GEORGIAN BIOMEDICAL NEWS

VOLUME 3 ISSUE 1. JAN-MAR 2025

Impact of Chronic Heart Failure on Clinical Outcomes in COVID-19 Patients

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DOI: 10.52340/GBMN.2025.01.01.95

ABSTRACT

Background: The relationship between chronic heart failure (CHF) and COVID-19 is complex, with COVID-19 exacerbating the clinical course of CHF due to systemic inflammation, myocardial injury, and thrombotic complications. CHF patients face worse outcomes, including prolonged hospitalization, increased mortality, and heightened inflammatory responses when infected with COVID-19. While studies on this topic are available globally, there is a lack of localized data from Georgia, where cardiovascular disease (CVD) is a leading cause of mortality.

Objectives: This study analyzed the clinical outcomes, inflammatory markers, and cardiac injury in CHF patients hospitalized with COVID-19 in Georgia. The goal was to identify key factors contributing to poor outcomes in this cohort, including prolonged hospital stays, inflammation, myocardial injury, and thrombotic risks.

Methods: A cohort of 100 hospitalized patients aged 40-80 with confirmed COVID-19 infection and cardiovascular disease was studied at Chapidze Heart Hospital in Tbilisi, Georgia. Data was collected on clinical symptoms, laboratory tests (including IL-6, CRP, D-dimer, and troponin), and imaging scores. Patients were categorized into two groups: those with CHF and those without CHF. The severity of the disease, length of hospitalization, and levels of inflammatory markers and biomarkers were analyzed using descriptive statistics, ANOVA, and Mann-Whitney U tests.

Results: Patients with CHF had significantly more extended hospital stays (11.8 vs. 8.34 days, p=0.0076) than non-CHF patients. Higher levels of IL-6, CRP, ferritin, and D-dimer were observed in CHF patients, indicating a more pronounced inflammatory and hypercoagulable state. Additionally, CHF patients exhibited higher troponin levels, signifying increased myocardial injury and more severe hypoxemia was observed in later stages of hospitalization.

Conclusions: CHF is a significant predictor of poor outcomes in COVID-19 patients, with increased inflammation, myocardial injury, thrombotic complications, and hypoxemia contributing to a more severe clinical course. These findings emphasize the need for targeted management, including anti-inflammatory treatments, anticoagulation strategies, and cardiovascular support to improve clinical outcomes in this high-risk group.

Keywords: Chronic heart failure; COVID-19; CRP; D-dimer; hospital outcomes; IL-6; inflammation; myocardial injury; thrombotic complications.

BACKGROUND

The relationship between heart failure (HF) and coronavirus disease 2019 (COVID-19) is complex and multifaceted. At first, COVID-19 was primarily perceived as a respiratory disease; however, it quickly became clear that the virus often affects more than one organ system (cardiovascular).[1] For example, heart failure is considered a complication of COVID-19. However, it can also be considered the end of an acute cascade that precedes the onset of clinical symptoms, which may prove critical during treatment. Current studies have described a significant decline in HF admissions throughout the pandemic (30–66% reduction) across several nations, leading paradoxically to excess mortality, perhaps via delayed care.[2]

Furthermore, pre-existing HF is defined as an adverse predictor of the poor course of COVID-19 and a robust independent determinant of in-hospital mortality. Acute decompensation of chronic HF, as well as de novo HF, has been reported in patients hospitalized for COVID-19, primarily attributed to myocardial injury and cardiovascular complications.[3] Myocardial injury is observed in at least 10% of COVID-19 cases, increasing to perhaps 41% among critically ill patients or those with cardiovascular comorbidities. In addition, cases of COVID-19-associated acute myocarditis have been described in which LV ejection fraction is depressed and has unique histopathological features. Other studies suggest LV diastolic dysfunction and pulmonary hypertension in patients with RV dysfunction with COVID-19.[4,5]

The clinical course of COVID-19 is heterogeneous; however, having a disease spectrum that varies from mild asymptomatic cases to adverse outcomes, including ARDS and multi-organ failure. In the initial phase of the pandemic, data from China and Italy indicated that comorbidities, including HF, were associated with more severe forms of COVID-19 and higher mortality. Among 72,314 cases in a large-scale study, the case-fatality rate was 10.5% among patients with cardiovascular disease compared with an overall case fatality of 2.3%. Much later, the studies showed that between 3.3 and 21% of COVID-19 patients present with HF, where myocardial

injury, severe disease, and hospitalization were higher in patients with a history of HF.[6] For example, a multicenter retrospective analysis in NYC identified heart failure (HF) in 10.1% of patients infected with SARS-CoV-2. These patients had significantly worse clinical outcomes, including higher rates of myocardial injury and more severe disease. HF has also been shown to be a significant predictor of hospitalization during the COVID-19 pandemic (OR 4.43; 95% CI, 2.59-8.04) and other critical illnesses (OR 1.9; 95% CI, 1.4-2.5).[5] However, the relationship between HF and COVID-19 continues to evolve, especially regarding echocardiographic features and systemic inflammation factors.

Georgia continues to be the eighth highest in cardiovascular disease (CVD) mortality rate, and CVD remains the state's leading cause of death, causing more than 28,000 deaths a year — almost one-third of all Georgia deaths. The high magnitude of the CVD burden, with an estimated 165,103 potential years of life lost annually due to CVD, underscores the need for a greater understanding of how COVID-19 serves as a critical and complex exacerbating factor distorting these outcomes.[7] COVID-19 inflicts much more disastrous progression and mortality in patients with heart failure, one of the most important sequent topographies of CVD. The main goal of this study is to fill the existing knowledge gaps related to the interaction of HF and COVID-19 globally and in Georgia.

The study aims to identify risk factors associated with clinical outcomes (disposition, intensive care needed, mortality) by comparing hospitalized patients with and without HF. Comprehending the interplay is crucial for optimizing patient care, especially in cohorts at higher risk of worse outcomes. The purpose of this research also focuses on reviewing the specific events that make COVID-19 a risk in HF patients, such as systemic inflammation, myocardial injury, and decompensated cardiac function.[8]

METHODS

This study was conducted at Chapidze Heart Hospital in Tbilisi, Georgia. It included 100 patients aged 40–80 years who presented with symptoms consistent with COVID-19 and had their diagnosis confirmed via RT-PCR testing. The inclusion criteria required participants to have cardiovascular disease, laboratory-confirmed COVID-19 infection, and to be hospitalized. The severity of the disease was evaluated based on clinical symptoms, respiratory rate, oxygen saturation, and CT imaging scores reflecting lung involvement. Ethical approval for the study was granted by the Ethics Commission of Tbilisi State Medical University, adhering to the Declaration of Helsinki. All patients provided informed consent before participation.

Cytokines and other laboratory parameters

Serum interleukin-6 (IL-6) levels were analyzed using an electrochemiluminescence immunoassay (ECLIA) performed on the Roche Cobas e411 analyzer (Hoffmann-La Roche Ltd., Switzerland). The detection range for IL-6 was 1.5 pg/ml to 5000 pg/ml without requiring pre-dilution. IL-6 measurements were taken at three key points during hospitalization: upon admission, within the first week of treatment, and before discharge. A variety of additional laboratory tests were performed to gather a comprehensive dataset, including measurements of liver enzymes (ALT and AST), kidney function (creatinine), lactate dehydrogenase (LDH), coagulation markers (prothrombin time, prothrombin index, INR, aPTT, fibrinogen), and inflammatory markers (D-dimer, CRP, procalcitonin, ferritin). A complete blood count (CBC) and IL-6 assessments were also included. These tests were conducted using advanced diagnostic tools like the Roche Cobas e411 to ensure high reliability and precision.

Statistical analysis

The statistical analysis was conducted using STATISTICA software (StatSoft, Inc., USA) and followed a structured approach: (i) Descriptive statistics, including calculating means and standard deviations (SD); (ii) Grouping and analyzing patients based on gender and age to identify differences; (iii) Analysis of variance (ANOVA) to evaluate variations in the measured parameters within and between groups. Patients were categorized into two groups for analysis: those with chronic heart failure and those without (1–with HF, 2–with HF). The normality of cytokine data distribution was assessed using the Kolmogorov–Smirnov and Lilliefors tests. As many biochemical markers exhibited skewed distributions, log transformation was applied to standardize the data. Outlier values exceeding four standard deviations were excluded from the final analysis. The Mann–Whitney U test was utilized to determine differences in cytokine levels between male and female groups—a two-way repeated measures ANOVA was used to assess variations at specific intervals for time-dependent comparisons. Statistical significance was defined as a p-value of 0.05 or less.

ISSN (Online): 2720-8796 ISSN (Print): 2720-7994

RESULTS

The results of our statistical analysis are shown in Table 1. As seen, patients with CHF had a more extended hospital stay (11.8 days vs. 8.34 days; p = 0.0076) compared to those without CHF. The extended stay is likely due to the increased difficulty in managing constipation in COVID-19 patients who also have heart disease. CHF affects the heart's ability to pump blood, making it harder for these patients to cope with the inflammation, low oxygen levels, and fluid changes caused by COVID-19. Patients with CHF often stay longer in the hospital because they experience more complications, which need careful monitoring and treatment, such as lung problems requiring oxygen or blood clots needing anticoagulation therapy.

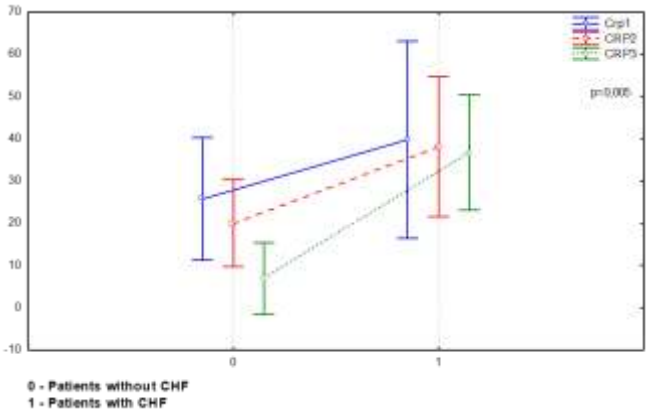
TABLE 1. Studied parameters in patients without or with chronic heart failure (CHF)

Metric	Without CHF	With CHF	p-value
Length of hospitalization, days	8.34	11.8	**0.0076**
CT scores	8.09	9.9	0.0704
Interleukine-6 (2nd measurement), pg/mL	101.19	406.4	**0.0180**
CRP (3rd measurement), mg/L	8.78	41.5	**0.0038**
Ferritin (3rd measurement), ng/mL	375.81	1080.9	**0.0212**
White blood cells (early), x10^9/L	6	7.6	**0.0262**
Platelets (late), x10^9/L	280.06	212.8	**0.0052**
D-dimer (1st measurement), mg/L	0.61	1.2	**0.0070**
Troponin, ng/mL	0.04	0.1	0.346
Oxygen Saturation (late), %	95.14	91.7	**0.0141**

55 Average CT scores of lung damage based on long-term imaging were higher in the CHF group (9.9) than in non-CHF patients (8.09), but the difference was not statistically significant (p = 0.0704). The data suggest that CHF could worsen hypoxemia and result in lung injury from secondary effects. Systemic congestion due to CHF could aggravate pulmonary edema and potentiate the effects of viral pneumonia.

We also studied inflammation markers in CHF patients, and the results showed that these patients had significantly higher levels of IL-6 than others. The total levels of IL-6, the main cytokine in the inflammatory response, were significantly higher at the second measurement (406.4 vs. 101.19 pg/mL; p=0.0180) and trended higher at the third (657.3 vs. 104.19 pg/mL; p=0.0800). Concomitantly high levels of cytokines suggest a persistent and aberrant cytokine storm in CHF patients. Significant systemic inflammation was also represented by CRP levels, especially later during hospitalization (CRP3: 41.5 vs. 8.78 mg/L; p = 0.0038) (Fig.1).

FIGURE 1. The changes in CRP level during hospitalization in patients with and without chronic heart failure (CHF)



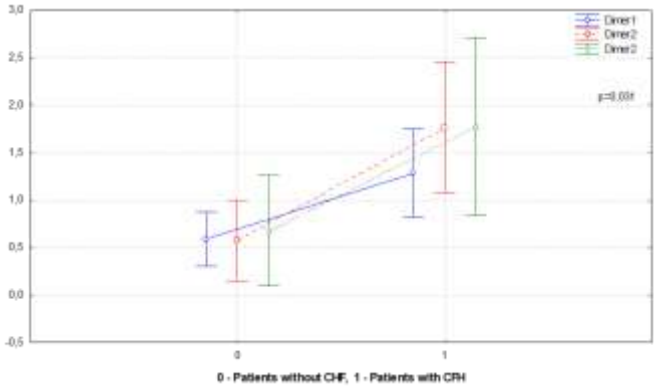
In CHF patients, high levels of CRP underline a chronic micro-inflammation process that repeated inflammatory stimuli could aggravate due to acute episodes of fluid overload and tissue hypoxia. During the third measurement, we also found that ferritin, an acute-phase reactant, was similarly higher in patients with CHF (1080.9 vs. 375.81 ng/mL; p=0.0212), consistent with altered iron metabolism and sustained inflammation. This trend could be associated with this situation's persistent inflammatory status characteristic, which COVID-19 worsened. Leukocyte counts were significantly elevated in CHF patients in the early (7.6 vs. 6.00 x10^9 /L; p=0.0262) and mid-hospitalization phases (11.1 vs. 7.16 x10^9/L; p=0.0018). Combined, all these origins and host responses may lead to exaggerated immune-stimulating activity in CHF patients that underlies high immunosuppression and the high inflammatory reactivity state that is also present, which can be worsened by associated bacterial infections due to tissue injury from low perfusion even though this immune activation, the platelet count in CHF patients was lower in the late stage of hospitalization (212.8 vs. 280.06 x10^9/L; p=0.0052). This decrease may indicate continued platelet use related to active coagulation and inflammatory mechanisms, reinforcing the venous thromboembolism risk in CHF patients.

D-dimer amounts were consistently higher in CHF patients at all three measurements (Figure 2), and the difference was significant at first (1.2 vs. 0.61 mg/l; p=0.0070), second (1.9 vs. 0.88 mg/l; p=0.0044), and third-time points (2.3 vs. 0.82 mg/l; p=0.0239) These results suggest the presence of a

ISSN (Online): 2720-8796 ISSN (Print): 2720-7994

hypercoagulable state in patients with CHF, mediated most likely through endothelial dysfunction in combination with systemic inflammation and stasis due to reduced cardiac output (Fig.2).

FIGURE 2. The changes in D-dimer Level during hospitalization in patients with and without chronic heart failure (CHF)



This increased thrombotic risk could lead to pulmonary embolism or microvascular thrombosis, both of which are associated with poor clinical outcomes in COVID-19. Myocardial Injury: CHF patients had significantly higher troponin (0.1 vs. 0.04 ng/mL; p=0.0346); hence, the more significant myocardial injury was reflected. Myocardial injury is likely worsened in CHF patients due to a constellation of factors, including systemic inflammation, hypoxemia, and increased cardiac workload. Moreover, the proinflammatory cytokines that are increased in COVID-19 (e.g., IL-6) may trigger direct myocardial injury and exacerbation of underlying heart failure.

The degree of hypoxemia in CHF patients was considerably more severe during the late phase of hospitalization (91.7% vs. 95.14%, p=0.014). The most consistent pathophysiological mechanism of this hypoxemia is a combination of reduced pulmonary function due to lung injury and impaired cardiac output.

The findings emphasize the critical role of D-dimer testing in the early identification of acute type A aortic dissection, enabling timely surgical intervention. This approach not only reduced diagnostic delays but also contributed to improved patient survival rates during the COVID-19 pandemic.

DISCUSSION

People with chronic heart failure (CHF) face more significant risks when they get infections like COVID-19. They may not always show typical heart problem signs, such as cardiogenic shock, but studies show they tend to stay in the hospital longer than those without CHF.[9] This occurs due to the incredible difficulty in treating COVID-19 in patients with heart disease. The heart's capacity to withstand additional strain brought on by inflammation, poor oxygen levels, and fluid accumulation is weakened by CHF. Because of this, these patients frequently require prolonged treatment, such as oxygen therapy and blood thinners, to treat conditions like blood clots or lung fluid. CHF patients typically have significantly elevated inflammatory markers such as IL-6 and CRP levels, particularly in hospitalization's middle and late phases. Elevated levels of IL-6 indicate a chronic inflammatory reaction, exacerbating heart issues and raising health hazards.[10,11] CHF patients also have higher levels of D-dimer, a marker of blood clots. This means they are more likely to develop severe conditions like pulmonary embolism. Research has confirmed that CHF patients face more significant clotting risks due to poor blood flow, inflammation, and reduced heart function. Therefore, using strong blood thinners is essential.[12,13] Troponin levels were higher in CHF patients, indicating more pronounced myocardial injury. Myocardial damage due to systemic inflammation, hypoxemia, and increased cardiac workload during COVID-19 may be responsible for this.[14-16] Proinflammatory cytokines like IL-6 can directly damage the myocardium by activating myocyte apoptosis and fibrosis, making previously damaged myocardium even worse through heart failure. Such results highlight the particular risk that patients with CHF face from COVID-19-related cardiac complications.[17,18] CHF patients often have worse lung function, with lower oxygen levels later in their hospital stay. This happens because viral pneumonia and a weak heart limit the lungs' ability to provide enough oxygen. These patients need careful monitoring and strong breathing support.[3,14] The reduced platelet counts in CHF patients during the later days of hospitalization imply that platelets are still being consumed at these times, consistent with ongoing coagulation and inflammatory activity. To prevent thrombotic problems and worsen clinical outcomes, the data supports the idea that CHF patients need extra support (Kok et al., 2021).[19]

Our research is significant since it focuses on CHF patients in Georgia and offers critical information about the impact of COVID-19 on them. Although CHF and COVID-19 have been the subject of numerous international studies, there is a dearth of information in this area. By examining local patients, we emphasize distinctive regional health characteristics and provide evidence that supports findings from more considerable international research. The necessity for vigorous

ISSN (Online): 2720-8796 ISSN (Print): 2720-7994

and individualized management was further supported by our study, which revealed that CHF patients in Georgia exhibit comparable patterns of inflammation, blood clotting, and heart damage, as observed in international studies.

Overall, CHF patients are more vulnerable to severe COVID-19 due to stronger inflammatory and clotting responses, worse heart damage, and reduced lung function. These findings highlight the importance of personalized care, including anti-inflammatory treatments, blood thinners, and heart and lung support. Early and aggressive treatment in future pandemics could lower deaths and long-term health problems for CHF patients.

CONCLUSIONS

This study highlights the significant burden of CHF on COVID-19 morbidity and mortality in hospitalized patients. CHF patients had prolonged hospitalization, increased systemic inflammatory response, enhanced myocardial injury and thrombotic activity, as well as worsened hypoxemia compared to non-CHF patients. The results identified CHF as an important predictor of COVID-19 severity and warrant targeted clinical management and therapeutic interventions. In CHF patients, the persistent increase in IL-6 and CRP shows an exaggerated response of circulating cytokines that may lead to multi-organ dysfunction and recovery delay. The increased production of 150 pro-thrombotic mediators, such as D-dimer with others, indicates a risk of thromboembolic complications; thus, there is a need for vigilant anticoagulation strategies. Moreover, higher troponin levels reflect important myocardial damage in CHF patients against a background of established ventricular dysfunction, which is responsible for the adverse clinical prognosis. Reduced oxygen saturations in CHF patients also reflect the dual load of injured hearts and lungs, needing more intensive respiratory assistance. The multifactorial basis for adverse outcomes during COVID-19 in CHF patients is apparent from the interplay of systemic inflammation, coagulation abnormalities, and myocardial vulnerability. These results highlight the need for individualized management approaches with anti-inflammatory therapies, anticoagulation, and advanced cardiac and respiratory support to reduce these risks in patients with CHF. These six pieces of research additionally highlight the importance of structured monitoring and early intervention in addressing some of the key challenges in this high-risk population.

Finally, CHF grossly worsens the clinical outcomes and mortality of COVID-19 by making it more complex. Such insights will advance our understanding of CHF in COVID-19 and lay the groundwork for specific therapeutic strategies to better care for CHF patients during future pandemics. Further investigations into interventions that may positively affect mortality and healthcare access for this high-risk population are warranted.

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ACKNOWLEDGMENTS

Tbilisi State Medical University supported this study under the unique program" Procedures for Encouraging Young Doctoral Students and Enhancing the Attractiveness of Doctoral Studies for Young Researchers." The Ethics Commission of Tbilisi State Medical University approved the study and complied with the Declaration of Helsinki. Tbilisi State Medical University and Chapidze Hospital established a legally certified bilateral agreement. All patients provided informed consent and voluntarily participated in the study. The authors express their profound gratitude to Chapidze Clinic for their dedicated efforts and to all staff members who worked tirelessly during the challenging times of the COVID-19 pandemic. The exceptional commitment of healthcare professionals worldwide, particularly during such unprecedented circumstances, is deeply acknowledged and valued. This work is especially significant given the considerable demands on technical, financial, and intellectual resources. The authors extend their heartfelt appreciation to all involved, recognizing that for a small country like Georgia, conducting high-level research of this caliber is both a commendable and invaluable achievement.

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ISSN (Online): 2720-8796 ISSN (Print): 2720-7994

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Georgian Biomedical News
ISSN (Online): 2720-8796 ISSN (Print): 2720-7994