

**“VICTOR BABES” UNIVERSITY OF MEDICINE AND PHARMACY
TIMISOARA**

**FACULTY OF GENERAL MEDICINE
DISCIPLINE OF PULMONOLOGY**

Ilona Eموke Sukosd



DOCTORAL THESIS

**EVALUAREA CALITATII VIETII PACIENTILOR CU
INSUFICIENTA CARDIACA SI COMPLICATII RESPIRATORII
IN CONTEXTUL COVID-19**

Scientific Coordinator

PROF. UNIV. DR. HABIL. OVIDIU FIRA-MLADINESCU

Timisoara

2024

TABLE OF CONTENTS

PERSONAL CONTRIBUTIONS	V
LIST OF ABBREVIATIONS	VI
LIST OF FIGURES	VIII
INTRODUCTION	IX
GENERAL PART	
CHAPTER 1: COPD	1
CHAPTER 2: HEART FAILURE	7
CHAPTER 3: COVID-19 AND ASSOCIATED COMPLICATIONS	14
CHAPTER 4: QUALITY OF LIFE IN CHRONIC DISEASE	20
CHAPTER 5: QUALITY OF LIFE ASSESSMENT TOOLS	25
SPECIAL PART	
I. STUDY 1: UTILITY OF KANSAS CITY CARDIOMYOPATHY QUESTIONNAIRE (KCCQ) IN ASSESSING QUALITY OF LIFE AMONG PATIENTS WITH HEART FAILURE UNDERGOING EXERCISE TRAINING REHABILITATION: A SYSTEMATIC REVIEW	32
I.1 INTRODUCTION	32
I.2 MATERIALS AND METHODS	34
I.3 RESULTS	36
I.4 DISCUSSIONS	49
I.5 CONCLUSIONS	53
II. STUDY 2: QUALITY OF LIFE OF CHRONIC HEART FAILURE PATIENTS DURING AND AFTER COVID-19: OBSERVATIONAL STUDY USING EUROQOL-VISUAL ANALOGUE SCALES	55
II.1 INTRODUCTION	55
II.2 MATERIALS AND METHODS	58
II.3 RESULTS	61
II.4 DISCUSSIONS	68
II.5 CONCLUSIONS	72
III. STUDY 3: EVALUATING THE HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH COPD AND CHRONIC HEART FAILURE AFTER COVID-19 USING THE EQ-5D AND KCCQ QUESTIONNAIRES	74
III.1 INTRODUCTION	74
III.2 MATERIALS AND METHODS	77
III.3 RESULTS	80
III.4 DISCUSSIONS	88
III.5 CONCLUSIONS	91
IV. FINAL CONCLUSIONS AND FUTURE PERSPECTIVES	93
BIBLIOGRAPHY:	97
ANNEX	I

STUDY 1: UTILITY OF KANSAS CITY CARDIOMYOPATHY QUESTIONNAIRE (KCCQ) IN ASSESSING QUALITY OF LIFE AMONG PATIENTS WITH HEART FAILURE UNDERGOING EXERCISE TRAINING REHABILITATION: A SYSTEMATIC REVIEW.

BACKGROUND

The management of heart failure and its complications has evolved significantly over the past decades, with an increasing emphasis on improving patient-centered outcomes, particularly quality of life. Heart failure, a chronic, progressive condition that is commonly associated with multiple respiratory comorbidities, not only impairs physical function but also profoundly impacts emotional and social wellbeing. As such, the assessment of QoL of life becomes a pivotal component of comprehensive management of HF. Among the tools developed for this purpose, the Kansas City Cardiomyopathy Questionnaire (KCCQ) has been widely recognized for its sensitivity and specificity in measuring the health status of HF patients. However, the effectiveness of the KCCQ in capturing the QoL improvements attributable to exercise training rehabilitation remains inadequately explored.

Despite the recognized value of exercise training, the measurement of its impact on QoL presents a challenge, attributed to the diversity of assessment tools, where each of these instruments evaluates different domains of QoL, making direct comparisons problematic. This heterogeneity in measurement complicates the aggregation of data across studies, thereby hindering a cohesive understanding of the effects of exercise rehabilitation on the QoL among HF patients. The KCCQ, with its comprehensive assessment of physical limitation, symptoms, self-efficacy, social interference, and q QoL, offers a potential solution to this challenge.

Given the variety of exercise rehabilitation modalities and the nuanced impacts these interventions can have on different aspects of a patient's life, a thorough examination of the KCCQ's performance across these dimensions is warranted. Therefore, the hypothesis of this systematic review was that the KCCQ effectively measures the QoL improvements in patients with HF participating in exercise training rehabilitation programs, including those delivered via telemedicine, and in all stages of HF, regardless of ejection fraction (EF) and clinical status. The aims and objectives of this study were to collate all studies and evaluate the application of the KCCQ in this context to compare its efficacy with other QoL assessment tools. By achieving these objectives, this review intends to contribute to the optimization of HF management practices, ensuring that they are both effective and patient centered.

SUMMARY OF FINDINGS

The systematic review compiled data from nine studies conducted across various countries like the United States, Germany, Taiwan, and Japan, between 2012 and 2022. This analysis primarily focused on employing the KCCQ to assess the quality of life in heart failure patients undergoing exercise training rehabilitation. The reviewed studies predominantly used randomized trial designs, highlighting a strong preference for rigorous methodologies to evaluate the efficacy of exercise interventions in HF care. The research settings varied from individual to group-based programs, reflecting diverse approaches in exercise rehabilitation for HF.

The participant demographic across these studies was quite varied, with a total of 3905 patients involved. The participant characteristics such as age and gender distribution varied significantly, with ages ranging from 56 to 73.1 years and a male proportion from 20% to 84.3%. This variation underscores the broad spectrum of HF populations studied. Moreover, the interventions targeted different HF characteristics, including those with preserved ejection fraction and others undergoing various intensity training programs, which points to the customized nature of exercise regimens suited to specific patient needs in HF rehabilitation.

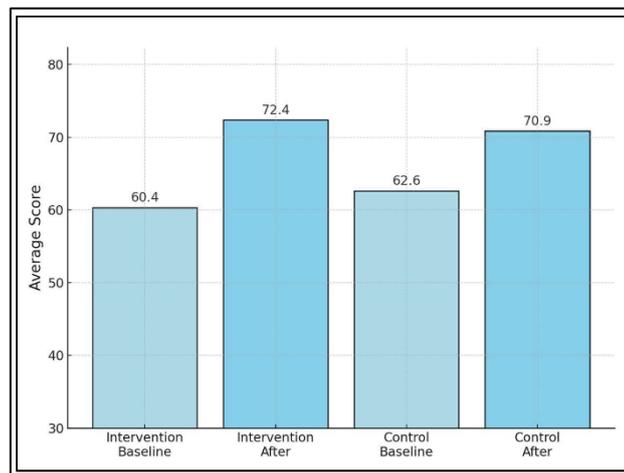
Regarding physiological measurements, left ventricle ejection fraction (LVEF) and body mass index (BMI) varied significantly across studies, indicating a focus on patients with

differing severities of HF, including those exclusively with HFpEF. Additionally, baseline biomarkers such as BNP and NT-proBNP levels were significantly high, reflecting the severe clinical profile of the HF participants. Such diversity in physical and clinical profiles highlights the tailored approaches in selecting HF patients for specific interventions based on their severity and other health characteristics.

The rehabilitation programs described in the studies were highly varied in terms of duration, frequency, and intensity of training, tailored to meet the distinct needs of the HF populations. The training programs ranged from several months to as long as 2.5 years, with most including aerobic exercises multiple times per week. This variability in exercise regimens underscores the efforts to optimize HF patient outcomes through personalized exercise plans based on individual health status and recovery goals.

Lastly, the outcomes from these studies, as measured by KCCQ and the 6 Minute Walk Test (6MWT), showed significant improvements in QoL and physical capacity. However, the effectiveness varied, with some studies showing no significant difference between intervention and control groups in QoL improvement, while others highlighted substantial benefits, particularly with high-intensity interval training. These findings emphasize the potential of tailored exercise programs to significantly enhance both the quality of life and physical health of HF patients, validating the critical role of structured exercise in managing heart failure.

Figure 1 – Average KCCQ scores comparison between intervention and control groups.



CONCLUSIONS

The KCCQ's effectiveness is highlighted by its ability to detect clinically meaningful improvements in QoL across diverse exercise modalities, including HIIT and MCT, tailored to the specific needs of heart failure populations. The consistent correlation between KCCQ score improvements and enhanced physical outcomes, such as the 6MWT, supports its reliability in capturing the nuanced benefits of exercise interventions on patient well-being. This correlation not only justifies the KCCQ's utility in clinical and research settings but also emphasizes its role in guiding the optimization of personalized exercise programs for heart failure patients.

STUDY 2: QUALITY OF LIFE OF CHRONIC HEART FAILURE PATIENTS DURING AND AFTER COVID-19: OBSERVATIONAL STUDY USING EUROQOL-VISUAL ANALOGUE SCALES.

BACKGROUND

The COVID-19 pandemic, instigated by the SARS-CoV-2 virus, has significantly altered the landscape of healthcare and impacted the quality of life (QoL) across all demographics, notably exacerbating conditions for those with chronic diseases such as heart failure. The added stress and health complications associated with COVID-19 have been particularly detrimental to these patients, whose QoL was already compromised due to their underlying conditions. This study focuses on these patients, aiming to delineate the changes in QoL during the acute phase of their COVID-19 infection and six months thereafter, comparing these findings to their pre-COVID status. This longitudinal analysis is crucial, as it provides a detailed view of the trajectory of their condition, highlighting the prolonged impact of COVID-19 on their daily lives and overall health.

To assess the QoL in this specific patient group, the study employs the EQ-5D-5L and EQ VAS tools, which are instrumental in quantifying aspects such as mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. These tools allow for a nuanced understanding of the health states through patient-reported outcomes, reflecting the severity and the breadth of issues these patients face. By evaluating these dimensions before and after the infection, the study aims to capture the direct and residual effects of COVID-19 on individuals with chronic heart failure. The findings could then potentially guide targeted interventions aimed at ameliorating the diminished QoL observed in these patients during and after their recovery from COVID-19.

The aim of this study was to evaluate the impact of a COVID-19 infection on the QoL of chronic heart failure patients during the acute phase of the infection (during their hospital stay) and at 6 months after the acute episode and to compare it with the pre-COVID phase QoL.

SUMMARY OF FINDINGS

Data shows that among all patients, the average QoL score was 75.81, which significantly dropped to 59.19 during the acute phase of COVID-19 (Q2). This represents a marked deterioration in health status across the board. By the six-month follow-up (Q3), a partial recovery was noted with the average QoL score increasing to 71.36, although it still remained lower than pre-COVID levels. The standard deviation highlights the variability among individual responses to the pandemic's progression.

Focusing on age-related differences, the study found that older patients (above 70 years) experienced a more pronounced decline in QoL compared to younger patients (under 70 years). At Q1, older individuals had a mean QoL score of 72.50 which plummeted to 53.44 by Q2, and slightly recovered to 66.50 at Q3. In contrast, younger patients started with a higher baseline QoL (79.33), which reduced less dramatically to 65.33 at Q2 and improved to 75.42 by Q3. The results, while showing a significant drop from Q1 to Q2 in both age groups, suggest a stronger resilience or quicker recovery in the younger subgroup.

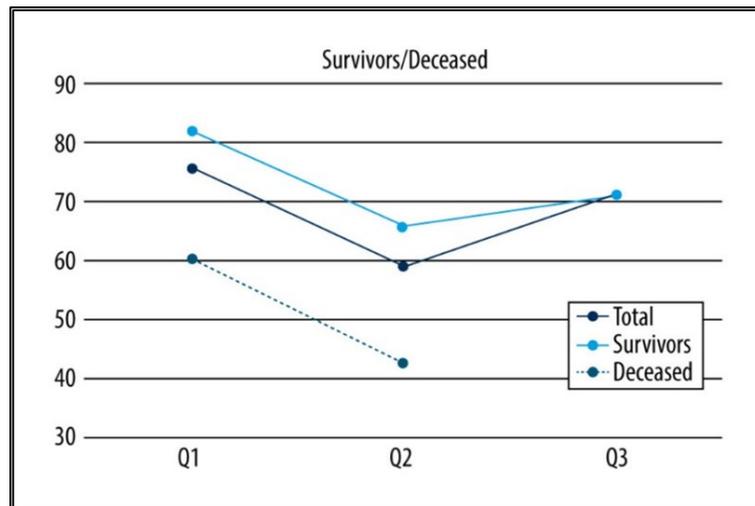
Gender disparities were also prominent, particularly during the acute phase of the disease. Female patients started with a lower QoL (Q1=71.54) compared to males (Q1=78.89) and saw a steeper decline to 49.62 at Q2. Males, although impacted, showed a lesser reduction to 66.11. This gender-based vulnerability persisted through the recovery phase, where females improved to 70.56 at Q3, closely catching up to males who recorded a Q3 score of 71.92. Interestingly, the gender differences were not statistically significant at the six-month follow-up, indicating a convergence in recovery rates.

The comparison between survivors and deceased individuals presented the most striking findings. At baseline, survivors had a significantly higher QoL (82.05) than those who

later succumbed to the disease (60.56). This trend was exacerbated during the acute phase, where the QoL of deceased plummeted further to 42.78, compared to 65.91 for survivors. These figures suggest that a lower initial QoL could be a predictive marker for a worse outcome in heart failure patients affected by COVID-19.

Statistical analysis, using the Mann-Whitney U test and Wilcoxon signed rank test, confirmed the significant impacts at various stages of the study. The longitudinal view indicated significant deterioration from pre-COVID to the acute phase, with a non-significant recovery noted overall. This study underscores the critical need for targeted interventions and enhanced monitoring of heart failure patients, particularly those older or female, during pandemics to mitigate adverse impacts on QoL.

Figure 2 – QoL in subgroups survivors/deceased pre-, acute, and post-COVID.



CONCLUSIONS

The study highlights the significant impact that chronic illnesses such as heart disease can have on both physical and psychological well-being. This underscores the need for comprehensive healthcare plans that address not only the medical needs of these patients but also their emotional and psychological well-being. Chronic cardiac diseases can cause great psychological stress on patients and their families, and a pandemic situation like COVID-19 can further worsen the physical and mental well-being of these compromised patients. Uncertainty regarding the disease's evolution further justifies the responses of questionnaires asking how you rate your current state of health, when asked in such scenarios. Ways to overcome the bias can further improve the accuracy of such studies where external factors have a major influence on patient responses. Larger studies with longer follow-up periods can help understand the time span required for regaining the pre-COVID-19 level of QoL, as in our study the 6-month results were improved but to previous levels.

STUDY 3: EVALUATING THE HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH COPD AND CHRONIC HEART FAILURE AFTER COVID-19 USING THE EQ-5D AND KCCQ QUESTIONNAIRES.

BACKGROUND

COPD itself is a major cause of disability and a critical factor in the health deterioration of individuals, particularly when co-existing with other chronic conditions such as heart failure. The presence of COPD in CHF patients can lead to worse health outcomes, increased hospitalization rates, and a more complicated disease management scenario. Understanding how COPD exacerbates heart failure symptoms and impacts the progression of CHF is crucial for developing tailored treatment strategies that address both conditions simultaneously.

Considering patients with chronic diseases, the assessment of HRQoL is paramount in understanding the full impact of illness on patient well-being. Several prominent tools are used in clinical and research settings to measure HRQoL, including the Short Form Health Survey (SF-36), the Health Utilities Index (HUI), and the Quality of Well-Being Scale (QWB). Each tool has its unique focus and method of capturing patient-reported health outcomes. Among these, the EQ-5D stands out because of its simplicity, comprehensiveness, and adaptability across diverse patient groups and health conditions. The EQ-5D questionnaire evaluates the following five dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, which collectively offer a holistic view of a patient's health status. Similarly, the KCCQ questionnaire proved to be an important and useful tool for evaluating quality of life in chronic heart disease.

The current study aims to investigate and compare the quality of life among three distinct groups of patients with different comorbid conditions, those with CHF, those with COPD, and those with both conditions, three months after SARS-CoV-2 infection. The objective is to determine the differential impact of these chronic conditions on recovery after acute COVID-19, which will provide insights for targeted healthcare interventions to enhance recovery and quality of life in these populations.

SUMMARY OF FINDINGS

In a comprehensive study examining the effects of chronic heart failure and chronic obstructive pulmonary disease on patient outcomes during COVID-19, 180 patients were categorized into three groups: those with both CHF and COPD, those with only CHF, and those with only COPD. The study revealed no significant differences in age or gender across these groups, with the average ages being 63.81, 65.22, and 66.96 years respectively. However, significant disparities were noted in smoking histories with 86.67% of the combined CHF and COPD group, compared to 13.33% of the CHF-only group and 90% of the COPD-only group being smokers.

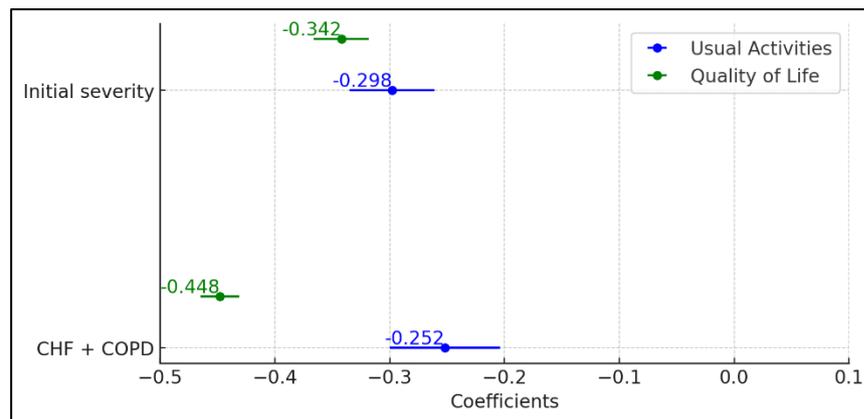
Clinical assessments at the time of COVID-19 admission showed that patients with both CHF and COPD had the lowest mean oxygen saturation at 88.7%, and the highest average body temperature at 38.4 °C. These patients also displayed the greatest extent of lung involvement on CT scans (56.2%) and the lowest ejection fractions (38.4%). Furthermore, 81.67% of this group had abnormal electrocardiograms, highlighting their severe physiological compromise compared to the other groups.

Three months post-admission, patients with both conditions continued to exhibit poorer health outcomes. Oxygen saturation in this group averaged at 92.6%, still the lowest among the groups, and their lung involvement remained higher at 22.5%. The recovery in ejection fraction was modest, reaching only 40.6%, indicating ongoing cardiac distress. Symptoms such as dyspnea affected 71.67% and tiredness 76.67% of these patients, significantly higher than in the other groups, underscoring the persistent and compounded impact of both CHF and COPD.

The patient questionnaires showed significant improvements in mobility, self-care, and usual activities over time across all groups. For example, the mobility scores in the CHF and COPD group improved from 2.87 to 2.34, indicating better functional status over time, though starting from a worse baseline. Similar trends were observed in the other health-related quality of life domains assessed by the EQ-5D.

Finally, regression analysis indicated that having both CHF and COPD was associated with significant negative effects on usual activities ($\beta = -0.252$) and overall quality of life ($\beta = -0.448$). The initial severity of COVID-19 also correlated with worse outcomes, emphasizing the lasting impact of severe acute conditions on long-term health status. These findings underscore the necessity for specialized care strategies to manage such high-risk patients effectively, particularly in the backdrop of a pandemic.

Figure 3 – Multivariate regression analysis.



CONCLUSIONS

This study underscores the significant burden of combined chronic heart failure and COPD on health-related quality of life among patients post-COVID-19. The presence of both conditions resulted in notably worse HRQoL outcomes, including longer hospital stays and lower oxygen saturation levels. Importantly, the severity of the initial COVID-19 infection significantly predicted poorer long-term outcomes. These findings highlight the necessity for tailored healthcare interventions that address the complex needs of patients with multiple chronic conditions, aiming to optimize recovery and enhance overall quality of life.