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The prognostic role of interatrial block among COVID-19 patients hospitalized in medicine wards

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Abstract

Introduction: Some abnormal electrocardiographic findings were independently associated with increased mortality in patients admitted for COVID-19; however, no studies have focussed on the prognosis impact of the interatrial block (IAB) in this clinical setting. The aim of our study was to assess the prevalence and clinical implications of IAB, both partial and advanced, in hospitalized COVID-19 patients.

Materials: We retrospectively evaluated 300 consecutive COVID-19 patients (63.22 ± 15.16 years; 70% males) admitted to eight Italian Hospitals from February 2020 to April 2020 who underwent twelve lead electrocardiographic recording at admission. The study population has been dichotomized into two groups according to the evidence of IAB at admission, both partial and advanced. The differences in terms of ARDS in need of intubation, in-hospital mortality and thromboembolic events (a composite of myocardial infarction, stroke and transient ischaemic attack) have been evaluated.

Results: The presence of IAB was noticed in 64 patients (21%). In the adjusted logistic regression model, the partial interatrial block was found to be an independent predictor of ARDS in need of intubation (HR: 1.92; p: .04) and in-hospital mortality (HR: 2.65; p: .02); moreover, the advanced interatrial block was an independent predictor of thrombotic events (HR: 7.14; $p < .001$).

Conclusions: Among COVID-19 patients hospitalized in medical wards, the presence of interatrial block is more frequent than in the general population and it might be useful as an early predictor for increased risk of incident thrombotic events, ARDS in need of intubation and in-hospital mortality.

KEYWORDS
acute respiratory distress syndrome, atrial fibrillation, COVID-19, interatrial block, mortality, novel coronavirus, outcome, SARS-CoV-2

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a highly pathogenic human coronavirus recently recognized as the cause of coronavirus disease 2019 (COVID-19). The outbreak sparked in China and spread rapidly to other countries, reaching a devastating pandemic proportion.[1] The clinical course of COVID-19 ranges from asymptomatic[2] to complicate by acute respiratory distress syndrome, thrombotic events or death.[3] The presence of abnormal electrocardiographic findings was independently associated with increased mortality in patients admitted for COVID-19.[4-7] The interatrial block (IAB) is considered a marker of risk of adverse outcomes, including death, in the general population.[8] In the clinical context of COVID-19, IAB might be the expression of SARS-CoV-2 induced atrial electrical remodelling[9,10]; however, no studies have evaluated its role in stratifying COVID-19 patients at increased risk of poor outcomes. The aim of our study was to assess the prevalence and clinical implications of IAB, both partial and advanced, among COVID-19 patients hospitalized in medical wards.

2 | MATERIALS AND METHODS

We retrospectively evaluated 365 consecutive patients with laboratory-confirmed COVID-19 admitted to the internal medicine wards of eight Italian Hospitals from February 2020 to April 2020 who underwent twelve lead electrocardiographic recording at admission. Information on patient baseline characteristics, clinical course (admission to intensive care unit and respiratory support measures) and in-hospital complications (myocardial infarction, stroke, pulmonary embolism and atrial fibrillation) were systematically recorded. The acute respiratory distress syndrome (ARDS) was defined according to the Berlin definition[11]; the severe form of ARDS based on the degree of hypoxemia was diagnosed when the ratio between arterial oxygen tension (PaO_2) and the fraction of inspired oxygen (FIO_2) was ≤100 mm Hg with positive end-expiratory pressure (PEEP) ≥5 cm H_2O.

The number of patients who had died or recovered was also recorded. Patients with rhythm other than sinus (*n*: 43) or with paced rhythm (*n*: 22) were excluded.

ECGs were transferred to a personal computer by an optical scanner and then magnified 400 times by Adobe Photoshop software (Adobe Systems Inc.). P wave analysis, both duration and morphology, was manually performed by two blinded investigators (A.C. and S.H.W.) with the use of a computer software (ImageJ, National Institute of Health). Intraobserver and interobserver coefficients of variation for P wave variables were found to be less than 5% and not significant. The study population has been dichotomized into two groups according to the presence of IAB on the electrocardiogram recorded at admission. IAB was defined partial (P-IAB) when the P wave duration was ≥120 ms, usually bimodal, without a negative terminal component in the inferior leads; or advanced (A-IAB) when the P wave morphology was biphasic (±) in leads II, III and aVF (typical pattern); the atypical pattern by duration and morphology was also included.[12,13] The differences in terms of ARDS development, in-hospital mortality, thrombotic events (a composite of myocardial infarction, stroke and transient ischaemic attack), pulmonary embolism and atrial fibrillation have been evaluated. This study was conducted according to the Declaration of Helsinki and approved by the institutional ethics committees. The requirement for informed consent from individual patients was waived due to the observational retrospective design of the study. Reporting of the study conforms to broad EQUATOR guidelines.[14]

2.1 | Statistical analysis

The distribution of continuous data was tested with the Kolmogorov–Smirnov and the Shapiro–Wilk test. Normally distributed variables were expressed as mean ± standard deviation (SD), whereas non-normal distributed ones as the median and interquartile range (IQR). Categorical variables were reported as numbers and percentages. Continuous normally distributed variables were compared by using the Student t-test; differences between non-normally distributed variables were tested with the Mann–Whitney U test. Categorical variables were compared with the chi-squared test or Fisher exact test, when appropriate. Furthermore, clinical events recurrence free-rates in the study groups during follow-up were evaluated with the Kaplan–Meier method and compared with the log-rank test. The unadjusted (univariate) and adjusted (multivariate) odds ratio (OR) of P wave duration, overall IAB, partial IAB and advanced IAB for the outcomes of interest (ARDS, thrombotic events and in-hospital mortality) were calculated using logistic regression models and presented as OR with their 95% confidence intervals (CI). In univariate analysis, P-IAB and A-IAB were compared to patients with normal P wave duration. The multivariate regression analysis included all the clinical variables with the statistically significant association with univariate analysis. For all tests, a *p* value < .05 was considered statistically significant. Analysis was performed by using R version 3.5.1 (R Foundation for Statistical Computing).

3 | RESULTS

Three hundred COVID-19 patients were included in the present study. The baseline characteristics of the study population are summarized in Table 1. The mean age was 63.22 ± 15.16 years; 210 (70%) were males. IAB was reported in 64 patients (21%), partial in 55 (85.9%) and advanced in 9 (14.1%) patients; all cases of advanced IAB (A-IAB) showed a typical pattern. COVID-19 patients with IAB were older than those without IAB (68.4 ± 12.2 vs. 61.84 ± 15.6; p = .002) and showed higher prevalence of obesity (23.4% vs. 13.1%; p = .04), COPD (26.6% vs. 13.5%; p = .01), chronic kidney disease (CKD; 15.6% vs. 5.9%, p: .011), history of AF (9.37% vs. 2.96%; p = .025), increased correct QT duration (416.94 ± 38.90 vs 400.39 ± 37.18; p: .0019), use of amiodarone (7.8% vs. 0%; p < .0001) and anticoagulants (9.37% vs. 2.96%; p = .025). A trend of higher prevalence of previous stroke was shown among IAB group (12.5% vs. 5.5%; p = .052). Patients with A-IAB (n: 9) showed more likely previous stroke (33.3% vs. 9.1%; p: .04) and heart failure (22% vs. 3.6%; p: .03) than those with P-IAB (Table S1).

TABLE 1 Baseline characteristics of the study population according to the presence of interatrial block

Variables	Overall Population n: 300	IAB Group n: 64	No-IAB Group n: 236	p Value
Age, years	63.22 ± 15.16	68.4 ± 12.2	61.84 ± 15.6	.002
Male, n (%)	210 (70%)	54 (84.4%)	156 (53.1%)	.0001
Obesity, n (%)	46 (15.3%)	15 (23.4%)	31 (13.1%)	.04
COPD, n (%)	49 (16.3%)	17 (26.6%)	32 (13.5%)	.01
AF history, n (%)	13 (4.3%)	6 (9.37%)	7 (2.96%)	.025
Dyslipidemia, n (%)	68 (22.7%)	18 (28.1%)	50 (21.2%)	.24
Dysthyroidism, n (%)	33 (11%)	4 (6.25%)	29 (12.3%)	.17
Diabetes mellitus. n (%)	83 (35.2%)	17 (26.6%)	66 (27.9%)	.83
Arterial hypertension, n (%)	121 (40.3%)	43 (67.2%)	136 (57.6%)	.16
CAD, n (%)	40 (13.3%)	11 (17.2%)	29 (12.3%)	.31
DCM, n (%)	7 (2.3%)	2 (3.1%)	5 (2.2%)	.17
CKD, n (%)	24 (8%)	10 (15.6%)	14 (5.9%)	.011
HF, n (%)	15 (5%)	4 (6.25%)	11 (4.7%)	.6
Previous stroke, n (%)	21 (7%)	8 (12.5%)	13 (5.5%)	.052
Heart rate, bpm	80.36 ± 16.63	83.48 ± 15.9	79.51 ± 16.7	.09
P wave duration, ms	88.7 ± 27.6	121.8 ± 9.5	79.8 ± 23.9	<.0001
PR interval duration, ms	155.75 ± 28.27	169.16 ± 33.434	152.10 ± 25.58	<.0001
QRS duration, ms	79.28 ± 25.94	86.89 ± 27.411	77.21 ± 25.19	.008
LBBB, n (%)	9 (3.0%)	2 (3.1%)	7 (3.0%)	.99
RBBB, n (%)	32 (10.7%)	7 (10.9%)	25 (10.6%)	.9
Correct QT, ms	403.92 ± 38.10	416.94 ± 38.90	400.39 ± 37.183	.0019
ACE-I/ARBs, n (%)	62 (20.7%)	26 (40.6%)	78 (33.1%)	.384
Beta-blockers, n (%)	79 (26.7%)	18 (28.1%)	61 (25.6%)	.68
Amiodarone. n (%)	5 (1.7%)	5 (7.8%)	0 (0%)	<.0001
Class IC AAR. n (%)	12 (4%)	2 (3.12%)	10 (4.24%)	.68
Digitalis drugs, n (%)	1 (0.3%)	1 (1.54%)	0 (0%)	.06
Ivabradine, n (%)	4 (1.35%)	2 (3.12%)	2 (3.12%)	.99
Azithromycin, n (%)	203 (67%)	0 (0%)	1 (1.54%)	.31
Antiplatelets, n (%)	90 (30%)	24 (37.5%)	76 (32.2%)	.42
Anticoagulants, n (%)	13 (4.3%)	6 (9.37%)	7 (2.96%)	.025
Statins, n (%)	124 (41.3%)	31 (48.4%)	93 (39.5%)	.19

Abbreviations: AAR, antiarrhythmic drugs; ACE-I/ARBs, angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers; AF, atrial fibrillation; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DCM, dilated cardiomyopathy; LBBB, left bundle branch block; RBBB, right bundle branch block.

	Unadjusted OR (95% CI; p value)	Adjusted* OR (95% CI; p value)
P wave duration (10 ms increase)	1.02 (1.01–1.03; $p < .0001$)	1.03 (1.01–1.04; $p = .001$)
Overall IAB	2.64 (1.46–4.74; $p = .001$)	1.99 (1.06–3.72; $p = .031$)
Partial IAB	2.64 (1.42–4.96; $p = .002$)	1.92 (1.03–3.36; $p = .04$)
Advanced IAB	2.37 (0.58–9.7; $p = .230$)	-

TABLE 2 Unadjusted and adjusted odds ratio for ARDS in need of intubation

Note: *Adjusted for obesity, chronic obstructive pulmonary disease, chronic kidney disease; heart rate, QRS duration, right bundle branch block.

Abbreviations: CI, confidence interval; OR, odds ratio.

	Unadjusted OR (95% CI; p value)	Adjusted* OR (95% CI; p value)
P wave duration (10 ms increase)	0.99 (0.98–1.01; $p = .72$)	-
Overall IAB	0.79 (0.26–2.44; $p = .69$)	-
Partial IAB	0.69 (0.20–2.46; $p = .58$)	-
Advanced IAB	5.95 (1.59–22.33; $p = .01$)	7.14 (2.51–20.36; $p < .001$)

TABLE 3 Unadjusted and adjusted odds ratio for thrombotic events

Note: *Adjusted for dilated cardiomyopathy and chronic kidney disease.

Abbreviations: CI, confidence interval; OR, odds ratio.

	Unadjusted OR (95% CI; p value)	Adjusted OR* (95% CI; p value)
P wave duration (10 ms increase)	1.01 (1.00–1.02; $p = .054$)	-
Overall IAB	2.98 (1.62–5.50; $p < .0001$)	2.51 (1.15–5.43; $p = .02$)
Partial IAB	3.17 (1.68–5.99; $p < .0001$)	2.65 (1.18–5.97; $p = .02$)
Advanced IAB	1.36 (0.27–6.78; $p = .71$)	-

TABLE 4 Unadjusted and adjusted odds ratio for in-hospital mortality

Note: *Adjusted for age, chronic obstructive pulmonary disease, dyslipidaemia, diabetes, hypertension, coronary artery disease, dilated cardiomyopathy, chronic kidney disease; heart rate.

Abbreviations: CI, confidence interval; OR, odds ratio.

Among the study population, 150 patients (50%) developed ARDS in need of intubation and 65 died (21.7%) during the hospitalization. 32 patients (10.6%) experienced thrombotic events, 16 patients (5.3%) and 14 (4.7%) patients developed incident atrial fibrillation and pulmonary embolism, respectively.

There was a statistically significant difference in ARDS (73.4% vs. 43.6%, p: .0001) and overall mortality incidence (37.5% vs. 17.4%, p: .0006) between IAB and No-IAB groups; moreover, no statistically significant difference in thrombotic events (15% vs. 9.3%, p: .79), incidence of AF (7.8% vs. 4.7%, p: .35) and PE (4.7% vs. 4.7% p: 1.0) was found.

In the adjusted logistic regression model, the partial interatrial block was found to be an independent predictor of ARDS in need of intubation (HR: 1.92; p:.04) and in-hospital mortality (HR: 2.65; p: .02); moreover, the advanced interatrial block was an independent predictor of thrombotic events (HR: 7.14; $p < .001$). Tables 2–4 shows the unadjusted and adjusted odds ratio of P wave duration, overall IAB, partial IAB and advanced IAB for the outcomes of interest. The results of univariate and multivariate analysis of all clinical factors tested for the association with the outcomes of interests were presented in the supplemental Tables 2–4.

Figures 1–3 show the Kaplan–Meier survival analysis estimating the risk of ARDS, thrombotic events and all-cause mortality in patients with or without IAB at admission. A significantly higher risk of ARDS in need of intubation ($p < .001$) and death ($p = .0001$) was found.

FIGURE 1 Kaplan–Meier survival analysis estimating the risk of ARDS in patients with or without IAB at admission
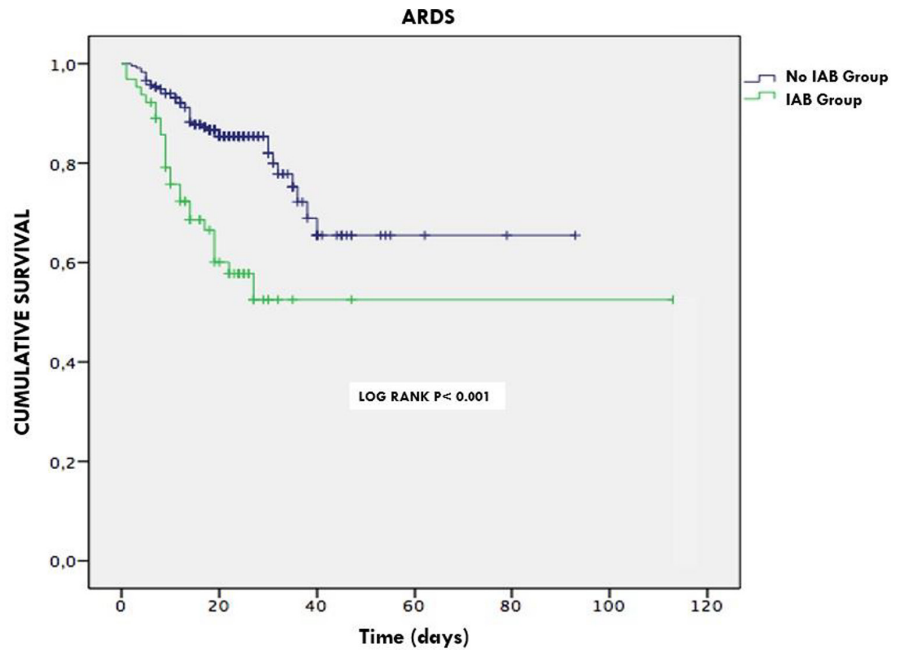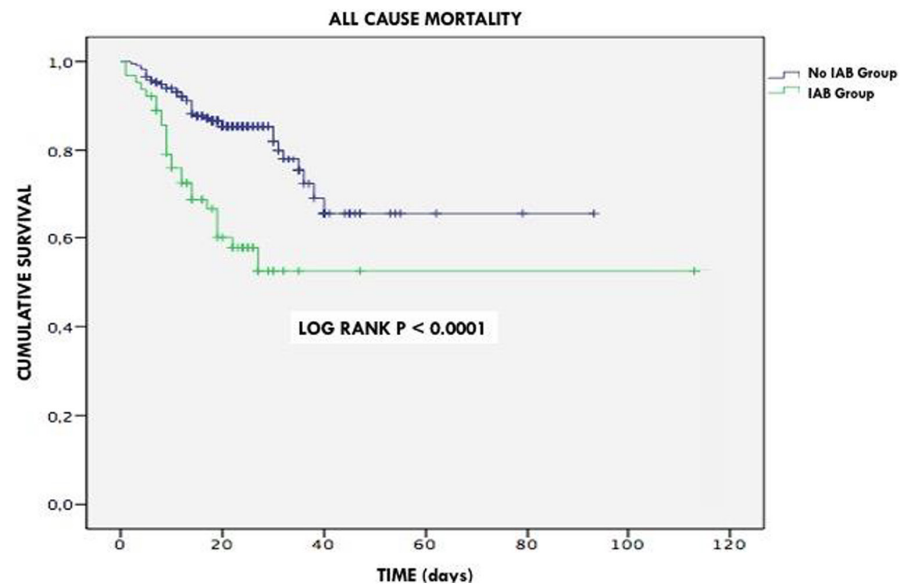

FIGURE 2 Kaplan–Meier survival analysis estimating the risk of all-cause mortality in patients with or without IAB at admission

4 | DISCUSSION

The main findings of the present study can be summarized as follows: more than one-third of patients admitted with COVID-19 manifested IAB, mainly partial IAB. IAB was associated with a higher prevalence of cardiovascular comorbidities. Patients with A-IAB showed higher prevalence of the previous stroke. The presence of partial IAB at admission is an independent predictor of ARDS and in-hospital mortality. Moreover, A-IAB is associated with incident thrombotic events during COVID-19 hospitalization.

Interatrial block is a well-described, but poorly recognized, cardiac rhythm disorder caused by delayed conduction across Bachmann's bundle that is located between the right and left atrium, resulting in a prolonged P wave duration with (advanced IAB) or without (partial IAB) biphasic morphology in the electrocardiographic inferior leads.[15] The prevalence of IAB increases with age[16] and it has been demonstrated to be a predictor of atrial fibrillation,[17,18] stroke,[19] cognitive impairment,[20,21] dementia[21] and mortality.[8,22] Moreover, advanced IAB stratifies heart failure patients with a higher degree of left atrial structural and functional remodelling.[23]

Despite previous studies that analyzed the role of electrocardiographic findings in predicting clinical outcomes among hospitalized COVID-19 patients,[4,5] no data have even been reported on IAB.
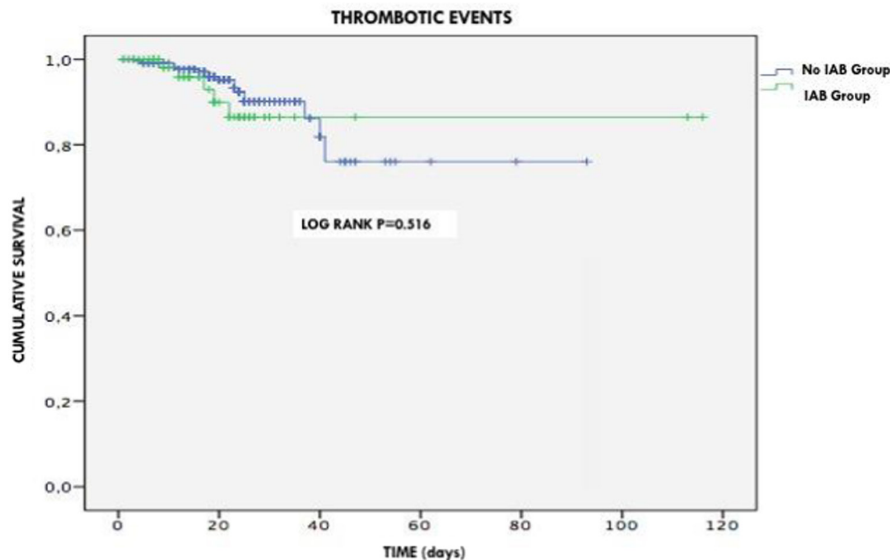
A recent metanalysis by Alsagaff MY et al.[5] including 2,539 COVID-19 patients across seven different studies showed that several ECG abnormalities on admission (longer QTc interval, prolonged QTc interval, longer QRS duration, faster heart rate, LBBB, premature atrial and ventricular complexes, T-wave inversion and ST depression) were associated with poor outcome, defined as a composite of intensive care unit admission, severe illness and mortality.

Recently Yenerc¸ag˘ M et al.[24] showed that P wave duration and P wave dispersion were longer in COVID-19 patients than in the healthy controls, in particular in those who developed atrial fibrillation during the hospitalizations; however, no data regarding the role of IAB were presented.[25]

Among our study population, the prevalence of partial and advanced IAB was 18.3% and 3%, slightly higher than those reported among 152,759 primary care patients aged 50 to 90 years.[26] This increased prevalence might be explained by the study cohort's mean age and the concomitant cardiovascular comorbidities, which may lead to atrial myopathy; however, we cannot exclude the hypothesis that COVID-19 may be responsible for atrial dysfunction as the expression of abnormal host inflammatory response.[9] A recent echocardiographic study by Goerlich et al.[10] showed that hospitalized COVID-19 patients have reduced left atrial function compared with COVID-19-negative controls with similar degrees of critical illness, and this dysfunction is more pronounced in COVID-19 patients who develop atrial fibrillation.

Among our study population, the interatrial block was the only independent electrocardiographic predictor of worse outcomes during the COVID-19 hospitalization. In particular, there was no association between pre-existing LBBB and mortality, differing from the results of a recent metanalysis,[27] which, however, included all patients with LBBB regardless of onset (before or during COVID-19). Increased heart rate was a weak independent predictor of all-cause mortality and ARDS in need of intubation, confirming its prognostic role in both COVID-19[5] and general population.[28]

4.1 | Limitations

Our results should be interpreted in light of the limitations related to the retrospective observational nature of the study; and the prognostic role of IAB, in particular A-IAB, should be investigated in a larger cohort prospective study. Although the multicenter study design might have improved the generalizability of data, we cannot exclude type II errors related to the small sample size. The selective inclusion of patients who needed hospitalization might also represent a potential bias of this study since only symptomatic patients were ascertained. The absence of data about patients' status at admission represents a limitation; however, only patients admitted to internal medicine wards were included and those who presented with ARDS at admission in need of intensive care unit (ICU) were excluded from the analysis.

5 | CONCLUSIONS

Among COVID-19 patients hospitalized in medical wards, the presence of interatrial block is more frequent than in the general population and it might be useful as an early predictor for increased risk of incident thrombotic events, ARDS in need of intubation and in-hospital mortality.

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