinical prognostic ability. Therefore, this study was designed to explore the relation of tomographic extent of lung involvement / pattern of lung injury with coagulopathy markers like D-Dimer; and whether tomographic features predict clinical outcome in ARDS due to COVID-19.

Methods

Study design and population

Longitudinal, prospective, observational, multi-center study, conducted at "*Corporativo Hospital Satélite" and "Xoco" General Hospitals, in Mexico City;* during the period from March to June 2020. The study aimed to evaluate whether the extent of lung involvement and/or the pattern of lung injury, both determined during recruitment phase, are related with D-Dimer; and further impact clinical prognosis in patients with ARDS due to COVID-19. Patients were included if Polymerase Chain Reaction-confirmed diagnosis of SARS-CoV-2 infection, and diagnosis of ARDS according to Berlin definition [17, 18], requiring non-invasive ventilation or high-flow cannula, as well as critical medical surveillance/care. Patients were excluded if evidence of previous lung damage such as COPD, asthma, recent pulmonary infection, alveolar hemorrhage, any clotting disorder and/or use of anticoagulants. The present study was approved by the Ethics and Research Committees from Xoco General Hospital, under the Research Protocol ID No. 2,121,100,323. Clinical trial number: not applicable. All the experiments were conducted in accordance with the Declaration of Helsinki and Mexican Guidelines for Research, as well as the National Guidelines for Health Research in Humans Guidelines (NOM-012-SSA3-2012). All the participants, or legal representatives, signed the informed consent previous to their enrollment.

Data collection

All laboratory data and clinical outcome (hospital stay, requirement of mechanical ventilation and mortality rate) were extracted from the electronic medical records using a standardized data collection form. Laboratory data were collected during recruitment phase, just after hospital admission. The extent of lung involvement was evaluated on the Chest CT-scan, also acquired during recruitment phase; and it was analyzed by the *'Image J'* Software, and estimated as percentage of lung damage. While the main pattern of lung injury (Ground Glass Opacity or late consolidation) was assessed by at least 2

experienced radiologists. Reproducibility of the measurements was verified by the calculation of acceptable intraclass correlation coefficients of > 0.88, in order to reduce potential bias.

Statistical analysis

Qualitative variables were expressed as n (%), while quantitative variables were presented as mean ± SD. Inferential analysis included mean comparison by one-way, independent T-test or U-Mann Whitney, as appropriate. Likewise, risk association analyses included OR and CI95% to evaluate association between D-dimer and the extent of lung involvement; as well as between D-dimer and the pattern of lung injury. These associations were compared, considering adjustments by sex and age (Model 2); comorbidities (Model 3) and inflammatory mediators, included C-reactive protein and ferritin (Model 4). Then, Forrest Plot containing such associations was generated. In addition, survival (Kaplan-Meyer) analyses were also performed. Statistical analyses were performed in GraphPad Prism (v.10) and SPSS statistical softwares. Statistical significance was considered when $p < 0.05$.

Results

A total of 104 patients aged 55 years old, 66% male and mean BMI 27 kg/m^2 constituted the study population. Two thirds of them showed one comorbidity at least, such as obesity (12.5%), high blood pressure (14.4%) and/or diabetes mellitus (9.6%), accompanied by increased values of D-dimer and pro-inflammatory mediators (Table 1).

Then, participants were grouped according to pulmonary tomographic findings; either by the extent of lung involvement, or the pattern of lung injury. Subpopulation with higher extent of lung involvement were older, higher prevalence of males, showing higher values of leukocytes and ferritin; while subjects with consolidation pattern had a higher BMI as compared with those showing ground glass opacity (Table 1). Of note, D-dimer similarly increased in both, higher extent of lung involvement and consolidation pattern (Table 1).

Particularly, D-dimer increased according to higher percentiles of the extent of lung involvement (Fig. 1A). Likewise, levels of D-dimer observed in cases of consolidation pattern were almost two times the levels of D-dimer from those with ground glass opacity.

Furthermore, D-dimer ≥ 1000 ng/mL was predictive of significant extent of lung involvement (higher than 50%, (OR 4.7, p<0.002, Fig. 2A, Model 1); and this effect was independent from variables like sex, age (Model 2), comorbidities (Model 3) or inflammatory mediators (Model 4). In the other hand, elevated D-Dimer showed a non-significant association with the consolidation pattern of lung injury (OR 2.2, p 0.06, Fig. 2A). A Forrest Plot was also provided (Fig. 2B) in order to facilitate visual data analyses of risk factors.

In order to explore whether the extent of lung involvement / pattern of lung injury impacted clinical prognosis,

Table 1 Study population ($n = 104$)

	ALL	By EXTENT of LI (CT scan)		By PATTERN of LI (CT scan)	
		< 50% ($n = 74$)	> 50% ($n = 30$)	GGO ($n = 69$)	Consolidation ($n = 35$)
Age (y-o)	54.9 ± 14.9	51.9 ± 15.5	**62.2 ± 10.7***	55.0 ± 16.3	54.6 ± 12.1
Male	69 (66.3)	45 (60.8)	**24 (80.0)***	44 (63.8)	25 (71.4)
Comorbidities					
t2DM	10 (9.6)	6 (8.1)	4 (13.3)	5 (7.2)	5 (14.3)
HBP (mm/Hg)	15 (14.4)	8 (10.8)	7 (23.3)	10 (14.5)	5 (14.3)
Obesity	13 (12.5)	11 (14.9)	2 (6.7)	8 (11.6)	5 (14.3)
t2DM, HBP, Obesity	17 (16.3)	10 (13.5)	7 (23.3)	9 (13.0)	8 (22.8)
Others[&]	13 (12.5)	10 (13.5)	3 (10.0)	11 (16.0)	2 (5.7)
None	36 (34.6)	29 (39.2)	7 (23.3)	26 (37.7)	10 (28.6)
Height (m)	1.65 ± 0.08	1.65 ± 0.08	1.67 ± 0.08	1.65 ± 0.08	1.67 ± 0.08
Weight (kg)	75.6 ± 15.7	75.4 ± 16.2	75.9 ± 14.4	73.6 ± 14.5	79.6 ± 17.4
BMI (kg/m^2)	27.5 ± 4.5	27.5 ± 4.7	27.4 ± 4.0	27.0 ± 4.4	**28.5 ± 4.4***
Leucocytes (x10^{3}cells/μL)	8.62 ± 4.10	8.14 ± 3.95	**9.85 ± 4.30***	8.13 ± 4.16	9.57 ± 3.86
Neutrophils (x10^{3}cells/μL)	7.50 ± 4.57	7.54 ± 4.75	7.41 ± 4.18	7.61 ± 5.11	7.30 ± 3.34
Lymphocytes (x10^{3}cells/μL)	0.98 ± 0.64	1.00 ± 0.57	0.93 ± 0.82	1.00 ± 0.73	0.93 ± 0.43
NtLR	10.35 ± 8.97	9.82 ± 8.76	11.65 ± 9.65	10.43 ± 9.51	10.22 ± 8.09
Mediators					
CRP (mg/L)	72.4 ± 94.3	71.6 ± 92.1	72.3 ± 102.1	72.8 ± 98.2	68.0 ± 88.3
Ferritin (mcg/dL)	765 ± 742	631 ± 535	**1141 ± 1070***	689 ± 573	882 ± 944
D-Dimer (ng/mL)	1631 ± 1602	1278 ± 1218	**2080 ± 2067***	1256 ± 1254	**2056 ± 2055***

Qualitative data are expressed as n (%), and quantitative data as mean ± SD. ([&]) Refers to Dyslipidemia, Hypothyroidism, Heart Disease, Asthma, Prostate Hyperplasia, Breast Cancer, Chronic Liver Disease and Stroke. (*) Statistically significant, non-paired, T-test. Abbreviations: GGO, Ground Glass Opacity; t2DM, type 2 Diabetes Mellitus; HBP, High Blood Pressure; BMI, Body Mass Index; NtLR, Neutrophil-Lymphocyte Ratio; CRP, C-Reactive Protein. (*) = $p < 0.05$

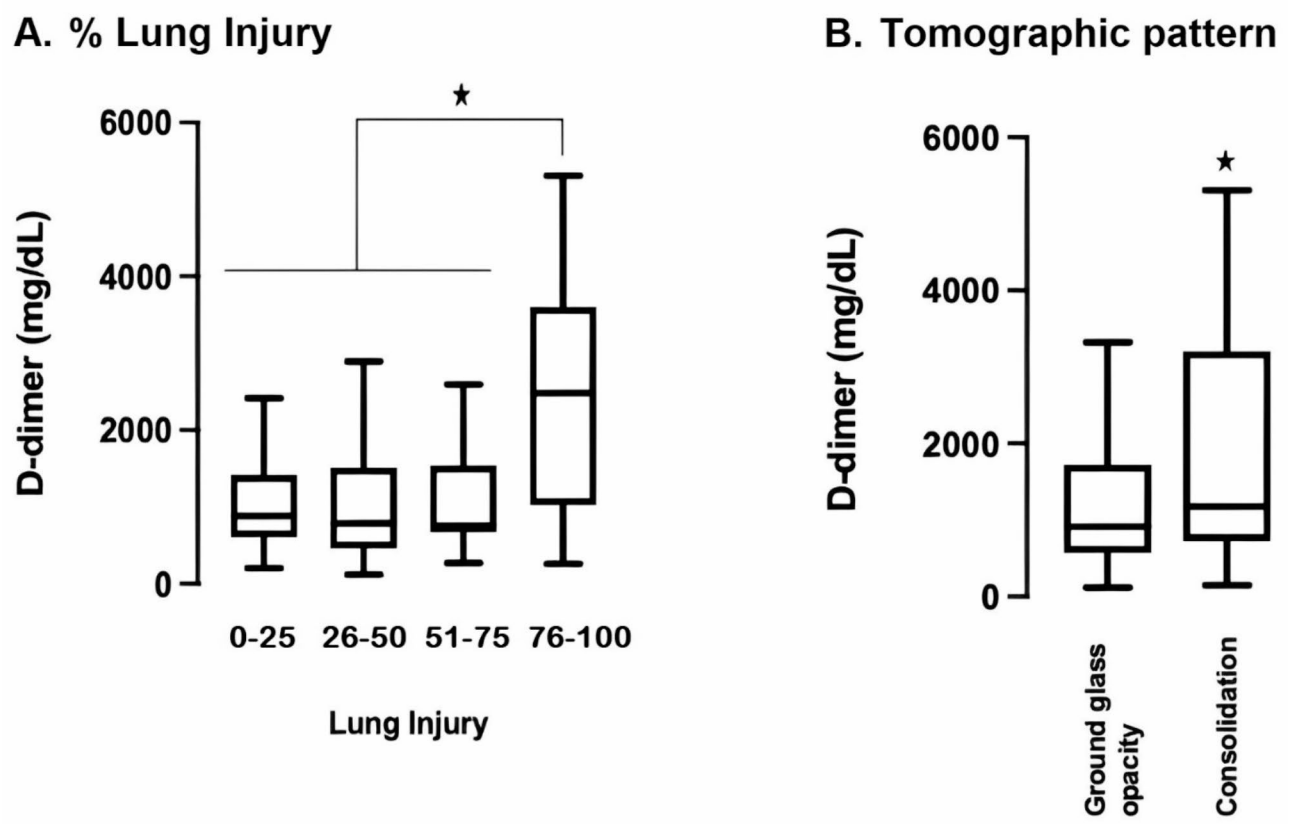

Fig. 1 D-dimer and extent of lung involvement and pattern of lung injury (CT scan). *Left.* D-dimer values according to the percentiles of the extent of lung involvement, estimated as % of lung injury. *Right.* D-dimer values corresponding to consolidation or ground glass opacity patterns. Cutoffs: P25 = 24.5%, P50 = 38.6, P75 = 54.0. (*) = $p < 0.05$, one-way, T-test

we evaluated outcomes of hospitalization time, mechanical ventilation and mortality. The extent of lung involvement was associated with longer hospital stay (10.9 days vs. 7.9 days, comparing the extent of lung involvement > 50% vs. ≤50%, respectively; $p = 0.04$). Likewise, a ≤ 50% extent of lung involvement conferred protection for mechanical ventilation (HR 0.12, $p < 0.01$; Fig. 3A, left) and mortality (HR 0.13, $p < 0.01$; Fig. 3A, right); whereas Ground Glass Opacity pattern of lung injury resulted in lower risk for mechanical ventilation (HR 0.23, $p < 0.01$; Fig. 3B, left); but non-significant effect in mortality (HR 0.41, $p < 0.05$; Fig. 3B, right).

Discussion

The study of pathophysiological mechanisms underlying tomographic lung patterns becomes relevant because they reflect different stages and severities during ARDS development. For example, ground-glass opacities have been related to interstitial/alveolar edema, formation of hyaline membranes, inflammation and alveolar damage with early alveolar filling that allows for residual air. While **p**arenchymal consolidation has been considered a more advanced stage of ARDS, where alveoli are completely filled with fluid, inflammatory cells and fibroproliferation; resulting in severe alveolar damage, lower aeration and more permanent loss of lung function. Despite potential implications, the role of mechanisms like coagulopathy, intimately related to fibrosis and inflammation, remains unclear [19–21].

The main finding of the present study is that specific features of lung injury, as evaluated by CT-Scan, are related with coagulopathy marker D-Dimer and exert significant impact on clinical prognosis in patients with ARDS due to COVID-19.

In the present study, a higher extent of lung involvement concomitant to increased D-Dimer, was observed in older, males with increased pro-inflammatory mediators, particularly in the ground glass opacity pattern. Similarly, previous studies have described the role of gender for a higher risk of complications during hospitalization in patients with COVID-19 [22]. Other studies had described the relation between the extent of lung involvement and pro-inflammatory biomarkers, such as C-reactive protein, Erythrocyte Sedimentation Rate, NLR and leukocytes, but not with coagulopathy biomarkers [23]. Such discrepancy with our findings may be explained by differences in patient selection, sample size and method used to evaluate the extent of lung involvement.

A

	OR	CI95%	p-value
MODEL 1			
DD & Lung Injury	4.77	1.81 to 12.60	**0.002**
DD & type of Injury	2.22	0.96 to 5.13	0.063
MODEL 2 (adjusted by sex and age)			
DD & Lung Injury	5.12	1.89 to 13.82	**0.001**
DD & type of Injury	2.21	0.96 to 5.13	0.062
MODEL 3 (adjusted by comorbidities)			
DD & Lung Injury	5.17	1.86 to 14.40	**0.002**
DD & type of Injury	2.16	0.92 to 5.06	0.078
MODEL 4 (adjusted by inflammatory mediators*)			
DD & Lung Injury	23.72	2.57 to 218.43	**0.005**
DD & type of Injury	3.64	0.97 to 13.70	0.056

B

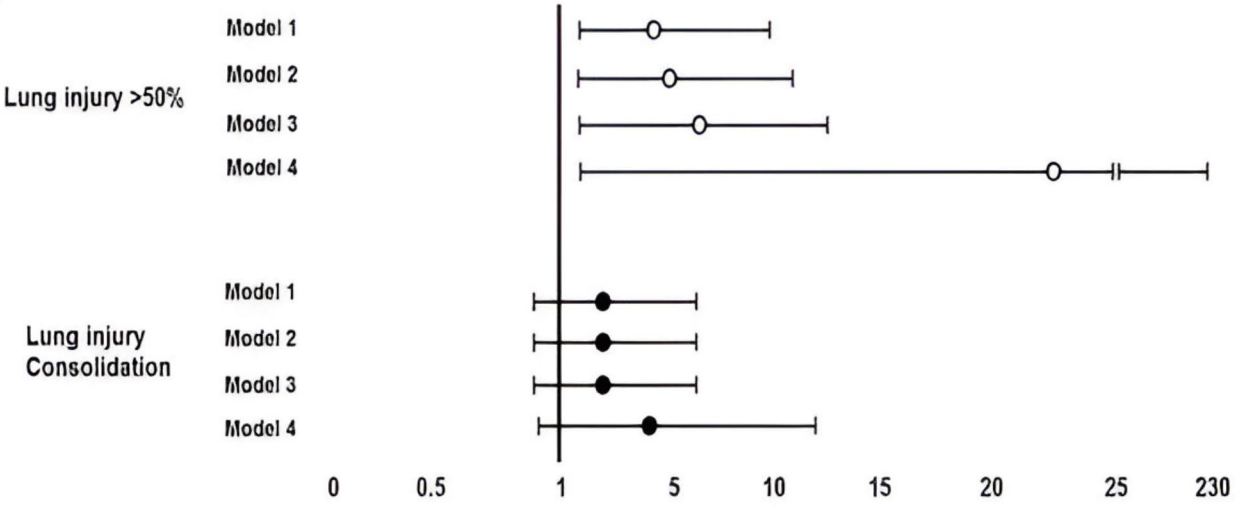

Fig. 2 D-dimer and risk of lung injury. **A**. Risk association between D-dimer and the extent of lung involvement / pattern of lung injury (CT-Scan). Model 1 (unadjusted), Model 2 (adjusted by sex and age), Model 3 (adjusted by comorbidities), Model 4 (adjusted by inflammatory mediators). (*) Inflammatory mediators included C-reactive protein and ferritin. **B**: Forrest Plot of risk association between D-dimer and the extent of lung involvement / pattern of lung injury

The association of the extent of lung involvement with D-Dimer suggests the pathophysiological implication of coagulopathy damage in ARDS due to COVID-19. Indeed, potential interactions between pro-inflammatory and pro-thrombotic mechanisms have been described. For example, ferritin and D-dimer are significantly related with the extent of lung involvement in COVID-19 [24]; where potential explanations include: (1) COVID-19 "cytokine storm" stimulation of endothelial cell dysfunction, leading to damage to the microvascular system and abnormal activation of the coagulation system, resulting in small vessel vasculitis and microthrombosis; (2) hypoxia and oxygen demand during abnormal hemodynamics may trigger molecular and cellular pathways leading to thrombosis; (3) sepsis, may activate abnormalities in inflammation and blood coagulation processes [11].

On the other hand, the progression to consolidation pattern was mainly related to higher BMI accompanied by higher D-dimer, suggesting a different underlying mechanism than that leading to the extent of

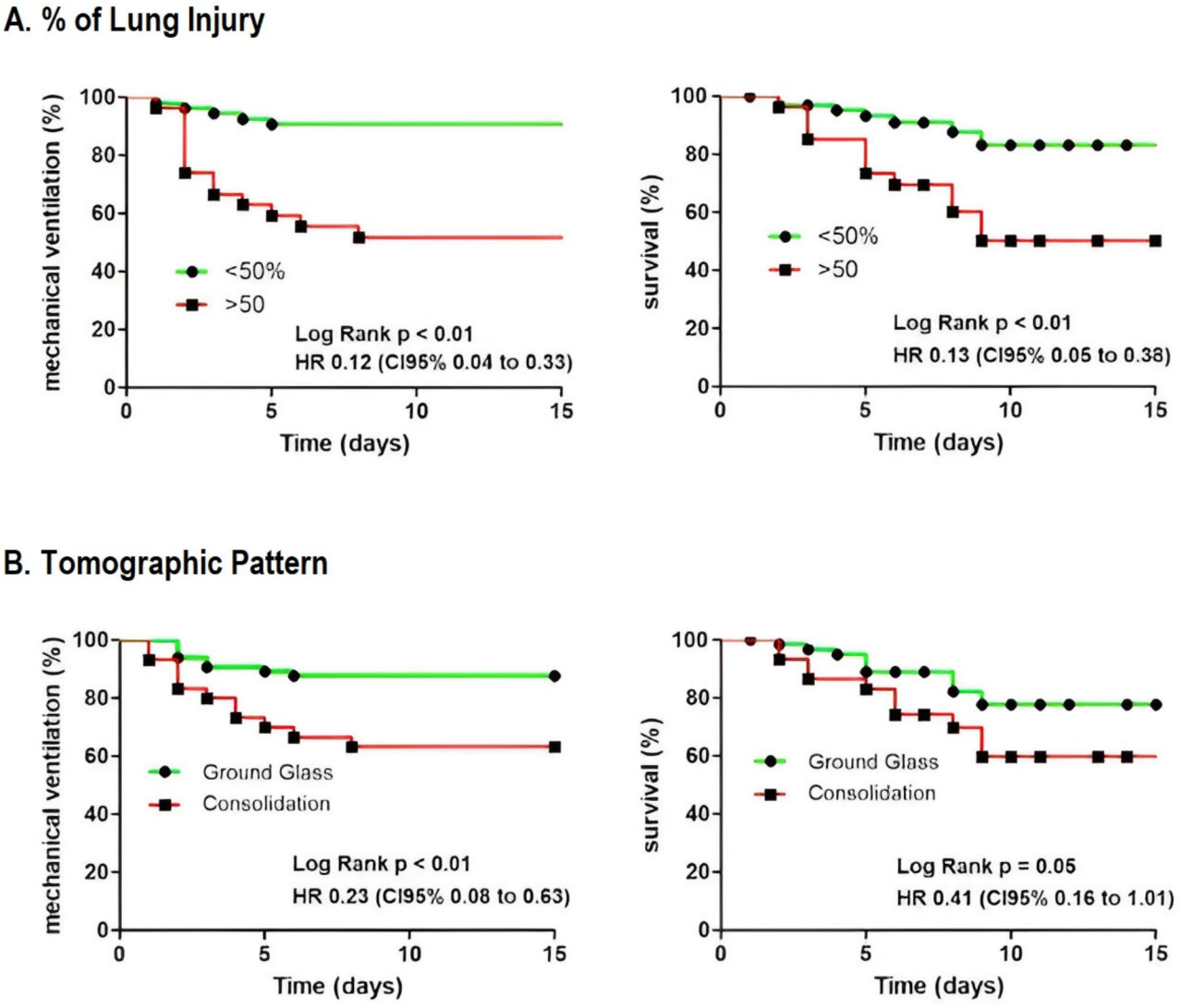

Fig. 3 Lung injury and clinical outcome. Survival curves show the effect of **A**. the extent of lung involvement and **B.** the pattern of lung injury on severity outcomes (requirement of mechanical ventilation and mortality)

lung involvement [25]. Such mechanism may be related with the expression of SARS-CoV co-receptor ACE2 in adipose tissue and or lungs, affecting the availability of its substrate angiotensin II, then promoting neutrophil accumulation, increased vascular permeability and exacerbated pulmonary edema [26] observed in the consolidation injury.

Taken together, these data suggest an early phase characterized by activation of clotting and pro-inflammatory cascades driving pulmonary edema and hyaline membrane formation; which would explain its relation with the extent of lung involvement and the pattern of lung injury, particularly with ground glass opacity pattern occurring at stages before development of consolidating lung injury, which involves additional processes like higher parenchymal damage and exudate [27].

Notably, the extent of lung involvement and pattern of lung injury at hospital admittance seem to predict clinical outcomes like hospital stay, requirement of mechanical ventilation and mortality in patients with COVID-19. Similar findings have been consistently observed by other studies that use different tomographic scoring systems [28, 29]; then, consolidating the prognostic ability of early CT-scan in ARDS due to COVID-19 and/or atypical pneumonia, particularly in clinical settings like emergency department, internal medicine or ICU. Moreover, tomographic extent of lung involvement showed higher prognostic performance than lung pattern of injury, which may be related to an early coagulopathy, as evidenced by its significant association with D-Dimer. Consistently, it has been described that coagulopathy and endothelial damage are observed in severe COVID-19

[30]. Unfortunately, only a scanty number studies have analyzed pathways underlying tomographic injuries in COVID-19; to our knowledge this is one of the first studies exploring pathophysiological mechanisms related with the extent of lung involvement and pattern of lung injury. Nevertheless, a careful interpretation of the results is recommended, due to limitations like the retrospective design of the study, a low sample size and/or the limited number of markers tested.

In conclusion, tomographic assessment of the extent of lung involvement and the pattern of lung injury own prognostic clinical ability, and maintain a significant association with D-dimer in patients with ARDS due to COVID-19.

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Author contributions
JAS-C, JFF-Z: Conceptualization, Investigation, Resources, Writing– original draft; LEC-R, PG-R, LAC-B, UA-O, AG-M, PMG-R, JR-S: Data curation, Investigation, Methodology, Writing– review & editing; AM-L: Data curation, Formal Analysis, Methodology, Validation, Writing– original draft, Writing– review & editing.

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Data availability
The datasets generated and analyzed during the current study are not publicly available due to privacy policies of the hospital and patients information; but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The present study was approved by the Ethics and Research Committees from Xoco General Hospital, under the trial authorization ID 2121100323. All the experiments were conducted in accordance with the Declaration of Helsinki and Mexican Guidelines for Research, as well as the National Guidelines for Health Research in Humans Guidelines (NOM-012-SSA3-2012). All the participants, or legal representatives, signed the informed consent previous to their enrollment.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

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