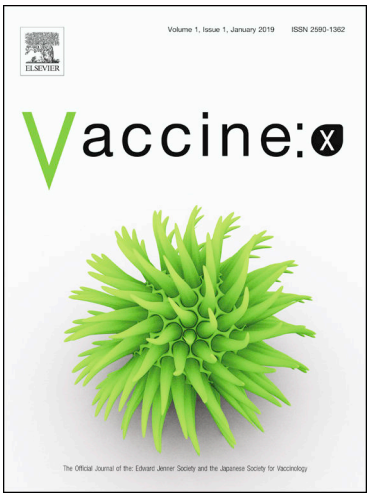

Impact of vaccination on electrocardiograms of hospitalized patients for Covid-19

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TITLE PAGE

(1) Title

Impact of vaccination on electrocardiograms of hospitalized patients for Covid-19.

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The manuscript:

1) the paper is not under consideration elsewhere

2) none of the paper's contents have been previously published

3) all authors have read and approved the manuscript

4) authors have no potential conflict of interest to disclose

Sincerely yours

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Abstract

Introduction We sought to assess the impact of SarsCov-2 vaccination on admission12-lead electrocardiogram of hospitalized patients.

Methods We retrospectively analyzed and compared admission 12-lead electrocardiograms of all patients hospitalized in dedicated Internal Medicine Unit for Covid-19 both in pre-vaccination period (PV) and after vaccination (V).

Results 667 consecutive Covid-19 in-patients were enrolled in the study: PV hospitalized patients were older (68vs57 years, p<0.01), had higher rates of atrial fibrillation/flutter (13%vs2.5%, p<0.01), any arrhythmia (26%vs8%, p<0.01), and ST-T abnormalities (22%vs7.4%, p< 0.01). Mortality rates in hospitalized Covid-19 patients were higher before vaccination period (20%vs4%, p<0.01). Minimal vaccination coverage of population (V period) was inversely and independently associated with in-hospital mortality (odds ratio 0.09, 95%CI 0.01-0.68, p<0.05).

Conclusions SarsCov-2 vaccination campaign and even partial coverage of local population was associated with less frequent abnormalities at admission ECG in hospitalized non-critically hill Covid-19 patients and lower mortality

Keywords: Covid-19; Electrocardiogram; Vaccination.

Introduction

Coronavirus disease-2019 (Covid-19), as declared by World Health Organization on March 11, 2020, is a global pandemic caused by severe acute respiratory syndrome-coronavirus-2 (SarsCov-2) [1]. Despite typical clinical manifestation represented by an acute respiratory distress, a not negligible proportion of patients present cardiac involvement. Myocardial injury has been associated with increased morbidity and mortality [2]**.** Oxygen supply-demand imbalance, cytokine-mediated damage, ischemic injury from microvascular thrombosis and direct viral damage are the proposed mechanisms that may explained myocardial injury [3].

Traditional 12-lead electrocardiogram (ECG) plays an important role in hospitalized patients for the screening of cardiac involvement because fast, widely accessible, and remotely interpretable. Furthermore, ECG at admission demonstrated to predict 30-day mortality in patients admitted for Covid-19 [4].

From December 2020, the introduction of coronavirus disease-2019 (COVID-19) vaccines determined a significant decrease in Covid-19 related morbidity and mortality worldwide. The approved Covid-19 vaccines have proven a favorable risk-benefit ratio [5,6].

According to agent-based model of SARS-CoV-2 transmission on United States demographics and age-specific Covid-19 outcomes, the vaccination, associated with non-pharmaceutical interventions, was expected to have a substantial impact on mitigating COVID-19 pandemic when a 40% vaccine coverage of the overall population is achieved [7].

However indirect and direct impact of large scale vaccination on cardiac involvement has not been largely investigated yet. The impact of vaccination of ECG findings and anomalies is also poorly described. We therefore sought to compare ECG findings in Covid-19 patients hospitalized during pre-vaccination period with post-vaccination findings.

Methods

We retrospectively analyzed the 12-lead electrocardiograms and patient's records of all patients hospitalized in dedicated Internal Medicine Unit (IMU) for Covid-19 in the Policlinico Riuniti University Hospital in 2 different periods: patients from October 1 2020 to February 28 2021 were included in the pre-vaccination period group (PV), while patients from July 16 2021 to September 30 2021 represented the post-vaccine period group (V).

The temporal threshold between pre-vaccination and vaccination period was defined according to agent-based model of SARS-CoV-2 transmission indicating an expected significant impact of vaccination on mitigating COVID-19 pandemic with at least 40% vaccine coverage of the overall population [7]. According to official data released by local Health Authorities, 40% of vaccine coverage in the local population was achieved in Apulia region, Italy, July 16 2021 and in the district referring to Policlinico Riuniti University Hospital in Foggia [8].

Gender, age and in-hospital survival data were recorded from all patients. Twelve-lead ECGs were recorded using 25 mm/s and 1 mV/cm calibration, 0.05–150 Hz filter (Schiller Cardiovit AT-102 G2, Schiller Inc., Baar, Switzerland); data were retrieved by accessing the hospital ECG storage server (Schiller SEMA, Schiller Inc., Baar, Switzerland). We also recorded: heart rate (HR), QRS duration, PR interval, ST-tract/T-wave abnormalities, Q waves, corrected QT (QTc) interval, Cornell and Sokolow-Lyon voltage (mV), presence of atrial fibrillation/flutter (AF), atrial tachycardia, premature supraventricular and ventricular complexes, ventricular tachycardia. Two expert cardiologists (M.M., N.D.B.) supervised ECG reporting and interpreted electrocardiograms.

We excluded patients hospitalized in intensive care unit, as clinical setting may affect both ECG abnormalities and outcome in Covid-19 patient [9].

Statistical analysis

Continuous variables were reported as mean with standard deviation and compared with Student's t-test, dichotomic as proportions and compared with $\chi^2 2$ test.

The association of individual clinical and ECG variables with death was assessed by calculating odds ratio with 95% confidence intervals (95% C.I.) by logistic regression analysis. Multivariable logistic regression analysis with a model including all variables significant at univariable analysis was used to identify independent predictors of in-hospital mortality.

P values <0.05 were considered as statistically significant.

Results

667 consecutive hospitalized patients were enrolled in the study and their admission electrocardiograms were analyzed; 546 were included in the first group (pre-vaccination group (PV), October 1 2020 to February 28 2021), 121 in the second (vaccination group (V), from July 16 2021 to September 30 2021). In V group, 31 subjects were hospitalized with Covid-19 infection despite vaccination.

ECG findings, age, and gender are summarized and compared in Table 1. Patients in the PV group were older (68±17 vs 57±20 years, p<0.01); atrial fibrillation (13% vs 2.5%, p<0.01), any arrhythmia (26% vs 8%, p<0.01) and ST-T abnormalities (22% vs 7.4%, p< 0.01) were detected more frequently. QTc interval (both with Bazett and Fredericia formulas) was significatively longer and a prolonged cQT was significantly more frequent. In-hospital death occurred more frequently in the PV period (20.9% vs 4.4%, p<0.01).

At univariable analysis death occurring during hospital stay was associated with post-vaccination setting, atrial fibrillation, presence of any arrhythmia, age and ST-T abnormalities were significantly associated with mortality (Table 2).

At a multivariable stepwise forward logistic regression analysis, age (OR 1.09, 95%CI 1.07-1.12, p<0.0001), AF/atrial flutter (OR 2.69, 95%CI 1.15-6.28, p<0.05), and heart rate (OR 1.02, 95%CI 1.01-1.03, p<0.01) were independently associated with in-hospital mortality; 40% vaccine coverage of local population (OR 0.09, 95%CI 0.01-0.68, p<0.05) and left ventricular hypertrophy (OR 0.20, 95%CI 0.06-0.65, p<0.01) were independently and inversely associated with in-hospital mortality (**Table 3**).

Discussion

In the present study we show changes in admission ECG findings in patients hospitalized for Covid-19 infection in a low intensity of care setting (medicine ward). Interestingly, the occurrence of electrocardiogram abnormalities (any arrhythmia, atrial fibrillation, ST-T anomalies, prolonged cQT) was lower in hospitalized patients after vaccination campaign. Furthermore, in-hospital mortality was lower after 40% vaccination coverage of population.

Several hypotheses can be made to explain such apparent influence of Covid-19 vaccination on admission electrocardiograms and outcome. Cardiac involvement influences the outcome in Covid-19 patients and may depend on different pathological mechanisms [2-3]. Myocardial oxygen supply/demand mismatch, direct interaction virus-myocardiocytes and cytokine-mediated apoptosis represent well-known mechanisms at the basis of myocardial injury. In addition, an underlying cardiac disease may be a pre-existing medical condition that adversely impacts the prognosis of patients with respiratory distress affected by SarsCov-2 infection [3]. In other words, when we assess cardiac conditions in Covid-19 patients we assess not only the degree of myocardial damage due to SarsCov2, but also the entity of respiratory distress and the presence of an underlying heart disease.

ECG can be considered a first line tool for cardiac assessment even in Covid-19 patients because easily performable, inexpensive and remotely interpretable.

In PV period, ECG abnormalities as AF and all arrhythmias occurred more frequently than in VP. Moreover, there were statistically significant higher mean age and in-hospital mortality in PV period in comparison to V period. At univariable analysis AF, all arrhythmias, ST-T abnormalities, prolonged cQT interval and pre-vaccine period were associated with in-hospital mortality (**Table 2**). At a multivariable analysis, age, atrial fibrillation/flutter and heart rate were independently associated with in-hospital mortality, while vaccination coverage and left ventricular hypertrophy were inversely and independently associated with in-hospital mortality (**Table 3**). These findings may be explained by indirect and direct protective effects of vaccine. In general, age reflects general clinical conditions and comorbidities so it may impact mortality and be associated with ECG abnormalities as atrial fibrillation and any other arrhythmia. The reduced mean age and consequently the lower rates of AF, arrhythmias and ST-T abnormalities in hospitalized patient during V period in comparison PV may be considered an indirect effect of vaccination. In fact, according to Italian vaccination campaign, the elderly (>70 year-old) received the vaccine before the rest of general population and, accordingly, were less hospitalized in comparison with PV period.

Another indirect and not age-related effect of vaccination on the severity of Covid-19 in hospitalized patients may be hypothesized. In pre-vaccine period, because of the huge number of cases with serious respiratory involvement, several patients with less severe respiratory distress were managed at home. During post-vaccine period, the number of hospitalizations for Covid-19 decreased substantially, so even less critical patients may have been hospitalized.

Consequently, clinical conditions of hospitalized Covid-19 patients were generally and apparently less critical in V than in PV.

Borderline results with prolonged cQT findings may be explained by the poorer clinical status, probable electrolyte abnormalities but also by larger initial utilization in PV period of drugs as azithromycin and hydroxychloroquine potentially affecting cQT interval [10].

Interestingly, rates of vaccinated patients were higher in surviving patients but individual vaccination was not an independent predictor of survival in hospitalized patients with Covid-19. Such apparent contrasting results may be explained by the fact that hospitalized patients despite vaccination in general were patients characterized by higher levels of frailty and higher number of comorbidities. So, this population, hospitalized Covid-19 patients despite vaccination, is not representative of the effect of vaccination in protecting Covid-19 patients from adverse outcome, and the protective effect of vaccination is much more evidently expressed by lower mortality rates observed after a minimal coverage of population with Covid-19 vaccination. Covid-19 vaccination estimated coverage of 40% was therefore associated with less frequent abnormalities at admission electrocardiogram in hospitalized Covid-19 patients.

Indirect and direct effects of SarsCov-2 vaccination may be hypothesized. Further studies are needed to confirm these observations.

Conclusions

Covid-19 vaccination estimated coverage of 40% was associated with less frequent abnormalities at admission electrocardiogram in hospitalized Covid-19 patients.

Limitations

The study is a single medical center study. No data are available on oxygen levels, pre-admission ECG, pre-existing atrial fibrillation, baseline QT levels, drug therapy, sedation, antibiotic therapy, diabetes, previous cardiovascular disease, thyroid disease. No echocardiographic findings were collected. The V period is definitely smaller than PV period in terms of days.

No data are available on type of vaccine used for vaccination even though all three types of vaccines authorized during the study by national authorities were presumably used: Vaxzevria, Comirnaty, and Spikevax.

Conflict of interest

None to disclose.

Tables

Table 1. ECG findings and main demographic characteristics in pre-vaccine era (VPV) and vaccine era (VP).

	Vaccination (n 121)	S.D.	Pre-vaccination (n 546)	S.D.	P- value
Age (y)	56.9	19.7	67.8	17.3	0.0000
Male sex (%)	19.8		56.2		0.0348
In hospital death (%)	4.1		19.8		0.0000
Sinus Rhythm (%)	79.3		66.9		0.0070
Atrial fibrillation / flutter (%)	2.5		13		0.0008
Heart rate (bpm)	84.9	18.2	81.7	22.3	0.1409
Any arrhythmias (%)[1]	7.7		25.8		0.0001
Ventricular arrhythmias (%)	3.4		6.8		0.2285
Sinus Tachycardia (%)	18.2		9.2		0.0008
Any AV block (%)[2]	7.7		4.2		0.1473
Any IV block (%)[3]	11		17.8		0.1097
Left axis deviation (%)	9.9		19.6		0.0118
cQT duration (b) (msec)	429.6	29.6	439.9	36.2	0.0034
cQT duration (f) (msec)	407.5	28.8	421	33.1	0.0000
Prolonged cQT (%)	5.8		17.3		0.0014
Left ventricular hypertrophy (%) [4]	12.4		7.1		0.0553
ST-T abnormalities (%)	7.4		22		0.0002

[1] Ectopic Ventricular Beats; Ectopic Supraventricular Beats; Ventricular Tachycardia
[2] First-degree AV block; Second-degree AV block Mobitz 1 and 2; Third-degree AV block
[3] Right bundle branch block; Left bundle branch block; Left anterior fascicular block; Left posterior fascicular block
[4] Based on Cornell and Sokolow Criteria

Table 2. Univariable analysis for in-hospital mortality

	Deceased during hospital stay (n 113)	S.D.	Survivors (n 554)	S.D.	p value
Age (y)	81	10	63	18	<0.01
Male sex (%)	11		59		0.0891
Sinus Rhythm (%)	48		74		<0.01
Atrial fibrillation/flutter (%)	33		7		<0.01
Heart rate (bpm)	93	27	80	20	<0.01
All arrhythmias[1] (%)	46		19		<0.01
Ventricular arrhythmias (%)	10		6		0.0801
Sinus Tachycardia (%)	13.3		10		0.3520
Any AV block[2] (%)	6		5		0.6856
Any IV block[3] (%)	33		14		<0.01
Left axis deviation (%)	23		17		0.1157
QTc duration (b) (msec)	460	37	434	33	<0.01
QTc duration (f) (msec)	432	40	416	30	<0.01
Prolonged QTc (%)	28		13		<0.01
Left ventricular hypertrophy[4] (%)	4		9		0.0514
ST-T abnormalities (%)	35		16		<0.01
Single dose vaccination (%)	2		3		0.4502
Complete vaccination (%)	2		3		0.3579
Any vaccination (%)	8		28		0.0009
40% of local population coverage with vaccination (%)	4		21		<0.01

Ectopic Ventricular Beats; Ectopic Supraventricular Beats; Ventricular Tachycardia
[2] First-degree AV block; Second-degree AV block Mobitz 1 and 2; Third-degree AV block
[3] Right bundle branch block; Left bundle branch block; Left anterior fascicular block; Left posterior fascicular block

Table 3. Multivariable logistic regression model for in-hospital mortality.

	odds ratio	95% C.I.		p
		Lower	Upper	
age	1.09	1.07	1.12	<0.0001
male	0.86	0.52	1.43	0.5672
heart rate	1.02	1.01	1.03	0.0013
atrial fibrillation/flutter	2.69	1.15	6.28	0.0222
any arrhythmia	0.53	0.24	1.18	0.1188
ventricular arrhythmia	1.17	0.44	3.05	0.7551
LBBB	0.58	0.15	2.22	0.4262
prolonged QT	1.81	0.99	3.31	0.0530
LV hypertrophy	0.20	0.06	0.65	0.0074
individual vaccination	1.50	0.06	38.31	0.8053
vaccination coverage	0.09	0.01	0.68	0.0200

LBBB: left bundle branch block; LVH: Left Ventricular Hypertrophy.

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

17/03/2023

Editor in Chief

Dear Editor,

We would thank you for the opportunity to consider our work for publication in Vaccine X. We highly appreciated the reviewer's comments. The paper was corrected according to the Editor's suggestions and we think that it is now ready for your attention. We therefore would like to submit a revised version of the manuscript entitled "**Impact of vaccination on electrocardiograms of hospitalized patients for Covid-19**" for your consideration for publication in your journal. We believe that this article will be of interest to your readers.

Editor

From the study description, however, it is not entirely clear to me whether the study was conducted from the review of patient records, or whether the study actually enrolled patients during this period (i.e. a prospective study). If it is a prospective study, please indicate the necessary ethical approval by your institution/hospital (e.g. IRB number). This is the only concern that I have. Otherwise, no response-to-reviewer is required from you.

We would thank our reviewer for the opportunity to improve the paper. We clarified in methods section that the study is retrospective. As we performed a retrospective study, an ethical approval by our Institution was waived.

All authors have read and approved submission of the manuscript and the manuscript has not been published and is not being considered for publication elsewhere in whole or part in any language. All authors were involved in the design or analysis and interpretation of data. All authors have no commercial association, such as consultancies, stock ownership or other equity interests or patent-licensing arrangements.

Yours sincerely,

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