Lung ultrasound scan score can identify pulmonary embolism high risk in patients with COVID-19: a retrospective analysis from a single center

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ABSTRACT

Background. Since the European Society of Cardiology (ESC) published guidelines to stratify the risk of pulmonary embolism (PE), the main goal of several physicians has been to find a biomarker able to identify patients with venous thromboembolism at high risk to die. Increased levels of pro-B-type natriuretic peptide (BNP) were suggested as useful biomarkers in the guidelines of ESC (*i.e.*, 2014) to identify patients with PE at high risk of death, but its role was not confirmed in other guidelines. Lung Ultrasound Scan (LUS) has been suggested as a diagnostic and prognostic test to identify patients with a high risk of mortality for lung failure. The aim of this study is to evaluate the prognostic role of pro-BNP together with the LUS evaluation in patients with COVID-19 and PE in particular regarding mortality for pulmonary embolism and overall death. Patients and Methods. We retrospectively analyzed records from 178 patients with confirmed COVID-19, admitted to our ward (*i.e.*, COVID Medicine Unit at Ospedale del Mare in the town of Napoli) between March 2020 and May 2021. For this study, we analyzed the LUS data of all 178 patients and the available data on the pro-BNP of 120 patients. For all selected patients, mortality for PE and overall deaths were recorded. Results. The Propensity Score Matching was used to minimize and erase confounding factors. Data showed that an association between serum levels of pro-BNP and pulmonary thrombotic events was neither present before nor after matching an association with adverse outcomes and was found for increased values of LUS. Discussion. During the first waves of the pandemic, patients with confirmed COVID-19 with severe lung failure frequently showed pulmonary embolism as a clinical acute complication inducing life-threatening evolution. Conclusions. An association between LUS score and severe PE and/or overall mortality in hospitalized patients with COVID-19 was found while a similar association was not confirmed for pro-BNP.

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Background

Since the European Society of Cardiology (ESC) published guidelines to stratify the risk of pulmonary embolism (PE), the main goal of several physicians has been to find a biomarker able to identify patients with venous thromboembolism (VTE) at high risk to die.[1]

Increased D-dimer in patients with PE showed a

prognostic role in this way but the increase of D-dimer may be found also in other clinical conditions as far as increased troponin in the same clinical setting and so the clinical interpretation of both markers may be difficult in patients with comorbidities;[2-4] on the other hand, increased levels of pro-B-type natriuretic peptide (BNP) was underlined as a useful biomarker in ESC guidelines (*i.e.*, 2014 edition) to identify patients with PE at high risk of death but its role was not confirmed in other guidelines.[1,5]

The recent pandemic due to SARS-CoV-2 was able to induce lung failure and underlined an increased rate of patients with COVID-19 and associated PE, so several scientific and clinical reports were addressed to identify biomarkers able to predict worse outcomes of COVID-19 with associated PE.[6] Despite the high-sensitivity troponin being a marker of right ventricular dysfunction and of poor prognosis in COVID-19 patients, no significant increase was observed in patients with PE probably due to the poor specificity of this marker.[7] Elevated C-reactive protein levels were correlated with the risk of progression to more severe clinical disease of COVID-19 but without a clear relationship with associated PE.[8] On the other hand, an increase in neutrophil count combined with higher D-dimer levels was associated with higher mortality among hospitalized patients with PE.[9]

In this way, the role of D-dimer and troponin was underlined several times since the first wave of the pandemic, while the prognostic role of pro-BNP in patients with COVID-19 is still a matter of discussion, although its prognostic role in patients with COVID-19 has been already underlined.[10-12]

Yet, the prognostic role was also deserved to high-resolution thoracic CT scan during the pandemic able to score lung damages. However, in several emergency departments, the use of lung ultrasound scans (LUS) took a relevant role in the daily clinical management of patients with COVID-19 and lung failure.[13]

In order to understand if LUS score may have a prognostic role in inpatients with COVID-19 and PE we performed a clinic retrospective analysis comparing in a parallel observation the prognostic role of PRO BNP that showed a prognostic role in this clinical setting. In any case, also other relevant outcomes such as overall mortality were taken into account in our analysis. Therefore, the aim of this study was to evaluate the prognostic role of pro-BNP together with the LUS evaluation in patients with COVID-19 regarding mortality for pulmonary embolism and overall death.

Patients and Methods

We retrospectively analyzed records from 178 patients with confirmed COVID-19 (confirmed by real-time PCR), admitted to our ward for COVID in the Medicine Unit of Ospedale del Mare in the town of Napoli between March 2020 and May 2021. Our COVID ward was organized into two different areas: "Non-intensive area" and "Sub-intensive Area" based on different needed ventilatory supports. Therefore, hospitalization in our COVID Medicine Unit was guaranteed if a patient needed a level of care between ordinary and sub-intensive. The "Non-intensive area" was a low-medium intensity area for patients referred to standard non-invasive treatments while the "Sub-intensive Area" is a high-intensity care area for patients who require non-invasive ventilation.

Data from 103 patients admitted to the "Non-intensive Area" and 75 patients admitted to the "Sub-intensive Area" were analyzed.

Viral variants were not typed for each patient because it was an early phase of the pandemic, therefore in that phase, only alpha, beta, gamma, and delta variants of SARS-CoV-2 were identified and associated with severe COVID-19. Clinical characteristics of studied patients were collected and summarized in Table 1.

For this study, we analyzed the LUS data of all 178 patients and the available data on the pro-BNP values of 120 patients (several patients missed samples because the turnover of patients during the first waves of the pandemic was really speed and sometimes patients in "Non-intensive area" were assigned to early discharge with home therapy). LUS and pro-BNP were evaluated at admission in the COVID Medicine Unit within 3 days from the onset of symptoms.

A standard LUS exam was performed bedside in all patients using an ultrasound system with the use of convex and linear transducer according to procedures suggested by Soldati *et al*.[14] The ultrasound system used in this was Esaote MyLab Sigma and E-cube i7 Alpinion.

The standardized image acquisition protocol involves the acquisition of 14 standard sequences for each patient able to maintain a sitting position (three posterior, two lateral and two anterior for each hemithorax) using reference points on the anatomical lines of the thorax.[14] According to the Soldati score, each scan can be identified with progressive numbering ranging from 0 to 3 (worst score 3) starting from the right posterior basal regions: Score 0: the pleural line is continuous and regular, the pattern A-lines is present (horizontal artifacts); Score 1: indented pleural line, vertical areas of white (B-lines) are present due to local alterations in the acoustical properties of the lung; Score 2: the pleural line is broken, small-to-large subpleural consolidations (darker areas) appear with associated areas of pre-dominant vertical artifacts below the consolidated area (white lung); Score 3: extended white lung with or without larger consolidations may be present. The total score (LUS score) was calculated from the sum of scores observed in each region with ranging from 0 to 42.

Being an ultrasound imaging, although, with a stan-

dardized method, different interpretations of such imaging and bias may be possible; for this reason, we performed the scan two times with two experts not blinded operators in order to reduce possible mistakes in the evaluation.

Pro BNP was measured using Cobas Roche analyzers. Values under 485 pg/ml were regarded as normal for pro-BNP, similar to those used in case of heart failure.[5]

All patients underwent high-resolution chest computed tomography to detect the damage of lung involvement from COVID-19 and computed tomographic (CT) pulmonary angiography for diagnosis of pulmonary embolism.[15] Pan score was used to select patients with severe COVID-19 at radiological CT scan.[16] For all selected patients, mortality for VTE and overall deaths were recorded.

Statistical analysis

All statistical analyses were performed using R statistical software.[17] Fisher's Exact Test for Count Data with Lancaster's correction and Mann-Whitney-Wilcoxon Test for Quantitative Data were performed using the built-in Stats package; the Receiver Operating Characteristic (ROC) curve and Z-test were performed using the ROCit package.[18] The Propensity Score Matching (PSM) was performed using the MatchIt package, using a neural network with 20 hidden layers and a genetic matching method with ratio =1 and population size =200.[19] Raincloud plots were performed using the Raincloudplots package.[19] Gender differences were underlined in Table 1 according also to their related different outcomes in inpatients with COVID-19.[20] Age, pro-BNP, and LUS were reported as median and its 95% confidence interval.

Results

The clinical characteristics of 178 patients selected retrospectively in the study are summarized in Table 1. For 3 of them, only pro-BNP was recorded, for 59 of them only LUS score was recorded and for 116 both pro-BNP and LUS Score were recorded. So, we had 119 records of pro-BNP and 175 records of LUS (Figure 1).

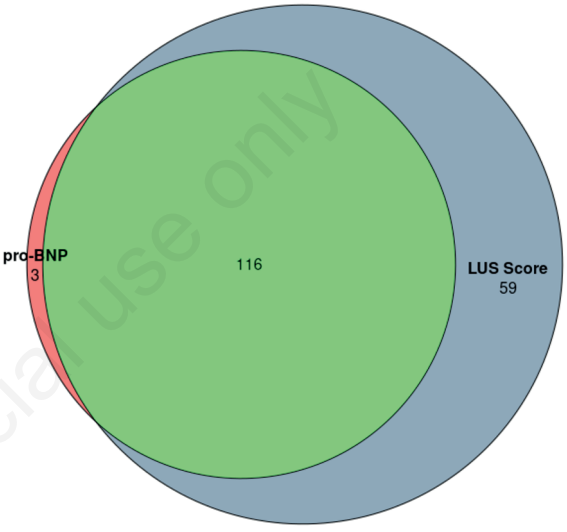

Figure 1. Eulero-Venn plots of pro-B-type natriuretic peptide and lung ultrasound scan records.

Table 1. Clinical characteristics of 178 patients selected retrospectively in the study.

Comorbidities	Males (124)	Females (54)	P value
Median age [95% CI]	65.50 [62-71]	74 [67.0-79.0]	0.01495
Hypertension	93 (75.0%)	43 (79.6%)	0.50586
Diabetes	37 (29.8%)	19 (35.2%)	0.32654
Atrial fibrillation	13 (10.5%)	9 (16.7%)	0.27209
Ischemic cardiopathy	36 (29.0%)	17 (31.5%)	0.79221
Ictus	12 (9.7%)	8 (14.8%)	0.25452
Dementia	24 (19.4%)	18 (33.3%)	0.04451
COPD	50 (40.3%)	20 (37.0%)	0.67881
Cancer	12 (9.7%)	8 (14.8%)	0.25452
Procalcitonin ≥0.5 ng/ml	35 (28.2%)	13 (24.1%)	0.652
Smoke	57 (46.0%)	12 (22.2%)	0.00203
Obesity	34 (27.4%)	26 (48.1%)	0.00756
Epatopaty	16 (12.9%)	6 (11.1%)	0.71522
Chronic kidney disease	29 (23.4%)	17 (31.5%)	0.23035
Median pro-BNP [95% CI]	800 [520-1600]	1379 [692-2300]	0.1443
Median LUS Score [95% CI]	28 [28-32]	28 [16-28]	0.001856

COPD, chronic obstructive pulmonary disease; CI, confidence interval; LUS, lung ultrasound scan; BNP, B-type natriuretic peptide.

Males and females were matched in comorbidities, but females had a median age greater than males; dementia and obesity cases were more frequent among females while smoking among males. No differences were highlighted in the pro-BNP distribution while were present in the distribution of the LUS score.

The PSM was used to minimize and erase confounding factors. This technique was used to isolate the ability of pro-BNP and LUS Score to predict thromboembolic events and death in COVID-19 patients. As shown in Table 2 and Figure 2, analyzing the skill of pro-BNP to predict Pulmonary Thromboembolic

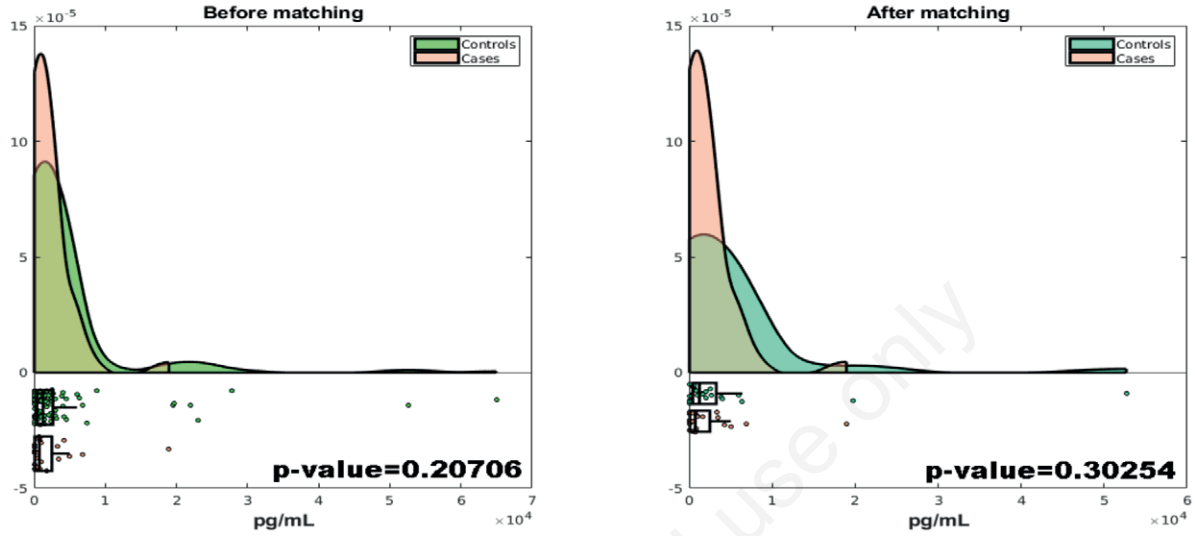

Figure 2. Rainclouds plots of pro-B-type natriuretic peptide concentrations in pulmonary thromboembolic events between controls and cases, before and after propensity score matching to minimize confounding factors.

Table 2. Correlation between pro-BNP and pulmonary thromboembolic events before and after propensity score matching to minimize confounding factors. All parameters were count numbers, except age and pro-BNP which are medians, and their 95% confidence intervals.

	Before matching			After matching		
	95 Controls (PTE=0)	24 Cases (PTE=1)	P-value	24 Controls (PTE=0)	24 Cases (PTE=1)	P value
Age	73 [61-90]	71 [27-83]	0.48851	71 [27-83]	71 [27-83]	0.79637
Males	61	18	0.40775	18	18	0.86998
Hypertension	81	17	0.10125	17	17	0.87582
Diabetes	34	10	0.55997	9	10	0.66673
Atrial fibrillation	13	4	0.63247	3	4	0.56185
Ischemic cardiopathy	33	7	0.72365	6	7	0.63781
Ictus	15	3	0.87908	3	3	0.83309
Dementia	32	4	0.10974	4	4	0.85039
COPD	41	10	0.90948	10	10	0.88508
Cancer	7	1	0.83092	1	1	0.74468
Smoke	40	5	0.047619	5	5	0.86190
Obesity	36	9	0.90708	8	9	0.66015
Epatopaty	11	1	0.35668	1	1	0.74468
Chronic kidney disease	30	6	0.54087	6	6	0.86998
pro-BNP	1258 [700-2000]	742 [200-1000]	0.20706	1250 [530-2500]	742 [200-1000]	0.30254
AUC Standard error Standardized AUC	0.58377 0.067227 1.2461		0.10636	0.58767 0.082625 1.0611		0.14432
Comment	Fail test			Fail test		

COPD, chronic obstructive pulmonary disease; AUC, area under the ROC curve; PTE, pulmonary thromboembolic events; BNP, B-type natriuretic peptide.

Events (PTE) we can see that it is unable to predict the event. Even erasing this mismatch using PSM (with an excess of zeal), it remains unable to predict PTE.

On the contrary, Table 3 and Figure 3 show that pro-BNP is skilled into predict death events (DE) and the ROC curve area shows a fine prediction test. Anyway,

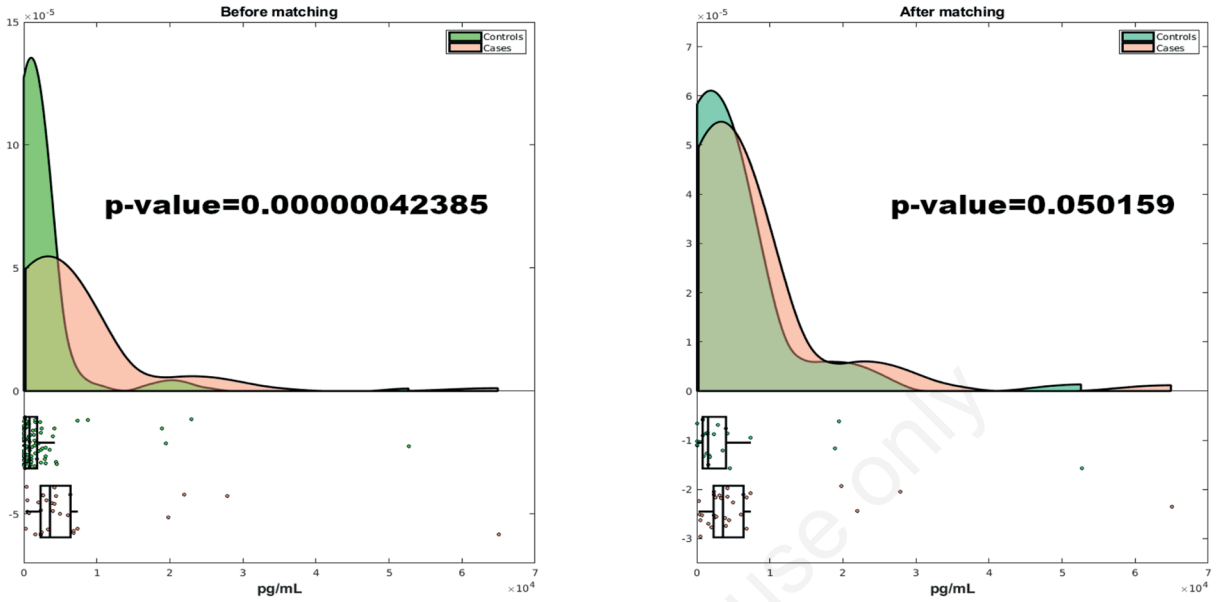

Figure 3. Raincloud plots of pro-B-type natriuretic peptide concentrations in death events between controls and cases, before and after propensity score matching to minimize confounding factors.

Table 3. Correlation between pro-BNP and death events before and after propensity score matching to minimize confounding factors. All parameters were count numbers, except age and pro-BNP which are medians, and their 95% confidence intervals.

	Before matching			After matching		
	93 Controls (Death=0)	26 Cases (Death=1)	P-value	26 Controls (Death=0)	26 Cases (Death=1)	P value
Age	68 [65-73]	79.50 [77-82]	$1.4615 \cdot 10^{-7}$	74 [73-81]	79.50 [77-82]	0.11289
Males	60	19	0.90933	17	19	0.094851
Hypertension	76	22	0.88567	22	22	0.85323
Diabetes	28	16	0.00240	12	16	0.25599
Atrial fibrillation	9	8	0.01358	7	8	0.18405
Ischemic cardiopathy	28	12	0.01799	15	12	0.89805
Ictus	10	8	0.03144	6	8	0.47900
Dementia	24	12	0.00144	11	12	0.52832
COPD	37	14	0.03825	15	14	0.52030
Cancer	5	3	0.16123	3	3	0.85323
Smoke	36	9	0.71993	10	9	0.89459
Obesity	38	7	0.06694	11	7	0.68467
Epatopaty	11	2	0.64402	1	2	0.23729
Chronic kidney disease	22	14	0.00063	11	14	0.16571
PTE	17	7	0.50141	5	7	0.88053
pro-BNP	779 [156-1773]	3210 [2300-6396]	$4.2385 \cdot 10^{-7}$	1539 [890-2844]	3210 [2300-6396]	0.050159
AUC	0.82587			0.65902		
Standard error	0.0548		$1.3691 \cdot 10^{-9}$	0.07580		0.017964
Standardized AUC	5.9466			2.0977		
Comment	Good test			Poor test		

COPD, chronic obstructive pulmonary disease; PTE, pulmonary thromboembolic events; AUC, area under the ROC curve; BNP, B-type natriuretic peptide.

the two groups are not matched for many comorbidities (diabetes, atrial fibrillation, ictus, dementia, chronic kidney disease): when these differences were balanced using PSM the situation was very different because pro-BNP revealed poor ability to predict DE.

Table 4 and Figure 4 show that regarding LUS score

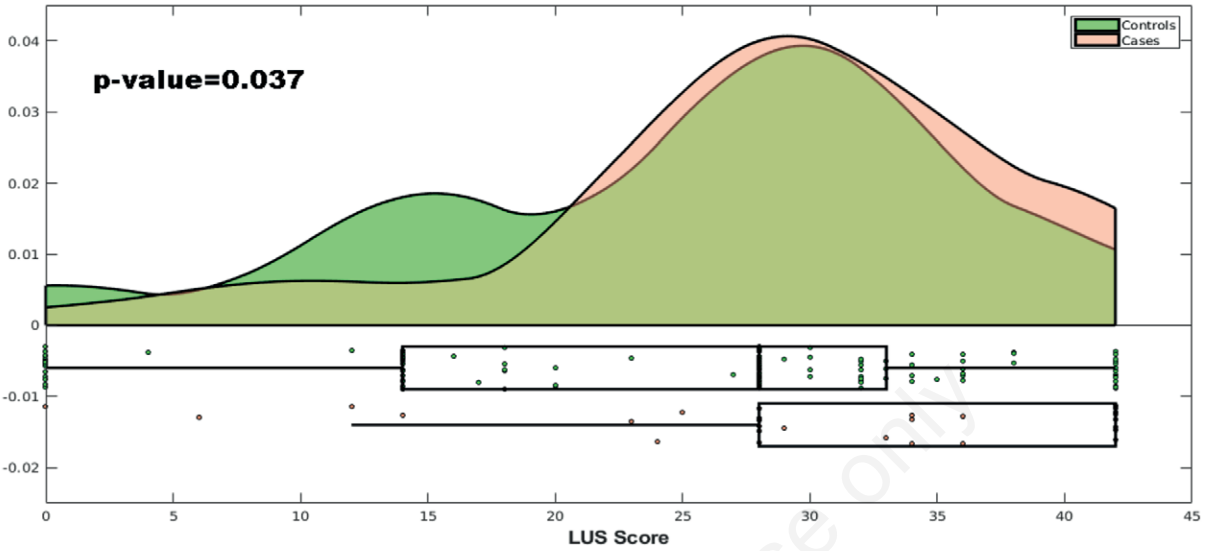

Figure 4. Raincloud plots of lung ultrasound scan scores in pulmonary thromboembolic events between controls and cases.

Table 4. Correlation between lung ultrasound scan score and pulmonary thromboembolic events. All parameters were count numbers, except age and LUS score which are medians, and their 95% confidence intervals.

	Before matching			After matching
	142 Controls (PTE=0)	33 Cases (PTE=1)	P value	
Age	68 [28-88]	64 [33-83]	0.67182	
Males	99	23	0.91694	Propensity Score Matching was not required because all comorbidities were matched
Hypertension	110	23	0.31368	
Diabetes	40	14	0.11913	
Atrial fibrillation	16	5	0.4642	
Ischemic cardiopathy	43	10	0.91694	
Ictus	16	4	0.88487	
Dementia	34	6	0.57137	
COPD	55	14	0.62549	
Cancer	16	4	0.88487	
Smoke	59	9	0.14012	
Obesity	48	11	0.91914	
Epatopaty	19	2	0.30612	
Chronic kidney disease	39	7	0.44905	
LUS Score	28 [0-42]	28 [2-42]	0.03709	
AUC	0.61492			
Standard error	0.056684		0.021316	
Standardized AUC	2.0273			
Comment	Poor test			
Pan's Score	16 [0-23]	18 [3-25]	0.003945	
AUC	0.6629			
Standard error	0.056574		0.001992	
Standardized AUC	2.8794			
Comment	Poor test			

COPD, chronic obstructive pulmonary disease; AUC, area under the ROC curve; LUC, lung ultrasound scan; PTE, pulmonary thromboembolic events.

and PTE, the use of PSM was not needed because cases and controls were already matched for all comorbidities. Also, in this case we have a weak association between the LUS score and its ability to predict PTE.

Table 5 and Figure 5 show that the LUS score is skilled into predict DE and the ROC curve area shows a Fair test. Anyway, the two groups are not matched for many comorbidities (age, diabetes, atrial fibrillation, ictus, ischemic cardiopathy, dementia, COPD, cancer, and chronic kidney disease), and when these differences were balanced using PSM, the skill of LUS score in predicting DE remain unchanged. Using 30 as the LUS score cut-off corresponding to the max cost-effective value, the sensitivity and specificity were equal (*i.e.*, 0.6977).

In order to have a comparison with common radiological findings of CT scans of inpatients with COVID-19, we compared AUC obtained by LUS and Pan's Score. Both tests were performed in the same manner (Table 5).

The death occurred in 19% of patients (*i.e.*, 33 patients) 75% of them for respiratory failures while others for reasons different from respiratory failures.

Discussion

Our combined retrospective analysis raises several items that need discussion. Whenever possible, we adapted our discussion as far as the patients and methods section to STrengthening the Reporting of OBservational studies in Epidemiology (STROBE).[21] The prognostic role of radiological extension of pulmonary embolism by radiological imaging is still a matter of discussion as reported in several studies.[22] In a similar way, also the interpretation of pro-BNP values in pulmonary embolism is still a matter of discussion and its use to stratify the risk of patients with PE was suggested in 2014 ESC guidelines but non-confirmed in those of 2019. The main reason for this failure was due to the validation of this marker in cohort studies and not in

Table 5. Correlation between lung ultrasound scan score and death events before and after propensity score matching to minimize confounding factors. All parameters were count numbers, except age and lung ultrasound scan score that are medians and their 95% confidence intervals.

	Before matching			After matching		
	132 Controls (Death=0)	43 Cases (Death=1)	P-value	43 Controls (Death=0)	43 Cases (Death=1)	P value
Age	63 [26-86]	78 [56-93]	$1.7642 \cdot 10^{-7}$	74 [50-89]	78 [56-93]	0.23268
Males	90	32	0.50902	29	32	0.41559
Hypertension	99	34	0.61122	36	34	0.5005
Diabetes	33	21	0.0032393	18	21	0.4561
Atrial fibrillation	12	9	0.042101	7	9	0.5005
Ischemic cardiopathy	32	21	0.002914	21	21	0.91469
Ictus	11	9	0.038937	7	9	0.5005
Dementia	23	17	0.0045068	15	17	0.74368
COPD	46	23	0.02584	25	23	0.5933
Cancer	10	10	0.0073673	7	10	0.35629
Smoke	51	17	0.92916	20	17	0.45372
Obesity	47	12	0.40862	14	12	0.73142
Epatopaty	17	4	0.69403	6	4	0.4196
Chronic kidney disease	27	19	0.0036856	15	19	0.32967
PTE	21	12	0.09441	6	12	0.09226
pro-BNP	28 [0-42]	36 [16-42]	$3.3517 \cdot 10^{-9}$	28 [0-42]	36 [16-42]	$7.6562 \cdot 10^{-5}$
AUC Standard error Standardized AUC	0.79598 0.043513 6.8022		$5.1501 \cdot 10^{-12}$	0.74202 0.053361 4.5356		$2.8721 \cdot 10^{-6}$
Comment	Fair test			Fair test		
Pan's Score >18 pts	16 [0-24]	18 [7-25]	$1.5918 \cdot 10^{-5}$	16 [1-24]	18 [7-25]	$1.3865 \cdot 10^{-4}$
AUC Standard error Standardized AUC	0.71905 0.71905 4.5488		$2.2982 \cdot 10^{-6}$	0.73743 0.053723 4.4194		$4.9487 \cdot 10^{-6}$
Comment	Fair test			Fair test		

COPD, chronic obstructive pulmonary disease; PTE, pulmonary thromboembolic events; AUC, area under the ROC curve; PTE, pulmonary thromboembolic events; BNP, B-type natriuretic peptide.

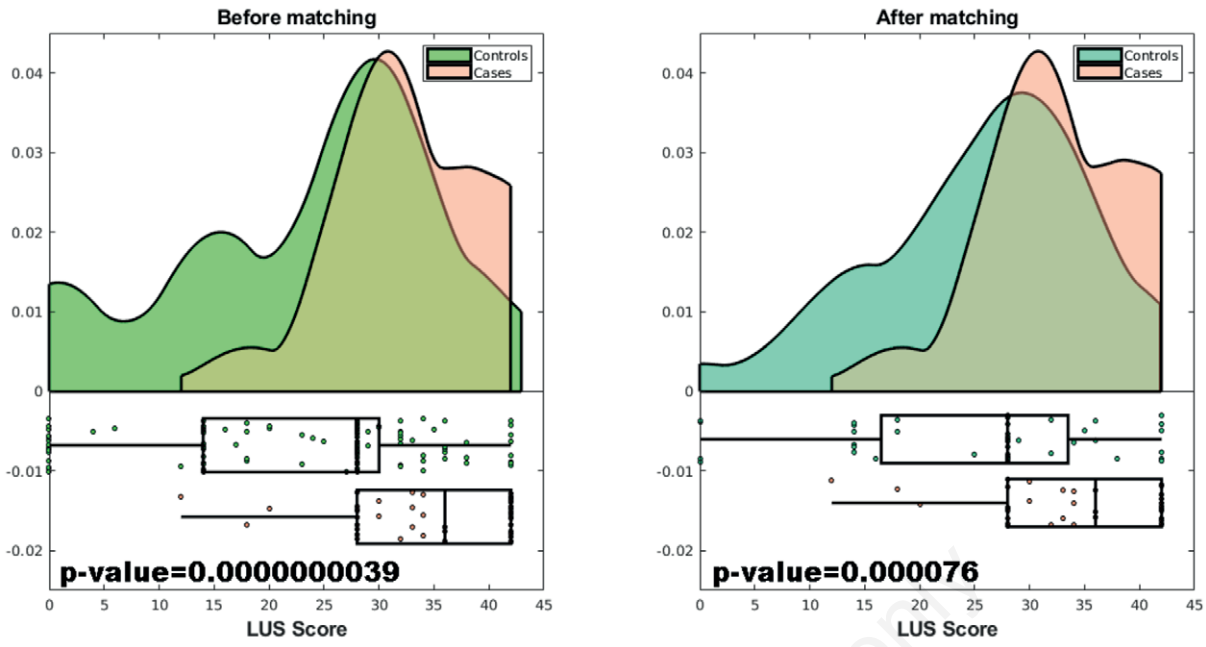

Figure 5. Raincloud plots of lung ultrasound scan scores in death events between controls and cases, before and after propensity score matching to minimize confounding factors.

large randomized trials as far as its validation in prospective studies more than in retrospective studies.[23,24] Together with the role of troponin values in high-risk patients with PE,[1,25-27] it has been used with a cut-off similar to that used in the case of right ventricular dysfunction during PE.[5]

The pandemic due to viral infection by SARS-CoV-2 inducing COVID-19 was characterized by the first cases of lung failure. Therefore, in order to better understand the performance of the LUS score and its prognostic role for patients with complex lung failure due to several causes, we performed a retrospective analysis on inpatients with COVID-19. In a similar way, the use of pro-BNP as a prognostic score in this clinical setting has been suggested in several articles and cohorts of patients with COVID-19 with and without PE.[28-32] These studies gave a relevant impact to identify subgroups of frail patients with COVID-19 at risk for mortality. Yet, studies that gave a role to serial values of pro-BNP during COVID-19 are lacking and for this reason, we decided to do also an evaluation with LUS score. The role of LUS in general wards or in sub-intensive areas for treatment of acute respiratory failure of any type, in fact, has been already underlined.[33-35]

Yet, studies that evaluated the combined prognostic role of pro-BNP and LUS score toward morbidity and mortality for PE or acute respiratory distress syndrome in inpatients with COVID-19 are lacking and with non-univocal results, in particular, because COVID-19 has been associated with an excess of PE per se since first wave.[36-40] Probably, because of the high impact of the pandemic also the role of traditional biomarkers (*i.e.*, troponin and D-dimer) in this clinical setting has been doubtful and for this reason, epidemiological studies looking for other prognostic biomarkers are still active.[9,32]

Therefore, in this report, we addressed our goals to identify a possible combined role of values of pro-BNP and LUS score in inpatients with COVID-19 in a regular ward or in sub-intensive areas in order to identify patients at high risk to die for PE. In this way, we found an association between increased values of pro-BNP and overall death, so confirming a prognostic role of this biomarker in inpatients with COVID-19 independently from the intensity of ventilator support (*i.e.*, regular ward or sub-intensive area), but this role was not confirmed when this biomarker was used to identify an association between increased pro-BNP values, COVID-19 and death for PE.

On the other hand, we found specific prognostic roles of thoracic ultrasound scans scored with methods suggested by Soldati *et al*. In particular, a score major than 30 was associated with an increased rate of death in inpatients with COVID-19 independently from the intensity of ventilator support (*i.e.*, regular ward or sub-intensive area). Intriguingly, the prognostic role of Soldati score major than 30 in our cohort was also associated with an increased rate of VTEs, so suggesting that an ultrasound scan may be a fast and more reliable prognostic method to identify inpatients with COVID-19 at high risk to develop severe complication as fatal VTE or death for any reason. Therefore, we also found clinical and statistical significance for these items, and we gave a prognostic role in this clinical setting to LUS score in an independent way when the intensity of care is considered.

Furthermore, when the role of the LUS score was compared also with the Pan score, no differences were found, confirming the utility of this instrumental approach and with similar results to the CT scan. A similar clinical experience was reported by our group in a different study.[38] Moreover, from a clinical point of view, the role of serial LUS in the daily clinical and therapeutic management of lung failure not related to COVID-19 has been already underlined.[41]

Of course, study limitations need to be also considered.

First of all, the type of analysis was retrospective in a moderate cohort so results, although very robust from a statistical and clinical point of view, need to be confirmed in a randomized clinical trial. Another clinical limitation is due to the fact that COVID-19 is a type of disease that is frequently associated with other lung dysfunctions such as overlapping of bacterial and fungal infections or heart failure and so on, so a pure result of several markers as proBNP is always difficult.

Conclusions

In conclusion, we tried to find a prognostic role to increased values of pro-BNP and LUS scores >30 in inpatients with COVID-19 toward the association of fatal VTE, because specific laboratory biomarkers able to identify patients with COVID-19 at high risk to die from PE are still needed. Confirming this difficult role, in this retrospective analysis we parallelly found a strong prognostic role for LUS score >30. This method underlined that an LUS score >30 was associated with overall mortality and mortality for PE. So, we suggest identifying a subgroup of patients at high risk of mortality using a specific laboratory marker as proBNP but also to associate a method that may have a specific prognostic role as LUS score. In this way, subgroups of patients at high-risk mortality can be monitored in a combined and easy way with tailored clinical and therapeutic updates.

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