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SARS-CoV-2 vaccine hesitancy in patients with heart failure: relationship with patient characteristics and pre-pandemic quality of life – a cohort study

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ABSTRACT

Heart failure (HF) patients are vulnerable to a complicated course of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. This research analysed the relationship between the decision not to be

immunised against SARS-CoV-2, clinical and epidemiological factors, and the pre-pandemic health-related quality of life (HRQoL) of HF patients. Before the onset of the SARS-CoV-2 pandemic, hospitalised HF patients were enrolled as a prospective cohort and interviewed using the World Health Organization's Quality of Life Brief Version questionnaire. On October 30, 2021, the immunisation status was verified. The association of vaccination hesitancy with epidemiological and clinical parameters and pre-pandemic questionnaire results was tested. Subsequently, independence from confounding factors such as age, sex, the New York Heart Association (NYHA) scale, and left ventricular ejection fraction (LVEF) was analyzed. Among the 136 included patients, 77.9% were vaccinated. Unvaccinated patients were younger (51.2 ± 13.2 vs 56.6 ± 10.3; p = 0.018) and more frequently had non-ischaemic aetiology of HF (73.3% vs 46.7%; p = 0.013). It was significant after adjustment for age, sex, NYHA class, and LVEF. There was no association of overall HRQoL or domain scores with vaccination status. Younger age as a factor associated with vaccine avoidance in this population is consistent with data from the general population despite higher exposure to the severe course of the disease.

Introduction

In December 2019, a new virus called severe acute respiratory failure coronavirus 2 (SARS-CoV-2) caused a global pandemic. SARS-CoV-2 spreads person-to-person by droplet transmission in aerosols [1,2]. Although most people infected with SARS-CoV-2 exhibit mild or moderate respiratory symptoms, some groups are at heightened risk of experiencing a more severe disease course and requiring medical attention [3]. The risk of severe COVID-19 is higher in elderly individuals and those with underlying health conditions.. Patients with HF are also prone to suffer from severe symptoms of COVID-19 [3].

The increase in COVID-19 cases resulted in the intensification of research related to COVID-19 treatment; moreover, vaccines were developed. The European Medicines Agency recommended the first vaccination on December 21 2020, changing the frequency and severity of symptoms and the number of deaths from COVID-19 [4]. Hence, the continuation of vaccination is essential in protecting people from risks associated with COVID-19 disease [5]. Despite clear and substantiated advantages of immunity gained with vaccinations, social movements deny the need to be artificially immunized. During the first pandemic, health professionals faced the challenge of unaware society and widespread perception of infectious diseases as not dangerous, which consequently contributed to questioning the need for vaccination [6–8]. One of the possible reasons could be concerns about vaccine effectiveness and safety [9,10]. However, many studies indicate the benefits and safety of COVID-19 vaccination [11]. The systematic reviews and meta-analysis proved that vaccines have reassuring safety and have an impact on reducing the severe cases, symptomatic cases, and deaths caused by SARS-Cov-2 in a global view, proving its safety [9–11]. The benefits and safety were also evidenced in patients with HF [12]. One of the arguments for refusing to vaccinate in the context of COVID-19 was the short time in which the vaccine was developed and approved by the European Medicines Agency, which was regarded as an experiment on human beings [9]. Among the arguments against vaccination, the theory of the non-existence of a vaccine and saline vaccination and the lack of responsibility of pharmaceutical companies for the side effects were also mentioned [9].

In 2021, the Heart Failure Association of the European Society of Cardiology published a position paper that guides all specialists regarding vaccinations against COVID-19 in patients with HF [13]. Due to that, vaccination is indicated in all patients diagnosed with HF, even those receiving immunosuppressive therapy after heart transplantation or with frailty syndrome. Patients should receive vaccination when in optimal clinical state with the optimized treatment of HF and other comorbidities; however, all corrections should not delay vaccination [13].

It is essential to identify the individuals who refuse SARS-CoV-2 immunization- given the growing problem of vaccine hesitancy. It could help to understand their motivation better and facilitate convincing them to embrace scientifically proven methods of disease prevention. For this study, we aimed to explore the correlation between the characteristics of heart failure patients, their pre-pandemic health-related quality of life, and their decision to decline the SARS-CoV-2 vaccination.

Material and methods

Study population

The HRQoL assessment with the World Health Organization Quality of Life – BREF (WHOQoL-BREF) questionnaire is a standard procedure and was also before the SARS-CoV-2 pandemic outbreak in Poland in patients hospitalized due to HF (the 10th revision of the International Statistical Classification of Diseases and Related Health Problems code for the primary diagnosis). They were enrolled as a prospective cohort from April 2019 to February 2020. After the outbreak of the COVID-19 pandemic and the introduction of vaccines, it was decided to search for an association between clinical and epidemiological factors, pre-pandemic health-related HRQoL and vaccination hesitancy. On October 30, 2021, when every citizen of Poland had the prospect of being immunized against SARS-CoV-2, it was inspected if the patients were vaccinated at least with one dose and if they were alive with the National Health Fund database. Patients who died before October 30, 2021, were excluded. The median time from enrollment to the study to October 30, 2021, was 725 (interquartile range: 480–876) days. Subsequently, the relation of the decision not to be immunized was analyzed in the context of pre-pandemic overall HRQoL and individual HRQoL domains (somatic, psychologic, environmental, and social).

Data collection and questionnaire used

The World Health Organization Quality of Life Brief Version (WHOQoL-BREF) was used to assess the HRQoL of patients with HF. This version has been designed to enable easier and faster assessment of HRQoL. Unlike the WHOQoL instrument, which is based on 100 questions divided into six domains and 24 sub-domains [14], the WHOQoL-BREF consists of 26 questions [15]. The 24 questions are divided into four domains: physical (somatic), psychological, social, and environmental, and there are two additional questions on self-rated HRQoL and satisfaction from health status [15]. It was validated and showed acceptable reliability to substitute the original form [16]. The Polish version of WHOQoL-BREF was used in the research. The acceptable internal consistency was demonstrated with Cronbach's alpha coefficients greater than 0.70 for all domains except the social domain [17]. Questions of the form are listed in Supplementary Materials [18] (**Supplementary Table S1**).

Statistical analysis

According to their distribution, continuous variables are presented as mean ± standard deviation (SD) or median and interquartile range (25th percentile of the data – 75th percentile). Categorical variables are featured as numbers of cases and corresponding percentages in brackets. The Kolmogorov-Smirnov test was used to verify normal distribution. U Mann-Whitney or t-Student's tests were calculated to confront continuous variables according to normality and variance compliance. Pearson's chi-square was used for categorical factors (Yates correction was applied when appropriate). Logistic regression univariable models were counted to define the association of vaccination status with HRQoL, its domains and selected factors (age, sex, NYHA class, LVEF). Predictors of vaccine hesitancy significant or nearly significant ($p < 0.10$) were adjusted for age, sex, NYHA class, and LVEF using logistic regression. The lack of multicollinearity was verified. The secondary analysis then compared unvaccinated patients with an appropriate control group similar in age, sex , disease severity, and comorbidities . A propensity score matching was used to select two control cases for each unvaccinated patient from the remaining 106 patients with the closest neighbourhood method. The propensity score was calculated using logistic regression, considering age, sex, NYHA class III or IV, and diagnosis of diabetes mellitus and chronic kidney disease. A p-value < 0.05 was recognized as significant. Statistical analyses were performed with STATISTICA 13.3 and its Plus Package Tibco Software Inc., Palo Alto, CA, USA.

Ethical statements

This research was approved by the bioethics committee at the Poznan University of Medical Sciences, Poland (no. of approval: 370/20). All human participants gave informed consent to the work.

Results

General characteristics

One hundred thirty-six patients were included in the analysis. The mean age was 55.5 ± 11.2 years, 22.8% were women, mean LVEF was 27.1 ± 11.0% (**Table 1**). Most patients were NYHA class II and III (41.9% and 43.4%, respectively). Concomitant dis-

eases were quite frequent: 53.7% suffered from hypertension, 39.7% had atrial fibrillation or atrial flutter, and 22.8% diabetes mellitus, chronic kidney disease, and chronic obstructive pulmonary disease (COPD) were less frequent (14.7% and 5.9%, respectively). Patients were treated according to the European Society of Cardiology (ESC) guidelines [19]: most of the patients received loop

Table 1. General characteristics of all patients involved in analysis (n = 136). Comparison of basic pre-pandemic parameters between patients who decided to vaccinate against SARS-CoV-2 (n = 106) and those who undertook contrary decision (n = 30).

Parameter	Whole study sample (n = 136)	Unvaccinated group (n = 30)	Vaccinated group (n = 106)	p
Age [years]	55.5 ± 11.2	51.2 ± 13.2	56.6 ± 10.3	0.018
Women	31 (22.8%)	10 (33.3%)	21 (19.8%)	0.14
BMI [kg/m^2]	28.6 ± 5.5	28.4 ± 7.3	28.7 ± 4.9	0.80
non-IHD etiology	72 (52.9%)	22 (73.3%)	56 (46.7%)	0.013
SBP on admission [mmHg]	114.6 ± 19.9	115.8 ± 25.1	114.2 ± 18.2	0.69
DBP on admission [mmHg]	74 (70–80)	71.5 (68–80)	74 (70–80)	0.99
HR on discharge [beats per minute]	73.5 ± 12.1	77.1 ± 9.3	72.4 ± 12.6	0.068
LVEF [%]	25 (20–35)	20 (20–35)	25 (20–35)	0.41
Comorbidities				
DM	31 (22.8%)	5 (16.7%)	26 (24.8%)	0.46
COPD	8 (5.9%)	2 (6.7%)	6 (5.7%)	1.00
CKD	20 (14.7%)	5 (16.7%)	14 (13.3%)	0.77
Hypertension	73 (53.7%)	14 (46.7%)	59 (55.7%)	0.41
AF	54 (39.7%)	9 (30%)	45 (42.5%)	0.29
NYHA class				
I	5 (3.7%)	0	5 (4.7%)	0.29
II	57 (41.9%)	10 (33.3%)	49 (46.2%)	
III	59 (43.4%)	17 (56.7%)	43 (40.6%)	
IV	12 (8.8%)	3 (10%)	9 (8.5%)	
NYHA class III or IV	71 (52.2%)	20 (66.7%)	52 (49.1%)	0.10
Biochemical parameters				
BNP [pg/ml]	398.3 (162.9–802.3)	407.5 (140.2–770.6)	374.9 (184.1–803.65)	0.91
NT proBNP [pg/ml]	1613.5 (590–3042)	1987 (753–4449)	1604 (439–2863)	0.48
Creatinine [µmol/L]	94.4 (79–109.9)	94.5 (75.5–110.1)	94.4 (79.1–109.0)	0.71
eGFR MDRD [mL/min]	75.0 ± 23.9	74.4 ± 25.9	75.1 ± 23.4	0.89
TSH [mIU/L]	1.72 (0.97–3.12)	2.27 (1.38–2.92)	1.46 (0.93–3.12)	0.31
HRQoL				
General HRQoL (0–400)	265.6 (237.1–288.3)	264.0 (240.9–307.9)	265.7 (236.6–288.2)	0.99
Somatic domain (transformed score 0–100)	53.6 (46.4–57.1)	50 (39.3–57.1)	53.6 (46.4–57.1)	0.22
Psychological domain (transformed score 0–100)	66.7 (58.3–70.8)	70.8 (58.3–79.2)	62.5 (58.3–70.8)	0.12
Social domain (transformed score 0–100)	75 (66.7–91.7)	75 (66.7–91.7)	75 (66.7–91.7)	0.86
Environmental domain (transformed score 0–100)	71.9 (62.5–81.2)	73.4 (59.4–78.1)	71.9 (62.5–81.2)	0.88
Medications				
Loop diuretics [%]	124 (91.2%)	30 (100%)	94 (88.7%)	0.068
Thiazides [%]	19 (14.0%)	7 (23.3%)	12 (11.3%)	0.13
β-blocker [%]	131 (96.3%)	30 (100%)	101 (95.3%)	0.59
ACEI/ARB [%]	89 (65.4%)	20 (66.7%)	69 (65.1%)	1.00
ARNI [%]	33 (24.3%)	6 (20%)	27 (25.5%)	0.63
MRA [%]	115 (84.6%)	24 (80%)	91 (85.9%)	0.41
Ca-blocker [%]	9 (6.6%)	2 (6.7%)	7 (6.6%)	1.00
Statin [%]	90 (66.2%)	15 (50%)	75 (70.8%)	0.048

Abbreviations: BMI – body mass index, IHD – ischaemic heart disease, SBP – systolic blood pressure, DBP – diastolic blood pressure, HR– heart rate, LVEF –left ventricular ejection fraction, COPD – chronic obstructive pulmonary disease, CKD – chronic kidney disease, AF – atrial fibrillation (paroxysmal, permanent or persistent), NYHA – New York Heart Association Classification, BNP – B-type natriuretic peptide, NT proBNP – N-terminal pro-B-type natriuretic peptide, eGFR – estimated glomerular filtration rate, MDRD – Modification of Diet in Renal Disease, TSH – thyroid stimulating hormone, HRQoL —health-related quality of life, ACEI – angiotensin-converting enzyme inhibitor, ARB – angiotensin receptor blocker, ARNI – angiotensin receptor-neprilysin inhibitor, MRA—mineralocorticoid receptor antagonist.

diuretics, beta-blockers, angiotensin-converting enzyme inhibitor ACEIs or angiotensin receptor blockers (ARBs) or angiotensin receptor-neprilysin inhibitor (ARNI), and mineralocorticoid receptor antagonist (MRA). As of the 30th of October 2021, 77.9% of patients had been vaccinated.

Comparison of basic parameters between vaccinated and unvaccinated

Patients who decided not to vaccinate against SARS-CoV2 in the follow-up period were significantly younger and more frequently had non-IHD aetiology (**Table 1**). Cohesively with differences in aetiology, they less frequently had statin prescribed. The relation of overall HRQoL or respective domains according to WHOQoL-BREF and immunization status was not demonstrated (**Table 2**). In multivariable analysis, younger age, independent of sex, NYHA class, and LVEF, is significantly associated with not vaccinating in the logistic regression multivariable model (OR 0.950 95% CI 0.913–0,990; p = 0.014) (**Table 2**). Similarly, non-ischaemic aetiology of HF was related to vaccine hesitancy independent of age, sex, NYHA class, and LVEF (OR 0.559 95% CI 0.334–0.935; p = 0.027).

Comparison of unvaccinated patients and matched control group

The control group was matched for age, sex, NYHA class III or IV, and diagnosis of diabetes mellitus and chronic kidney disease (**Supplementary materials**, **Supplementary Table S2**). It was not significantly different from unvaccinated patients regarding overall HRQoL and any of its domains.

Discussion

The SARS-CoV-2 pandemic changed the world, including daily routines, businesses, and people's well-being. In this study, we examine the relationship between the characteristics of the HF patients, pre-pandemic HRQoL, and their resignation from vaccination against SARS-CoV-2. Understanding the reasons for the lack of vaccination acceptance is crucial for better clinician-patient cooperation. The younger age of the HF patients was a predictor of non-vaccination, independent of sex, NYHA class, and LVEF. It has yet to be studied in a distinct group of patients with heart failure. However, there are numerous reports that in the general population, younger age is associated with vaccine hesitancy [10–12,20–22], as well as in the Polish population [23,24]. There are a few possible causes for this. Firstly, they could feel less at risk of severe infection [25–28] – the risk increases with older age, which is well known [10,29–32]. However, despite their relatively young age, heart failure patients are also at risk of severe course of the disease. Therefore, there may be another explanation for their hesitancy towards vaccination.

On the other hand, there were concerns about the impact of the vaccine on future fertility [33]. Women in the perinatal period were

Table 2. Logistic regression results: univariable and multivariable after adjustment for age, sex, NYHA class, and LVEF.

Variable	Univariable OR 95%CI	p- value	Adjusted* OR 95%CI	p- value
Age (years)	0.959 (0.925–0.995)	0.026	0.950 (0.913–0.990)	0.014
Male sex	0.525 (0.215–1.281)	0.16	-	-
NYHA III/IV	1.694 (0.734–3.912)	0.22	-	-
LVEF (%)	0.994 (0.958–1.032)	0.75	-	
Non-ischaemic aetiology	0.564 (0.360–0.883)	0.012	0.559 (0.334–0.935)	0.027
Total HRQoL	0.997 (0.988–1.007)	0.60	-	-
Somatic D	0.902 (0.789–1.031)	0.13	-	-
Psychological D	1.106 (0.948–1.291)	0.20	-	-
Social D	0.925 (0.776–1.103)	0.39	-	-
Environmental D	0.988 (0.900–1.084)	0.80	-	-

* Variables significant or nearly significant in univariate analysis (with p < 0.10) were adjusted for age, sex, NYHA class, and LVEF.

Abbreviations: NYHA – New York Heart Association Classification, LVEF – left ventricular ejection fraction, HRQoL – health-related quality of life, D – domain, OR – the odds ratio (with 95% confidence interval), CI – confidence interval, p-value – probability value, indicate significant values (p < 0.05).

reluctant to vaccinate against COVID-19 due to fears about the vaccine's safety [34]. Moreover, the general belief in conspiracy theories among younger people is more abundant than in older ones [35]. Another factor could be the higher risk of myocarditis following vaccines [36], which is most prominent in younger men after the second dose of the messenger ribonucleic acid vaccine [37]. However, studies have shown that overall, the risk of myocarditis is higher after SARS-CoV-2 infection than after SARS-CoV-2 vaccination [38]. The latter may also have been the reason for higher vaccination hesitancy in the non-ischaemic aetiology of HF, as myocarditis is one of the triggers for chronic HF, and patients could be afraid of its recurrence.

This study found no differences in pre-pandemic HRQoL between vaccinated and unvaccinated patients. Minimal data on the relation between HRQoL and vaccination status were found, with no studies on HF patients. One study involved a sample of almost 30,000 Chinese in the general population [10]. Authors reported that HRQoL measured with the EQ-5D instrument was worse in the unvaccinated population [10]. In our study, we observed no significant differences. However, there are numerous differences in the study population and design. Several studies have examined the relationship between HRQoL and vaccination decisions, but none have focused on patients with heart failure [26,39–41]. Lin et al. [39], in a subgroup of general population participants aged below 50, reported significantly worse physical HRQoL in the unvaccinated people than in the vaccinated subjects. Wu et al. [40] examined heart transplant recipients with the 36-item Short Form Survey. Patients vaccinated against COVID-19 had better physical and mental components of the survey results [40]. Nguyen et al. [26] related worse HRQoL measured in lower educational attainment and lower income with COVID-19 vaccine hesitancy in a representative sample of adults in the United States. Babicki et al. [41] revealed better scores in the Manchester Short Assessment of Quality of Life survey and lower levels of anxiety measured by the Generalized Anxiety Disorder Assessment in a vaccinated sample of the general population compared to non-immunized.

This study's results are valuable because data were gathered with face-to-face interviews with consecutive hospitalised patients, providing better data quality than online surveys used in most of the mentioned studies [10,25,26,41].

When it comes to sex differences, many studies, including meta-analyses based on numerous papers, have shown that women are less willing to vaccinate [10,24,42,43]. At the same time, other reports have found no significant differences [21,44–46] or, on the contrary, found that men are more hesitant to get vaccinated [22,47]. These sex differences may be related to cultural and socioeconomic differences. In a recent study on the Polish population, based on online surveys of young adults (mean ages: 22.8 and 31.2 years compared to 55.5 years in this article), men were less likely to avoid vaccination. Considering the available meta-analysis [42], most of the analysed studies were surveys, often conducted online, that included much younger patients, especially those working in the healthcare or government sector, and asked about attitudes towards vaccinations rather than verifying actual decisions. The study by Williams et al. revealed no significant sex differences in the population of vulnerable to the severe course of COVID-19 patients – those aged above 65 years and younger patients with chronic respiratory disease [46]. This study is based on registry data, analyzing older patients with chronic disease with a poor prognosis. Therefore, extrapolating data from cited works on this population is unjustified. On the other hand, the lack of statistically significant sex differences in the results may be related to population size, so analysis of sex differences in vulnerable HF patients would require the inclusion of a larger population.

Study limitations

The article provides only a limited view of the unvaccinated patients with HF, and the results should not be generalized. However, the analyzed population was homogenous, including only HF patients prone to severe course of COVID-19. The group of non-immunized constituted a minority, which resulted in a relatively low number of unvaccinated patients in the study. Unvaccinated people should not be equalized as anti-vaccines; they were not asked to explain their motivation and did not check if some of them had permanent contraindica-

tions to vaccination with available specimens (although they are infrequent, including anaphylactic reactions to the vaccine or its ingredients [48]). However, such an approach allowed to avoid non-response bias due to resignation from the study of some unvaccinated people. Patient comorbidities and other unrecognized factors could influence HRQoL. To reduce this limitation, we used multivariable analysis and a control group matched with propensity score (**Supplementary materials: Table S2**) . Propensity score matching itself has some significant limitations. Firstly, the method may need to include all clinically essential factors that can influence the results.

Moreover, there are usually still non-significant differences between both groups regarding factors included in score counting. Furthermore, it reduces the size of the sample, decreasing statistical significance. At last, patients were assessed about two years before the pandemic had begun, and their clinical status could have deteriorated, and HRQoL could have changed. However, age differences and the aetiology of HF are stable over time.

Conclusions

Younger HF patients are more hesitant to vaccinate for COVID-19. Moreover, non-ischaemic aetiology is associated with resignation from vaccination independently from age, sex, NYHA class, and LVEF. The study found no significant association between pre-pandemic overall HRQoL, its domains and vaccination status. The group most prone to COVID-19 vaccine hesitancy in HF are relatively young patients with non-ischaemic aetiology of HF.

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Conflict of interest statement
The authors declare no conflict of interest.

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