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Diagnostic Approach to COVID-19-Associated Myocarditis in Pregnant Women

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Abstract Objective: The aim is to formulate an optimal diagnostic search algorithm for myocarditis associated with COVID-19 in pregnant women. Methods: The research was conducted as an observational, prospective, cross-sectional study, involving a comprehensive examination of patients with the active participation of a cardiologist. Various diagnostic methods were assessed using parameters such as sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), negative likelihood ratio (LR-), and diagnostic accuracy (Acc, %). Results: The study findings provide an assessment of the effectiveness of different features and parameters on MRI for detecting myocarditis in pregnant women. Notably, indicators like myocardial edema on T2 and high signal intensity on T2 images exhibit high sensitivity and accuracy, whereas pericardial shadow enlargement shows lower sensitivity but higher specificity. Verification of the diagnosis facilitated the computation of specific indicators reflecting the effectiveness of diagnostic methods for COVID-19-associated myocarditis in pregnant women. The results and established diagnostic criteria led to the proposal of a specialized Diagnostic Search and Diagnosis Verification Algorithm. Conclusion: The developed diagnostic search algorithm for confirming the diagnosis of COVID-19-associated myocarditis in pregnant women is based on the evaluation of the diagnostic effectiveness of various clinical, instrumental, and laboratory methods. This algorithm emphasizes the identification of the most informative signs of myocardial involvement, considering limitations associated with pregnancy.

Keywords COVID-19, Pregnancy, Myocarditis, Diagnostic approach

1. Introduction

In the context of cardiovascular pathology associated with coronavirus infection in pregnant women, one of the understudied aspects is myocarditis [1]. There are very few publications [1,2,3] in the literature dedicated to this issue. Clinical observations of patients have shown that a significant number of cases have been recorded where clinical and laboratory symptoms of acute myocarditis were frequently noted against the backdrop of COVID-19 in pregnant women.

Myocarditis is a significant cause of sudden cardiac death in young individuals, accounting for up to 12% of cases, according to the results of pathological studies [4]. Timely identification of myocarditis can influence the choice of tactics and treatment methods for patients and the prognosis of the disease. One of the controversial aspects in the management of patients with myocarditis currently is the question of diagnostic criteria [2,5].

Overall, the issue of diagnosing and differentially diagnosing myocarditis was relevant and not entirely resolved even before the onset of the pandemic. Literature data indicate that the sensitivity of an electrocardiogram for diagnosing myocarditis is quite low (47%). Echocardiography is primarily useful for ruling out other causes of heart failure, as there are no specific signs of acute myocarditis [6]. Cardiac magnetic resonance imaging (MRI) is currently used as a diagnostic method when there is suspicion of myocarditis; however, it should be noted that MRI is most effective when using modes with special contrast enhancement, which poses significant challenges for pregnant women [7,8]. Laboratory biomarkers of cardiac damage are elevated in a small number of patients with acute myocarditis but can help confirm the diagnosis. Troponin I has high specificity (89%) but limited sensitivity (34%) in diagnosing myocarditis [9,10,11,12]. Histological examination with biopsy material collection also does not guarantee confirmation of the diagnosis, even in cases where the technical feasibility of this procedure exists and there are no contraindications [4].

In light of the above, there is interest in research to develop optimal approaches to confirm the diagnosis in cases of suspected myocarditis associated with coronavirus infection.

Research Objective. To develop an optimal diagnostic search algorithm for COVID-19-associated myocarditis in

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pregnant women.

2. Materials and Methods

The work was conducted from 2020 to 2022. Clinical material was collected at the Republican Specialized Scientific and Practical Medical Center of Obstetrics and Gynecology under the Ministry of Health of the Republic of Uzbekistan, the 1st Republican Multidisciplinary Infectious Diseases Hospital, and temporary COVID centers in the city of Tashkent, which operated during the coronavirus infection pandemic.

Inclusion criteria for patients in the main group:

- pregnancy in the first to third trimesters of gestation;
- availability of data on COVID-19 during pregnancy, confirmed by corresponding laboratory tests (PCR and ELISA);
- presence of clinical, instrumental (echocardiography, MRI), or laboratory signs of myocarditis, the development of which has a chronological and presumptive cause-and-effect relationship with COVID-19.

Exclusion criteria for patients in the main group:

presence of chronic cardiovascular diseases in pregnant women's medical history (congenital and acquired heart defects, rheumatism, systemic diseases, etc.).

The age of women in the overall sample ranged from 18 to 40 years, with an average age of 26.6±4.1 years. The majority of women (36.4%) were in the age group below 20 years.

The study was conducted as an observational prospective cross-sectional investigation. Patient examination was comprehensive and involved the participation of a cardiologist. The diagnostic minimum for all pregnant women included, in addition to general clinical examinations, performing ECG, echocardiography, cardiac MRI (Lake Louise criteria), and special blood biochemical analyses to assess the levels of troponin I (cTnI) and N-terminal pro-B-type natriuretic peptide (NT-proBNP).

Each diagnostic method was evaluated based on several parameters, including sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), negative likelihood ratio (LR-), and diagnostic accuracy (Acc, %).

The research materials underwent statistical analysis using parametric and non-parametric methods. Accumulation, correction, systematization of the initial information, and visualization of the obtained results were carried out using Microsoft Office Excel 2016 electronic tables.

3. Results and Discussion

Table 1 presents the results of assessing the effectiveness of various diagnostic methods for COVID-19-associated myocarditis in pregnant women. The analysis of key indicators for each method showed that the ECG has high sensitivity (Se) - 96.6%, moderate specificity (Sp) - 62.9%, moderate positive and negative predictive values (PPV and NPV) - 68.3% and 95.7% respectively, as well as moderate positive (LR+) and negative (LR-) likelihood ratios - 2.6 and 0.1 respectively. The overall accuracy (Acc) was 78.1%.

If each of the diagnostic ECG parameters is analyzed, it can be noted that sustained sinus tachycardia has sensitivity (Se) - 93.1%; specificity (Sp) - 65.7%, meaning that with an ECG, 65.7% of cases of the absence of sustained sinus tachycardia in myocarditis can be correctly excluded; positive predictive value (PPV) - 69.2%, meaning the probability that a patient with the disease will not have sustained sinus tachycardia; negative predictive value (NPV) - 92%, meaning the probability that a patient with a negative diagnosis will not have sustained sinus tachycardia; overall accuracy (Acc) - 78.1%.

The ECG feature of the presence of an isoelectric or negative T-wave has sensitivity (Se) - 69%; specificity (Sp) - 98.6%; PPV - 97.6%; NPV - 79.3%; Acc - 85.2%. The ECG feature of the presence of depression or elevation of the ST segment has Se - 27.6%; Sp - 98.6%; PPV - 94.1%; NPV - 62.2%; Acc - 66.4%. The ECG feature of the presence of a pathological Q-wave has Se - 8.6%; Sp - 98.6%; PPV - 83.3%; NPV - 56.6%; Acc - 57.8%. The ECG feature of the presence of rhythm disturbances such as extrasystoles, paroxysms of supraventricular tachycardia, paroxysms of atrial fibrillation or flutter, paroxysms of ventricular tachycardia has Se - 46.6%; Sp - 94.3%; PPV - 87.1%; NPV - 68%; Acc - 72.7%. The ECG feature of the presence of conduction disturbances has Se - 41.4%; Sp - 94.3%; PPV - 85.7%; NPV - 66%; Acc - 70.3%.

These diagnostic indicators provide information on how effective the specified methods are in detecting corresponding cardiac changes on the ECG. For example, isoelectric or negative T-waves demonstrate high specificity and accuracy, while depression or elevation of the ST segment has low sensitivity and moderate accuracy in COVID-19-associated myocarditis in pregnant women.

The statistical analysis results demonstrated that echocardiography has a sufficiently high sensitivity (Se) of 79.3%, high specificity (Sp) of 97.1%, high positive and negative predictive values (PPV and NPV) of 95.8% and 85%, positive likelihood ratio (LR+) of 27.8, and negative likelihood ratio (LR-) of 0.2, with an overall accuracy (Acc) of 89.1%.

Analyzing individual echocardiographic features revealed that reduced left ventricular ejection fraction (LV EF) has a sensitivity (Se) of 62.1%, specificity (Sp) of 98.6%, PPV of 97.3%, NPV of 75.8%, and Acc of 82%. Signs of systolic dysfunction of the left ventricle (LV) showed Se of 36.2%, Sp of 98.6%, PPV of 95.5%, NPV of 65.1%, LR+ of 25.3, LR- of 0.6, and Acc of 70.3%. Enlarged heart size had Se of 17.2%, Sp of 100%, PPV of 100%, NPV of 59.3%, LR- of 0.8, and Acc of 62.5%. Areas of hypo- and akinesia of the left ventricle (LV) demonstrated Se of 25.9%, Sp of 98.6%, PPV of 93.8%, NPV of 61.6%, LR- of 0.8, and Acc of 65.6%. Increased thickness of the left ventricle (LV) walls had Se of 63.8%, Sp of 98.6%, PPV of 97.4%, NPV of 76.7%, LR+ of

44.7, LR- of 0.4, and Acc of 82.8%. Relative mitral valve insufficiency showed Se of 27.6%, Sp of 97.1%, PPV of 88.9%, NPV of 61.8%, LR+ of 9.7, LR- of 0.7, and Acc of 65.6%. Signs of pericardial effusion had Se of 10.3%, Sp of 100%, PPV of 100%, NPV of 57.4%, LR- of 0.9, and Acc of 59.4%.

These data describe the effectiveness of detecting changes in the left ventricle (LV) and other cardiac parameters on echocardiography. For example, increased thickness of the left ventricle (LV) walls exhibits high sensitivity and specificity, while enlarged heart size and signs of systolic dysfunction of the left ventricle (LV) have lower sensitivity.

MRI demonstrated very high sensitivity (Se) of 96.6%, high specificity (Sp) of 97.1%, high positive and negative predictive values (PPV and NPV) of 96.6% and 97.1%, LR+ of 33.8, LR- of 0, and overall accuracy (Acc) of 96.9%. Analyzing individual MRI features, signs of myocardial edema on T2 showed Se of 91.4%, Sp of 100%, PPV and NPV of 100% and 93.3%, LR- of 0.1, and Acc of 96.1%. High signal intensity on T2 images exhibited Se of 77.6%, Sp of 95.7%, PPV of 93.8%, NPV of 83.8%, LR+ of 18.1, LR- of 0.2, and Acc of 87.5%. Local or global hypokinesia showed Se of 74.1%, Sp of 97.1%, PPV of 95.6%, NPV of 81.9%, LR+ of 25.9, LR- of 0.3, and Acc of 86.7%. Enlargement of the pericardial shadow (a sign of pericarditis) had Se of 19%, Sp of 100%, PPV of 100%, NPV of 59.8%, LR- of 0.8, and Acc of 63.3%.

These findings allow for the assessment of the effectiveness of various features and parameters on MRI in detecting myocarditis in pregnant women. For instance, signs of myocardial edema on T2 and high signal intensity on T2 images demonstrate high sensitivity and accuracy, while the enlargement of the pericardial shadow has lower sensitivity but higher specificity.

The determination of troponin I (cTnI) in the blood showed maximum sensitivity (Se) of 100%, no specificity (Sp) - 0%, low positive predictive value (PPV) of 45.3% (insufficient specificity for myocarditis diagnosis), LR+ of 1.0, and overall accuracy (Acc) of 45.3%.

The determination of N-terminal pro-B-type natriuretic peptide (NT-proBNP) in the blood exhibited high sensitivity (Se) of 96.6%, high specificity (Sp) of 91.4%, high positive and negative predictive values (PPV and NPV) of 90.

Verification of the diagnosis allowed for the corresponding calculations to determine specific indicators reflecting the effectiveness of diagnostic methods for COVID-19-associated myocarditis in pregnant women. These indicators include sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), negative likelihood ratio (LR-), and diagnostic accuracy or precision. The obtained data were necessary for determining the most informative diagnostic test and developing a specific diagnostic algorithm for COVID-19-associated myocarditis in pregnant women.

Table 1. Results of the assessment of the effectiveness of diagnostic methods for COVID-19-associated myocarditis in pregnant women

Diagnosticindicators	**Se, %**	**Sp, %**	**PPV, %**	**NPV, %**	**LR+**	**LR-**	**Acc, %**
ECG	**96,6**	**62,9**	**68,3**	**95,7**	**2,6**	**0,1**	**78,1**
Persistent Sinus Tachycardia	93,1	65,7	69,2	92,0	2,7	0,1	78,1
Isoelectric or Negative T-waves	69,0	98,6	97,6	79,3	48,3	0,3	85,2
Depression or Elevation of ST Segment	27,6	98,6	94,1	62,2	19,3	0,7	66,4
Pathological Q-wave	8,6	98,6	83,3	56,6	6,0	0,9	57,8
Rhythm Disturbances	46,6	94,3	87,1	68,0	8,1	0,6	72,7
Conduction Disturbances	41,4	94,3	85,7	66,0	7,2	0,6	70,3
Echocardiography (Echo)	**79,3**	**97,1**	**95,8**	**85,0**	**27,8**	**0,2**	**89,1**
Reduced Left Ventricular Ejection Fraction (LV EF)	62,1	98,6	97,3	75,8	43,4	0,4	82,0
Signs of Systolic Dysfunction of the Left Ventricle (LV)	36,2	98,6	95,5	65,1	25,3	0,6	70,3
Enlarged Heart Size	17,2	100,0	100,0	59,3	-	0,8	62,5
Areas of Hypo- and Akinesia of the Left Ventricle (LV)	25,9	98,6	93,8	61,6	18,1	0,8	65,6
Increased Thickness of the Left Ventricle (LV) Walls	63,8	98,6	97,4	76,7	44,7	0,4	82,8
Relative Mitral Valve Insufficiency	27,6	97,1	88,9	61,8	9,7	0,7	65,6
Pericardial Effusion	10,3	100,0	100,0	57,4	-	0,9	59,4
MRI	**96,6**	**97,1**	**96,6**	**97,1**	**33,8**	**0,0**	**96,9**
Signs of Myocardial Edema on T2	91,4	100,0	100,0	93,3	-	0,1	96,1
High Signal Intensity on T2 Images	77,6	95,7	93,8	83,8	18,1	0,2	87,5
LocalorGlobalHypokinesia	74,1	97,1	95,6	81,9	25,9	0,3	86,7
Pericardial Shadow Enlargement, a sign of Pericarditis	19,0	100,0	100,0	59,8	-	0,8	63,3
cTnI	**100,0**	**0,0**	**45,3**	-	**1,0**	-	**45,3**
NT-proBNP	**96,6**	**91,4**	**90,3**	**97,0**	**11,3**	**0,0**	**93,8**

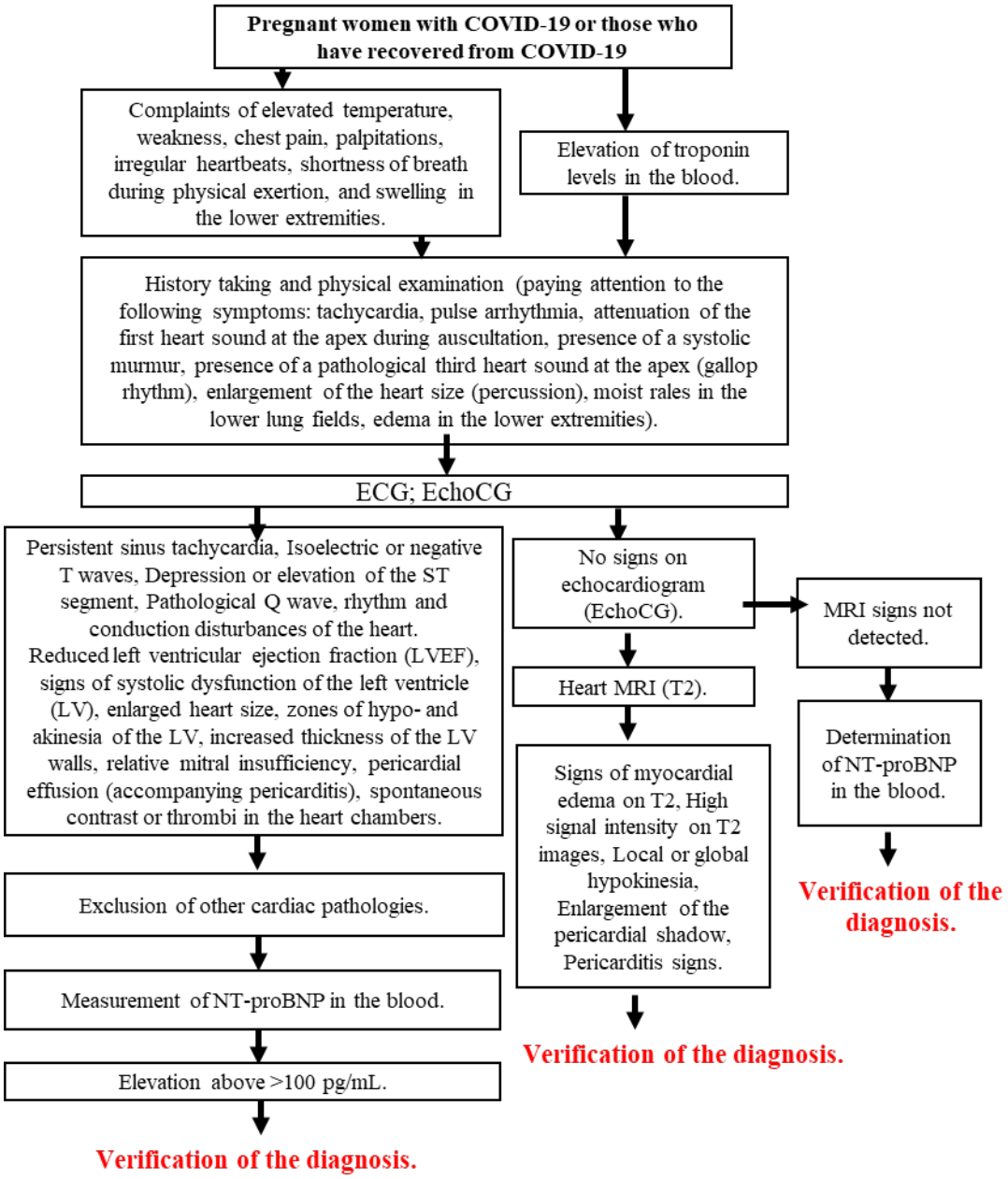

Figure 1. Diagnostic search and verification algorithm for COVID-19-associated myocarditis in pregnant women

Based on the obtained results and developed diagnostic criteria for COVID-19-associated myocarditis in pregnant women, a special Diagnostic Search and Diagnosis Verification Algorithm has been proposed, presented in Figure 1.

4. Conclusions

Thus, based on the evaluation of the diagnostic effectiveness of various clinical, instrumental, and laboratory methods, a diagnostic search algorithm was developed to confirm the diagnosis of COVID-19-associated myocarditis in pregnant women. This algorithm is based on identifying the most informative signs of myocardial involvement, taking into account limitations associated with pregnancy.

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