ISSN 1949-8462 (online)

World Journal of *Cardiology*

World J Cardiol 2022 December 26; 14(12): 617-664

Published by Baishideng Publishing Group Inc

World Journal of Cardiology

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NAME OF JOURNAL

World Journal of Cardiology

ISSN

ISSN 1949-8462 (online)

LAUNCH DATE

December 31, 2009

FREQUENCY

Monthly

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PUBLICATION DATE

December 26, 2022

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https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE

https://www.wjgnet.com/bpg/gerinfo/242

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https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION

https://www.f6publishing.com

World Journal of Cardiology

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World J Cardiol 2022 December 26; 14(12): 617-625

DOI: 10.4330/wjc.v14.i12.617

ISSN 1949-8462 (online)

ORIGINAL ARTICLE

Observational Study

Conduction system disorders and electro-cardiographic findings in COVID-19 deceased patients in 2021, Shiraz, Iran

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Specialty type: Cardiac and cardiovascular systems

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Al-Ani RM, Iraq; Mao EQ, China

Received: September 5, 2022
Peer-review started: September 5, 2022
First decision: October 13, 2022
Revised: October 21, 2022
Accepted: October 31, 2022
Article in press: October 31, 2022
Published online: December 26, 2022

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Abstract

BACKGROUND

Cardiac conduction disorders and electrocardiographic (ECG) changes may occur as a manifestation of coronavirus disease 2019 (COVID-19), especially in severe cases.

AIM

To describe conduction system disorders and their association with other electro-cardiographic parameters in patients who died of COVID-19.

METHODS

In this cross-sectional study, electrocardiographic and clinical data of 432 patients who expired from COVID-19 between August 1st, 2021, and December 1st, 2021, in a tertiary hospital were reviewed.

RESULTS

Among 432 patients who died from COVID-19, atrioventricular block (AVB) was found in 40 (9.3%). Among these 40 patients, 28 (6.5%) suffered from 1st degree AVB, and 12 (2.8%) suffered from complete heart block (CHB). Changes in ST-T wave, compatible with myocardial infarction or localized myocarditis, appeared in 189 (59.0%). Findings compatible with myocardial injury, such as fragmented QRS and prolonged QTc, were found in 91 patients (21.1%) and 28 patients (6.5%),

respectively. In patients who died of COVID-19, conduction disorder was unrelated to any underlying medical condition. Fragmented QRS, axis deviation, and ST-T changes were significantly related to conduction system disorder in patients who died of COVID-19 (P value < 0.05).

CONCLUSION

Conduction system disorders are associated with several other ECG abnormalities, especially those indicative of myocardial ischemia or inflammation. Most patients (73.14%) who died of COVID-19 demonstrated at least one ECG abnormality parameter. Since a COVID-19 patient's ECG gives important information regarding their cardiac health, our findings can help develop a risk stratification method for at-risk COVID-19 patients in future studies.

Key Words: COVID-19; Conduction system disorder; Electrocardiography; Atrioventricular block

Core Tip: No study has yet transpired to assess the correlation of conduction system disorders with other electrocardiographic findings in the setting of coronavirus disease 2019 (COVID-19). This paper can shed light on different conduction disorders seen in COVID-19.

Citation: Nikoo MH, Sadeghi A, Estedlal A, Fereidooni R, Dehdari Ebrahimi N, Maktabi A, Kamgar M, Mehran F, Mehdibeygi O, Esfandiari H, Taherinezhad Tayebi M, Heydari ST. Conduction system disorders and electrocardiographic findings in COVID-19 deceased patients in 2021, Shiraz, Iran. *World J Cardiol* 2022; 14(12): 617-625

URL: https://www.wjgnet.com/1949-8462/full/v14/i12/617.htm

DOI: https://dx.doi.org/10.4330/wjc.v14.i12.617

INTRODUCTION

In December 2019, a cluster of pneumonia cases was reported in Wuhan, Hubei Province, China, caused by a novel coronavirus. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) triggered the respiratory infection coronavirus disease 2019 (COVID-19). Due to the rapid transmission of COVID-19, WHO declared a pandemic on March 11th, 2020[1].

The initial studies of COVID-19 considered it to be predominantly a respiratory disease. However, recent evidence highlights multiple organ system involvements in COVID-19, including coagulation system disorder, acute kidney injury, hepatocellular injury, and cardiac and central nervous system complications[2]. The cardiac complications include thromboembolic events, heart failure, heart block, acute coronary syndrome, myocarditis, arrhythmias, and sudden cardiac death[3,4].

More recently, a growing body of literature on COVID-19 has investigated the electrophysiological changes that arise as a clinical manifestation of COVID-19 and highlighted the variety of arrhythmias observed in patients with COVID-19[5]. Moreover, multiple case reports introduce atrioventricular block as a potential manifestation of COVID-19[6-14]. In a retrospective study about the prognostic significance of electrocardiographic (ECG) findings in 319 patients with COVID-19, T-wave change (31.7%), QTc interval prolongation (30.1%), and arrhythmias (16.3%) were three most common found ECG abnormalities and atrioventricular block was presented in 3.9% of the patients[15]. First-degree atrioventricular block (AVB) was seen in 10 patients (3.3%), and second-degree AVB Mobitz type I was found in 2 patients (0.7%). In-hospital mortality risk increased with increasing abnormal ECG parameters[15]. In another study investigating the association between electrocardiographic features and mortality in COVID-19 patients, the overall prevalence of AVB was 11.8%, with deceased patients showing higher incidence than recovered patients (25% *vs* 9%)[16]. Another study conducted a rigorous patient-level analysis to determine the association of acute malignant cardiac arrhythmias, such as tachy- or bradyarrhythmias, and mortality in 140 hospitalized patients with COVID-19 and AVB was found in 5 patients, 2 of whom were associated with myocardial infarction (MI), and another 2 had metabolic abnormalities, suggesting that refractory shock was primarily responsible for conduction block, and the remaining patient had AVB in the setting of non–ST-segment–elevation myocardial infarction and newly diminished left ventricular ejection fraction[17]. However, no association between the presence of AVB and mortality was reported in these studies. Finally, it is evident that the knowledge of electrophysiological abnormalities, conduction system disorder, and particularly atrioventricular blocks is largely based on very limited data.

We designed the present study to investigate whether disruption of the conduction system can herald other ECG abnormalities in the setting of COVID-19, and whether it is associated with underlying diseases.

MATERIALS AND METHODS

This is a cross-sectional descriptive study that retrospectively reviewed demised COVID-19 patients who were admitted to Faghihi Hospital of Shiraz University of Medical Sciences from August 1st until December 1st, 2021. The inclusion criteria were all the admitted patients aged 18 or older who died with the diagnosis of COVID-19. Faghihi Hospital, located in Shiraz, Fars Province, Southern Iran, is one of the major tertiary teaching hospitals responsible for treating COVID-19 patients.

Data collection

Electronic demographic and on-paper medical records were evaluated. The data was gathered into a planned-out questionnaire. The questionnaire included demographic data, underlying diseases, and ECG factors. The data were collected by six independent practitioners. ECGs were interpreted by two cardiologists blinded to the patients' information and confirmed by an electrophysiologist.

Basic ECG parameters (rhythm, rate, axis, and ventricular hypertrophy), new findings attributable to COVID-19 (ST elevation and atrioventricular conductance disturbances), repolarization variants (J elevation, early repolarization, Brugada pattern, U wave, QTc prolongation, QT dispersion (QTd), the slope of terminal part of T wave (T-slope), depolarization abnormalities BBBs, low voltage QRS, poor R wave progression, and fragmented QRS (fQRS), QRS duration prolongation), and ECG pulmonary patterns such as S1Q3T3 were evaluated and recorded. Conduction system disorders were defined as BBBs and AVBs, and their coincidence with other ECG abnormalities was evaluated.

All ECGs were taken by the hospital's employed and trained technicians who were blinded to the purpose of the study and the patient's medical information using "Electrocardiogram Dena650" produced by SAADAT Company, Tehran, Iran.

COVID-19 was confirmed in these patients by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA detection with nasal and pharyngeal swabs, performed at admission or during hospitalization.

Statistical analysis

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS), version 19.0 (IBM corp.) for windows. Categorical variables were shown as frequency and percentages, and continuous variables as mean ± SD. Chi-square test was performed to assess the relationships between ECG parameters and patients' medical conditions with conduction system disease. The presence of conduction system disorders was considered the outcome variable, and ECG parameters were regarded as dependent variables. Then, the association of conduction system disorders and ECG parameters was calculated using logistic regression, and adjusted odds ratios were reported for univariate analysis and multivariate analysis after adjustment for the presence of other ECG parameters, sex, age, and underlying diseases. A two-sided *P* value less than 0.05 was considered statistically significant.

RESULTS

Among the 432 deceased patients, 261 (60.4%) were male, with a mean age of 67.02 (± 14.44) years and age range of 28 - 96. The most prevalent comorbid diseases were hypertension (47.9%/207 cases), diabetes mellitus (36.3%/157 cases) and cardiac diseases (35.2%/158 cases). The prevalence of other co-morbidities in order of frequency is as follows: coronary disease (18.5%/80 cases), hyperlipidemia (12.5%/54 cases), pulmonary disease (8.6%/37 cases), and chronic kidney disease (6.3/27 cases). Evaluating the association between patients' past medical conditions and conduction system disorders in patients who died of COVID-19 revealed that conduction disorders were not related to any underlying medical condition. A summary of demographic and comorbid diseases is shown in Table 1.

Regarding heart rate and rhythm, sinus tachycardia (HR > 100) and bradycardia (HR < 60) were noticed in 100 (23.1%) and 9 (2.3%) patients, respectively. Abnormal rhythms were noted in 66 (15.2%) patients. The most prevalent arrhythmia was atrial fibrillation (12.5%). Reviewing electrocardiographic findings, AVB was found in 40 (9.3%) patients. 28 (6.5%) of the patients suffered from 1st degree AVB, and 12 (2.8%) suffered from CHB. Changes in ST-T wave compatible with myocardial infarction or localized myocarditis appeared in 189 (59.0%) patients. Other abnormal conduction system findings were bundle branch blocks. Left bundle branch block was seen in 25 (5.8%) patients, and right bundle branch block was seen in 50 (11.6%) patients. Moreover, the prevalence of findings compatible with pulmonary diseases such as S1Q3T3, poor R progression, axis deviations, and low voltage ECG was 14.4% (62 patients), 41.0% (177 patients), 21.7% (94 patients), and 11.3 (49 patients), respectively.

Table 1 Association of patients' past medical conditions and conduction system disorder in coronavirus disease 2019 deceased patients

Medical condition		Patients without conduction system disorder (*n* = 317)	Patients with conduction system disorder (*n* = 108)	*P* value
Sex	Female	125 (73.1)	46 (26.9)	0.654
	Male	196 (75.1)	65 (24.9)	
Age, yr	≤ 50	46 (79.3)	12 (20.7)	0.147
	51-60	65 (81.3)	15 (18.8)	
	61-70	82 (75.2)	27 (24.8)	
	> 70	128 (69.2)	57 (30.8)	
IHD	Yes	57 (71.3)	23 (28.8)	0.477
	No	260 (75.4)	85 (24.6)	
DM	Yes	113 (72.0)	44 (28.0)	0.357
	No	204 (76.1)	64 (23.9)	
Renal disease	Yes	42 (79.2)	11 (20.8)	0.501
	No	275 (73.9)	97 (26.1)	
Pulmonary disease	Yes	23 (62.2)	14 (37.8)	0.078
	No	292 (75.6)	94 (24.4)	
Hyperlipidemia	Yes	38 (70.4)	16 (29.6)	0.503
	No	279 (75.2)	92 (24.8)	
CKD	Yes	19 (70.4)	8 (29.6)	0.648
	No	298 (74.9)	100 (25.1)	
HTN	Yes	151 (72.9)	56 (27.1)	0.504
	No	165 (76.0)	52 (24.0)	

IHD: Ischemic heart disease; DM: Diabetes mellitus; CKD: Chronic kidney disease; HTN: Hypertension.

Findings compatible with myocardial injury, such as fragmented QRS, and prolonged QTc, were assessed, with a prevalence of 21.1% (91 patients), and 6.5% (28 patients). Primary electrical cardiac diseases such as prominent J wave, Brugada pattern, and early repolarization were observed in 4.4% (19 patients), 1.2% (5 patients), and 4.2% (18 patients), respectively.

Regarding ECG parameters in patients who died of COVID-19, in univariate analysis, ST-T changes, fragmented QRS, axis deviation, presence of S1Q3T3, and poor R wave progression were significantly related to conduction system disorders in patients who died of COVID-19 (P value < 0.05, Table 2). However, when adjusted for age, sex, underlying diseases, and other ECG parameters, only fragmented QRS, ST-T changes, and axis deviation were significantly associated with conduction system disorders.

DISCUSSION

This is a single-center study conducted retrospectively. The small sample size of a single-center could result in less generalizability. Unfortunately, assessing the presence of myocarditis was not possible due to the absence of data on serum markers and echocardiographic examination for most of our enrolled patients. This descriptive study aims only to report the incidence of ECG abnormalities and their relationship with conduction system disorders in patients who died of COVID-19. To determine which conduction disorders are independently associated with mortality, case-control or cohort studies are recommended.

By reviewing previous literature, mounting evidence supports the association between influenza pneumonia and heart diseases, and it has been reported that influenza have been associated with a six-fold increased risk of acute MI[18,19]. COVID-19 also directly and indirectly affects the cardiovascular system and the heart in particular[3]. Previous studies have proved that COVID-19 augments the risk of cardiovascular complications, including dysrhythmias, both in the short and long term, and given that

Table 2 Electrocardiographic parameters in conduction system disease in COVID-19 deceased patients

ECG parameters		Patients without conduction system disorder (*n* = 317)	Patients with conduction system disorder (*n* = 108)	Univariate OR (95%CI for OR)	*P* value	Adjusted[1] odds ratio (95%CI for OR)	*P* value
Fragmented QRS	Yes	53 (58.2)	38 (41.8)	2.63 (1.61-4.30)	< 0.001	2.27 (1.23, 4.16)	0.008
	No	268 (78.6)	73 (21.4)	1	-	1	-
ST-T change	Yes	125 (66.1)	64 (33.9)	2.14 (1.38-3.31)	0.001	1.81 (1.07, 3.08)	0.030
	No	196 (80.7)	47 (19.3)	1	-	1	-
Rhythm	Sinus rhythm	279 (76.2)	87 (23.8)	1	-	1	-
	AF	34 (63.0)	20 (37.0)	1.89 (1.03-3.45)	0.039	1.70 (0.78-3.71)	0.179
	Others	8 (66.7)	4 (33.3)	1.60 (0.47-5.45)	0.450	0.75 (0.15, 3.62)	0.700
Rate	Bradycardia (HR < 60)	5 (55.6)	4 (44.4)	2.10 (0.55-8.01)	0.279	1.67 (0.31-9.06)	0.554
	Normal (60 < HR < 100)	234 (72.4)	89 (27.6)	1	-	1	-
	Tachycardia (HR > 100)	82 (82.0)	18 (18.0)	0.58 (0.33-1.02)	0.057	0.55 (0.27, 1.09)	0.086
Axis deviation	Normal	283 (83.7)	55 (16.3)	1	-	1	-
	Left	14 (48.3)	15 (51.7)	5.51 (2.52-12.07)	< 0.001	3.74 (1.50-9.33)	0.005
	Right	24 (36.9)	41 (63.1)	8.79 (4.92-15.71)	< 0.001	7.67 (3.95-14.88)	< 0.001
QTc 1	< 500	211 (75.1)	70 (24.9)	1	-	1	-
	> 500	110 (73.3)	40 (26.7)	1.10 (0.70-1.72)	0.691	0.94 (0.53, 1.66)	0.819
QTc 2	Male ≤ 440 and female ≤ 460	300 (74.4)	103 (25.6)	1	-	Not included due to collinearity with the above variable	
	Male > 440 and female > 460	21 (75.0)	9 (25.0)	0.97 (0.40-2.35)	0.948		
QTd	< 40	45 (81.8)	10 (18.2)	1	-	1	-
	≥ 40	276 (73.2)	101 (26.8)	1.65 (0.80-3.39)	0.176	1.42 (0.58-3.47)	0.446
J wave	Yes	13 (68.4)	6 (31.6)	1.35 (0.50-3.65)	0.550	0.98 (0.28-3.49)	0.978
	No	308 (74.6)	105 (25.4)	1	-	1	-
U wave	Yes	32 (71.1)	13 (28.9)	1.20 (0.60-2.38)	0.605	1.10 (0.47, 2.63)	0.815
	No	289 (74.7)	98 (25.3)	1	-	1	-
Early repolarization	Yes	15 (83.3)	108 (26.1)	0.57 (0.16-2.00)	0.377	1.00 (0.26-3.93)	0.998
	No	306 (73.9)	108 (26.1)	1	-	1	-
T slope	< 30	12 (75.0)	4 (25.0)	1	-	1	-
	30-60	302 (74.6)	103 (25.4)	1.02 (0.32-3.24)	0.969	0.79 (0.21, 2.98)	0.728
	> 60	7 (63.6)	4 (36.4)	1.71 (0.32-9.11)	0.527	1.87 (0.249-14.01)	0.551
S1Q3T3	Yes	38 (61.3)	24 (38.7)	2.05 (1.17-3.61)	0.012	1.83 (0.92-3.64)	0.086
	No	283 (76.5)	87 (23.5)	1	-	1	-
Low voltage QRS	Yes	42 (85.7)	7 (14.3)	0.45 (0.20-1.03)	0.058	0.38 (0.14-1.05)	0.063
	No	279 (72.8)	104 (27.2)	1	-	1	-
PRP	Yes	121 (68.4)	56 (31.6)	1.68 (1.09-2.60)	0.019	1.32 (0.77-2.26)	0.317
	No	200 (78.4)	55 (21.6)	1	-	1	-

[1]Adjusted for age, sex, underlying diseases, and other electrocardiography findings.
AF: Atrial fibrillation; HR: Heart rate; QTc: Corrected Q-T interval; QTd: Q-T interval dispersion; T slope: T-wave terminal slope; PRP: Poor R wave progression.

they are the most prevalent viral pneumonia at the time of writing this article, their complications impose a considerable burden on healthcare[20]. This study discusses the prevalence of arrhythmias and conduction system disorders in patients with COVID-19.

The mechanism underlying the development of arrhythmias in COVID-19 has not been specified. However, potential triggers are as follows[21]. First, electrolyte imbalance caused by COVID-19 symptoms such as diarrhea and complications such as acute kidney injury or severe sepsis is a notable cause[22]. Second, SARS-CoV-2-induced myocardial injury due to the upregulation of angiotensin-converting enzyme 2 (ACE2) receptor during viral invasion and severe hypoxia-induced myocyte necrosis are other potential causes of arrhythmias[23]. In addition, acute myocardial infarction due to demand/supply imbalance and arterial thrombotic events secondary to hypercoagulable state can cause acute arrhythmias[24,25]. Stress and cytokine storm in relation to sepsis and high inflammatory state is another potential mechanism[21]. Moreover, prolonged QTc-induced malignant ventricular arrhythmias and channelopathies induced by off-label medical therapy and antiviral therapy could be introduced as direct triggers of arrhythmias[26].

The most remarkable result acquired from the data was the prevalence of advanced AVB in patients who died of COVID-19. This prevalence was not yet assessed in deceased COVID-19 patients; however, the reported prevalence of AVB in COVID-19 patients ranged from 3 to 12% in different studies[14,15]. All types of AVBs were seen in 40 (9.3%) cases in our study. Among those with AVB, 12 (2.8%) cases suffered from 3rd degree complete heart block (CHB). CHB has been assumed to be a rare ECG feature of COVID-19, and this novel finding has only been reported in a few case studies[6,8,10].

Another interesting result was the high prevalence of fragmented QRS, prominent J wave, and ST-T wave change. These parameters can be directly related to myocardial injury induced by SARS-CoV-2 infection. In addition, the high incidence of S1Q3T3 and LBBB in this study could indicate pulmonary involvement in deceased COVID-19 cases. S1Q3T3 is a relatively specific pattern for pulmonary thromboembolism and a potential cause of death[27].

Moreover, ST-T changes, fragmented QRS, and axis deviation were significantly related to conduction disorders in our patients, suggestive of new-onset myocardial infarctions during the infection and increased mortality risk. Our study provides further evidence for the observed ST-T wave changes in COVID-19 patients, suggestive of myocardial infarction or localized myocarditis[28]. This indicates that disturbances in the conduction system are associated with COVID-19-related myocardial injury, either ischemic or inflammatory.

Compatible with previous studies, atrial fibrillation was the most prevalent arrhythmia[29]. It is notable that we witnessed these findings in patients who had no evidence of arrhythmia before their admission. Therefore, we suggest future studies to focus on the mechanism of arrhythmogenicity of COVID-19 and discover the proper screening and therapeutic strategies mitigating the adverse outcomes of COVID-19-induced arrhythmias.

CONCLUSION

To the best of our knowledge, this is the first study that exclusively assessed expired COVID-19 patients and illuminated the AVB and BBB prevalence among them. The myocardial injury appears to be closely associated with conduction system disorders and has a role in COVID-19 morbidity and mortality. Our findings can help develop a risk stratification method for susceptible COVID-19 patients in future studies. Consequently, we recommend that health policymakers should consider separate catheterization laboratories that provide service only to COVID-19 patients.

ARTICLE HIGHLIGHTS

Research background

Coronavirus disease 2019 (COVID-19) is associated with a wide range of cardiovascular compilations, especially in severe cases. Electrocardiogram is a cheap, useful and readily available tool to investigate these complications.

Research motivation

We designed this study to better understand the conduction system disturbances in the setting of severe COVID-19.

Research objectives

To discover the prevalence and types of conduction system disorders in COVID-19 deceased patients as a population representing severe COVID-19.

Research methods

All electrocardiograms of patients who died of COVID-19 in our center were analyzed, and any abnormalities were reported.

Research results

Changes in ST-T were the most common (59%), which indicate myocardial infarction or localized myocarditis. Also, 21.1% showed fragmented QRS and prolonged QTc indicative of myocardial injury. Atrioventricular block (AVB) was found in 9.3% of patients.

Research conclusions

Among patients who expired from COVID-19, ST-T changes are the most common which heralds myocardial damage. Conduction disturbances like AVBs are also important findings and are associated with myocardial damage.

Research perspectives

ECG findings in COVID-19 are variable but mostly involve two pathologies, myocardial damage and conduction system disturbances. Clinicians should be aware of these two complications in the setting of COVID-19 and future research should focus on devising preventive measures to mitigate the cardiovascular complications of COVID-19.

ACKNOWLEDGEMENTS

The present study was supported the Vice-chancellor for Research, Shiraz University of Medical Sciences, Shiraz, Iran. This study is a part of the thesis by the author, Alireza Sadeghi, for obtaining a medical doctor degree in Shiraz University of Medical Sciences. We sincerely thank Professor Firoozeh Abtahi, dean of research operations of the cardiovascular department, for facilitating the bureaucratic procedures of this survey. We also acknowledge Erfan Taherifard for guidance in composing and revising the manuscript. The authors also wish to express their sincere gratitude to Maryam Saket, head of the archives section in Faghihi hospital, and her staff, who dedicatedly provided us the required data.

FOOTNOTES

Author contributions: Nikoo MH contributed to conceptualization, design, data curation, final edit and review, and project administration; Sadeghi A, Estedlal A, and Fereidooni R contributed to writing of the primary draft, final editing and review; Ebrahimi N, Maktabi A, Kamgar M, Mehran F, Mehdibeygi O, Esfandiari H, and Taherinezhad Tayebi M contributed to data collection; Heydari ST contributed to formal analysis and design; all the authors verify the data and are accountable for all aspects of the work.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of Shiraz University of Medical Sciences (Approval No. IR.SUMS.MED.REC.1400.270).

Informed consent statement: The informed consent was waived from the patinets.

Conflict-of-interest statement: The authors declare that they have no competing interests.

Data sharing statement: Data are available for academic researchers *via* the research deputy of Shiraz Medical School (med_thesis@sums.ac.ir) upon reasonable request.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

Country/Territory of origin: Iran

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S-Editor: Chen YL
L-Editor: Ma JY- MedE A
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World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2022 December 26; 14(12): 626-639

DOI: 10.4330/wjc.v14.i12.626

ISSN 1949-8462 (online)

ORIGINAL ARTICLE

Randomized Clinical Trial

Impact of the virtual anti-hypertensive educational campaign towards knowledge, attitude, and practice of hypertension management during the COVID-19 pandemic

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Specialty type: Cardiac and cardiovascular systems

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Wondmagegn H, Ethiopia; Zhang JW, China

Received: August 13, 2022
Peer-review started: August 13, 2022
First decision: September 5, 2022
Revised: September 11, 2022
Accepted: November 22, 2022
Article in press: November 22, 2022
Published online: December 26, 2022

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Abstract

BACKGROUND

One of the efforts to reduce hypertension rates in the community is through an educational campaign that refers to the NIH's National Heart, Lung, and Blood Institute curricula or abbreviated as NHLBI. However, during the coronavirus disease 2019 (COVID-19) pandemic, one of the hardest hit areas is health promotion, and there is a significant obstacle regarding the most effective way to transfer knowledge, attitude and practice towards society without transmitting the virus.

AIM

To evaluate the impact of the virtual anti-hypertensive educational campaign towards knowledge, attitude, and the practice of hypertension management in the primary care setting during the COVID-19 pandemic.

METHODS

An online action research with a randomized crossover-controlled trial using a pretest-posttest control group design. The study was conducted in October 2020-April 2021. The population in this study were patients with hypertension who were treated in the Mojo primary health care setting. A purposive sampling technique was done to receive 110 participants using an online questionnaire and invitation letter.

RESULTS

A total of 110 participants were included in the analysis, 55 in the intervention group and 55 in the control group. Following the Virtual Anti-Hypertensive Educational Campaign implementation, the only parameter that showed significant improvement was knowledge and attitude ($P < 0.001$). There is no significant change in the practice parameters ($P = 0.131$).

CONCLUSION

The Virtual Anti-Hypertensive Educational Campaign implementation in our study population seems to be effective to improve knowledge and attitude of participants, nevertheless, this program seems to be ineffective to improve the practice of hypertension management aspect in participants. Future study with longer durations and more comprehensive programs need to be done to scrutinize the clinical impact of this program nationwide.

Key Words: Hypertension; Awareness; Knowledge; Attitude; Practice; Public health

Core Tip: In the unprecedented times of the coronavirus disease 2019 (COVID-19) pandemic, many offices shut down across the world. Onsite classes and events were postponed and as a result, the educational health campaign has changed dramatically. With the distinctive rise of e-learning, health campaigns can be undertaken remotely by digital platforms. With this sudden shift away from the conventional campaign, in many parts of the globe, some are wondering whether the adoption of virtual learning will continue to persist post-pandemic and how such a shift would impact the perception and transfer of knowledge towards hypertensive patients. To keep the community safe, but still well-informed about the dangers of hypertension and how to build a healthy lifestyle, we decided to create a Virtual Anti-Hypertensive Educational Campaign. The importance of this paper is to evaluate the impact of the Virtual Anti-Hypertensive Educational Campaign towards knowledge, attitude, and the practice of hypertension management in the primary care setting during the COVID-19 pandemic.

Citation: Andrianto A, Ardiana M, Nugraha RA, Yutha A, Khrisna BPD, Putra TS, Shahab AR, Andrianto H, Kikuko IH, Puspitasari AN, Hajjrin MR. Impact of the virtual anti-hypertensive educational campaign towards knowledge, attitude, and practice of hypertension management during the COVID-19 pandemic. *World J Cardiol* 2022; 14(12): 626-639

URL: https://www.wjgnet.com/1949-8462/full/v14/i12/626.htm

DOI: https://dx.doi.org/10.4330/wjc.v14.i12.626

INTRODUCTION

From early 2020, the world has been living in a state of public health disruption due to the novel coronavirus disease 2019 (COVID-19) pandemic[1]. COVID-19 has added various challenges and changes to human life worldwide, causing an unprecedented impact on human health, lifestyle, and social life, and has affected the local and international economy[2]. In Indonesia, schools and offices have been suspended during the pandemic and many people have been staying at home[3]. Amid the confinement due to the COVID-19 pandemic, offline activities involving large numbers of people were nearly interrupted[4]. Educators are scrambling to adapt to social distancing (self-quarantine) and the durations of quarantine and social isolation are unpredictable[5].

The COVID-19 pandemic also highlights the fact that the lack of health literacy is an underestimated public health problem in Indonesia[6]. The lack of health literacy is linked to the spread of communicable disease and also gives an opportunity to the increased burden of several non-communicable diseases such as hypertension and cardiovascular diseases[7]. There is no doubt that during times of quarantine and social isolation, food accessibility and availability may be affected, which in turn affects diet quality[8]. Levels of physical activity were also negatively affected during self-isolation and quarantine, due to closure of sport facilities and parks, overall movement restrictions have reduced the ability to engage in physical activity[9]. This was accompanied with an increase of sedentary behaviors related to self-isolation and quarantine, including distance learning and telework [10].

Hypertension can be prevented or delayed through mitigation of modifiable risk factors, such as healthier eating, weight loss, and increased physical activity[11]. Efforts to improve population health literacy can bring spectacular benefits in terms of building the populations' resilience to health threats, promoting healthy lifestyle changes, and empowering individuals to make a well- informed health decision[12]. One of the effective non-pharmacologic strategies to combat hypertension is a dietary

campaign[13]. One of the examples of effective diet to combat hypertension is Dietary Approaches to Stop Hypertension (DASH) Diet. DASH diet is one of the flexible and balanced dietary plans that is proven to reduce blood pressure[14]. The DASH eating plan requires no special foods and instead provides daily and weekly nutritional goals. Current evidence showed that a DASH diet could reduce blood pressure within 2 to 4 wk (by 6 mmHg systolic and 3 mmHg diastolic)[15-17]. Unfortunately, the COVID-19 pandemic which locked down policy in Indonesia have disrupted the opportunity for the conventional health education process and has increased the necessity to find alternative health campaign strategies[18].

Therefore, we try to build the anti-hypertensive educational campaign based on the DASH diet. Since the pandemic will undeniably continue to disrupt the conventional health campaign activity, some virtual alternatives are being used to continue health education activities. As we face the prospect of many urban people who have easy access to the internet and social media, we try to assess their feasibility and determine whether they are adequate in getting health education virtually.

Objective

Our teams designed a virtual anti-hypertensive educational campaign curriculum for community health care advocates in the community health care of the Mojo District, Surabaya, Indonesia to identify and prevent health risks of hypertension. The first goal is to conduct research on the risks of hypertension and identify an educational model for community health advocates. The second goal is to educate people to improve health literacy in the field of hypertensive healthy plans. The virtual anti-hypertensive educational campaign aims to help dispel misinformation while promoting healthy lifestyle recommendations and medical guidelines set by the Ministry of Health of the Indonesian Government and Indonesian Cardiologist Association. Therefore, the purpose of this paper is to highlight the impact of the virtual anti-hypertensive educational campaign towards knowledge, attitude, and the practice of hypertension management during the COVID-19 pandemic.

MATERIALS AND METHODS

Ethical approval

In order to conduct the study, approval was obtained on July 1st, 2020 with a decision of the Bioethics Committee at the Faculty of Medicine Universitas Airlangga (Ref. number 532/UN3/2020) under the name of Andrianto as the principal investigator. All participants provided virtual informed consent prior to participating in the study, without identifiable data. The schedule of enrollment, intervention and measurements according to Standard Protocol Items: Recommendations for Intervention Trials requirements. The study's data were collected in accordance with the Helsinki Declaration. The consent form documented the aims, nature, and procedure of the study. Anonymity and confidentially were strictly maintained.

Study design and study setting

The trial was a randomized double-blind, placebo controlled, crossover design. The study was completed over a 6 mo duration (1 October 2020-30 April 2021) of the virtual anti-hypertensive educational campaign with randomization (1 mo); treatment period one (2 mo); washout (1 mo); and finally, treatment period two (2 mo). Subjects were randomly assigned among patients with established hypertension using a pre-test, post-test, controlled group design. This study was conducted in October-December 2020 in the Mojo District, Surabaya City. We conducted an online survey from October to December, 2020. The survey involved an online questionnaire that was distributed virtually, either by email or by WhatsApp and social media, to more than 500 hypertensive patients in the Mojo district of Surabaya, Indonesia, of which, 110 participants actively replied. The questionnaire was self-administered without intervention by the authors or any specific person, and it did not contain any identifying data of the participants to ensure confidentiality. Questionnaires with incomplete information or missing data were excluded from the analysis. Completed paper questionnaires were collected anonymously to ensure confidentiality and to prevent any response bias. Unreturned or uncompleted questionnaires were recorded as missing. Participants were not aware of the study aim or outcomes to reduce the risk of any possible bias. The survey included only hypertensive patients who were living in the Mojo district of Surabaya city.

Study tool and study protocol

In accordance with the aim of the study, a questionnaire consisting of "knowledge, attitudes, and practices" was prepared using the literature. The questionnaire covered participants' basic demographic data, such as their sex, age, and marital status, as well as general questions about their financial status, occupation, level of education, internal displacement, history of health problems, psychological illness, and learning disabilities, if present. The questionnaire also addressed their experience with telemedicine, including questions related to sphygmomanometer usage proficiency, type and quality of

sphygmomanometer used, daily antihypertensive drugs, and daily diets. We improved the previous questionnaire by conducting it virtually and adapting local wisdom for our hypertensive patients. Items in the questionnaire were then modified and new items were added based on the qualitative data collected in these interviews. We developed the questionnaire in Bahasa and tested its internal consistency in a pilot study comprising 40 subjects. We revised the questionnaire several times to ensure high internal consistency, which was determined by Cronbach's alpha. The sample from the pilot study was not included in the final analysis. We provided the questionnaire in Bahasa to accommodate respondents' native language. After designing the Bahasa version, three independent translators translated the questionnaire separately and compared the three versions to reach a consensus after consultation with a linguistic expert and three authors to ensure the same intended meaning. The "knowledge, attitudes, and practices" questionnaire had a high internal consistency, as evidenced by Cronbach's alpha values of 0.88 and 0.86 for the Bahasa versions.

Participants

The population in this study were all patients with hypertension who were treated in the Mojo primary health care setting or referred by general practitioners in the Mojo district of Surabaya city. Participants included in this study were adults, aged 18 years and older, with a grade I hypertension according to the ESC/ESH 2018 guideline (SBP of 140 to 159 mmHg and DBP of 90 to 99 mmHg) based on the average BP across three screening visits. Persons with a prior diagnosis of coronary heart disease, renal insufficiency, poorly controlled dyslipidemia, diabetes mellitus or heart failure were excluded from participation. Participants who have already taken more than 1 antihypertensive agent or insulin, education level higher than graduate school, subjects with cognitive impairment, and subjects who were unable to join or complete 7 virtual sessions had been excluded. Invitation letters to the study were sent to all subjects who met eligibility criteria.

Sample size

To detect a blood pressure difference of 10 mmHg (clinically relevant) with 90% power and $\alpha = 0.05$, 40 patients are needed in crossover design[19]. Silagy *et al*[20] detected a difference of 10 mmHg with less than 50 patients per group in a parallel trial. We have carried out a pilot cross-over virtual educational campaign study that detected a difference of 10 mmHg units with 40 patients, confirming that cross-over design substantially reduced the sample size required (unpublished results). To account for drop-out or non-compliance, this trial included 55 participants in the intervention group and 55 participants in the control group. Sample size calculation was performed with nQuery 7.0. Purposive sampling techniques were done to receive 110 participants.

Intervention

After the Indonesian government called for cooperation of its residents to practice social distancing measures, the Department of Cardiology and Vascular Medicine Universitas Airlangga created an approachable Virtual Anti-Hypertensive Educational Campaign using social media and a webinar-based platform to educate hypertensive patients in the Mojo District of Surabaya. The virtual campaign consisted of 7 sessions, between 1 October, 2020 and 30 April, 2021. The virtual campaign was held once a week and the duration of each session was approximately 2 h. The virtual anti-hypertensive educational campaign had been focusing on hypertensive prevention strategy towards society. The curriculum of our virtual anti-hypertensive educational campaign was based on NIH's National Heart, Lung, and Blood Institute curricula, with several improvisations in the usage of Bahasa and virtual content based on local wisdom. The schedule and subjects for the Virtual Anti-Hypertensive Educational Campaign can be seen in (Table 1).

The intervention and control periods were 2 mo, designed to coincide with the length of the virtual anti-hypertensive educational campaign curricula. The control arm was given a standard medical check and medical treatment without any anti-hypertensive education. Subjects were assigned to the group by random allocation based on block to assign sample numbers equally to each group and assign the block.

Outcomes

The knowledge concerning high blood pressure was measured using a 22-item Hypertension Knowledge Level Scale (HK-LS), from a previous study regarding patient knowledge of hypertension translated into Bahasa Indonesia[21,22].

The attitude towards hypertension was assessed with a 28-item instrument called Treatment Adherence Questionnaire for Patients with Hypertension (TAQPH), using a 4-point Likert-type scale (alpha-reliability = 0.74) in the Bahasa version[23].

Practice was assessed by the 8-item Morisky Medication Adherence Scale (MMAS-8) translated into Bahasa[24].

Data analysis

We used descriptive statistics to examine respondents' characteristics and responses using frequencies and percentages. We described categorical variables as frequencies and percentages, and continuous

Table 1 Schedule for virtual anti-hypertensive educational campaign

No.	Sessions	Subjects	Duration
1	Session 1	Hypertension awareness campaign, definition and how to measure home blood pressure monitoring, understanding the silent killer of hypertension: dangerous effect towards cardiovascular diseases	2 h
2	Session 2	Healthy lifestyle: focusing on health diet, physical activity, and avoiding stress. Health benefits of the DASH eating plan and why DASH eating plan works	2 h
3	Session 3	Dietary recommendation for hypertension: getting started on DASH (live demo)	2 h + 2 h of live demo
4	Session 4	Tips to reduce salt and sodium intake (live demo: weigh salt before cooking)	2 h + 2 h of live demo
5	Session 5	Meal plans, measure each ingredients and oil products for cooking (live demo)	2 h + 2 h of live demo
6	Session 6	Living with the DASH eating plans. How to choose grains, fruits, vegetables, low fat and non-daily product (live demo)	2 h + 2 h of live demo
7	Session 7	How to educate others about dispelling misinformation in the healthy diet	2 h

variables as mean (SD) or median (lower-upper) values, as appropriate. The Kolmogorov-Smirnov test revealed that several variables did not follow a normal distribution. We conducted independent sample *t*-tests, paired sample *t*-tests, Wilcoxon signed rank tests and the Mann-Whitney *U*-test to identify differences between two groups of continuous variables. The Pearson's and Spearman's rank correlation coefficient was used to explore the relationship between knowledge, attitudes, and practice scores in respect to the virtual health education program and the studied variables. We performed all statistical analyses using SPSS version 25.0 (IBM Corp., Armonk, NY, United States).

Study validity and bias

Selection bias was reduced by ensuring high participation rates and reducing the subject's loss to follow-up. Interviewer bias was reduced by using standardized questionnaires. The "knowledge, attitudes, and practices" questionnaire had a high internal consistency, as evidenced by Cronbach's alpha values of 0.88 and 0.86 for the Bahasa versions. The Kaiser-Meyer-Olkin measure of sampling adequacy was 0.78. Bartlett's test of sphericity was significant ($\chi^2 = 3300.796$, df = 231, $P < 0.001$). The stability of our instrument over time was tested by the test-retest reliability methods. In instances, where clinic records were available, they were utilized for triangulation and to reduce information bias.

RESULTS

Flow diagram

All participants ($n = 110$) were recruited from the Mojo District, Surabaya City. A total of 110 study participants included in the cross-over study, 55 in the intervention group and 55 in the control group (Figure 1).

Demographic characteristics of participants

The demographic characteristics of participants in (Table 2) are outlined by sex, occupation, age and education level. Patients with hypertension who follow a virtual anti-hypertensive educational campaign at Mojo District, Surabaya City amounted to 41 males (37.27%) and 69 females (62.72%). The number of participants with hypertension who follow the virtual anti-hypertensive educational campaign at Mojo District, Surabaya City with the status of employed (civil servants/police, laborers, traders/entrepreneurs and private employees) was fewer, *i.e.*, 38 people (34.54%) compared with unemployed (unemployed, retired and housewife), *i.e.*, 72 people (65.45%). The average age of hypertensive patients who follow a virtual anti-hypertensive educational campaign at Mojo District, Surabaya City is 54.26 years, with the lowest age being 19 years and the highest age is 77 years. Among them, participants with the lowest level of education were 0 years (not attending school) and the highest level of education was 19 years (magister student). All patients completed the double-blind protocol. Of the 55 participants in the control group who started combined intervention, one interrupted and declined further participation. The age of the 109 remaining participants averaged 45 ± 5 years. Baseline sitting BP was 152 ± 15/93 ± 13 mmHg and the 24-h ambulatory pressure was 149 ± 12/87 ± 10 mmHg.

Knowledge

For each question of knowledge, the distribution of responses from participants is presented in (Table 3). The HK-LS was generated based on content, face, and construct validity, internal consistency,

Table 2 Distribution of characteristics in hypertensive subjects following a virtual anti-hypertensive educational campaign

Characteristics	Intervention, *n* = 55	Control, *n* = 55	*P* value
Sex			
Male	22 (40.0)	19 (34.5)	0.23
Female	33 (60.0)	36 (65.5)	
Age group, yr			
< 20	0	1 (1.8)	0.33
20-29	3 (5.4)	4 (7.2)	
30-39	12 (21.8)	10 (18.2)	
40-49	19 (34.5)	20 (36.4)	
50-59	16 (29.1)	16 (29.1)	
60-69	4 (7.2)	2 (3.6)	
> 70	1 (1.8)	2 (3.6)	
Marital status			
Single	2 (3.6)	1 (1.8)	0.35
Married	30 (54.5)	29 (52.7)	
Widowed	23 (41.8)	25 (45.4)	
Religion			
Muslim	42 (76.4)	47 (85.5)	0.28
Christianity	9 (16.4)	5 (9.1)	
Others	4 (7.2)	3 (5.4)	
Educational degree			
Not attending	4 (7.2)	4 (7.2)	0.41
Elementary school	16 (29.1)	18 (32.7)	
Junior high school	8 (14.5)	5 (9.1)	
Senior high school	20 (36.4)	19 (34.5)	
Diploma	5 (9.1)	4 (7.2)	
Undergraduate	2 (3.6)	4 (7.2)	
Graduate (magister)	0	1 (1.8)	
Occupation			
Civil servants	2 (3.6)	3 (5.4)	0.38
Police	1 (1.8)	0	
Laborers	7 (12.7)	4 (7.2)	
Entrepreneurs	5 (9.1)	7 (12.7)	
Private workers	5 (9.1)	4 (7.2)	
Housewives	25 (45.5)	29 (52.7)	
Retired	10 (18.2)	8 (14.5)	
Antihypertensive drugs			
ACE-inhibitor	17 (30.9)	15 (27.3)	0.27
ARBs	2 (3.6)	1 (1.8)	
Beta blocker	3 (5.4)	2 (3.6)	
CCBs	31 (56.4)	29 (52.7)	
Diuretics	2 (3.6)	8 (14.5)	

Baseline systolic BP	153 ± 15 mmHg	151 ± 15 mmHg	0.49
Baseline diastolic BP	96 ± 13 mm Hg	91 ± 13 mm Hg	0.42

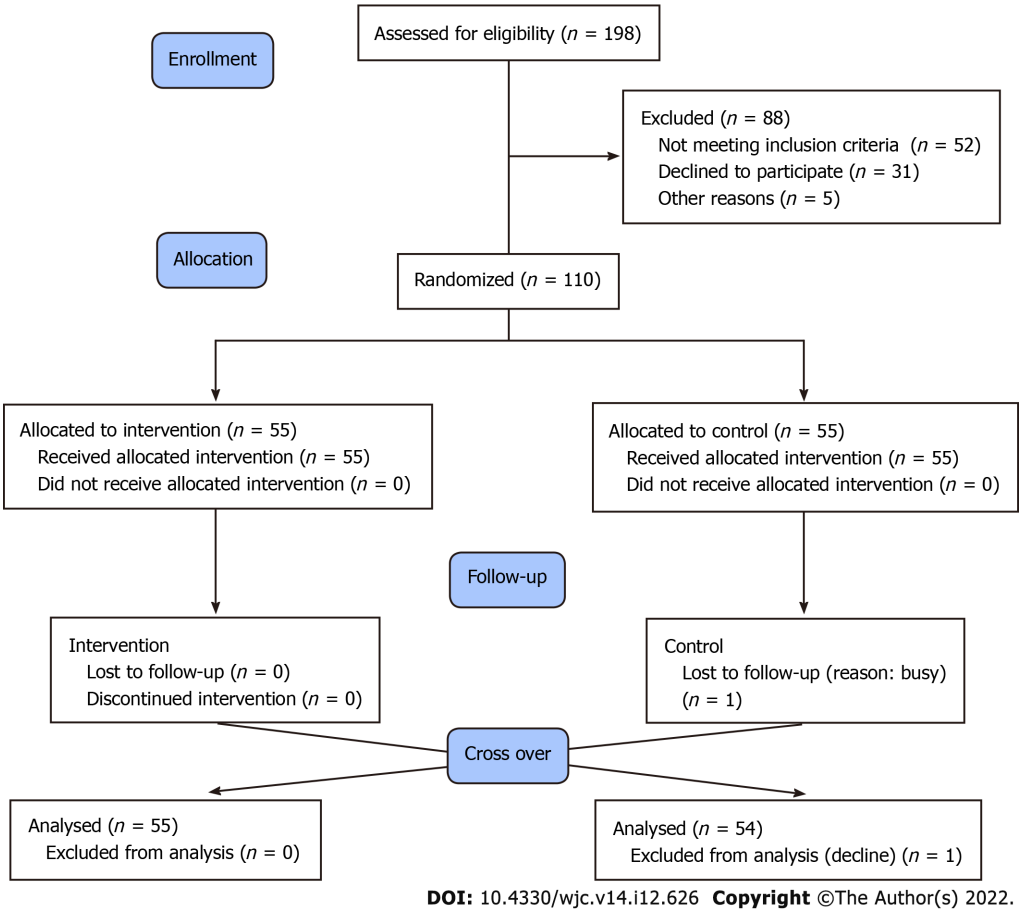
Data are presented as *n* (%) or mean ± SD. Comparative study used independent *t*-test for normally distribution data and Mann-Whitney *U* test for data that did not follow normal distribution. ACE: Angiotensin-converting enzyme; ARBs: Angiotensin II receptor blockers; CCBs: Calcium channel blockers; BP: Blood pressure.

Table 3 Results of the knowledge section evaluated with a 22-item Hypertension Knowledge Level Scale before and after virtual anti-hypertensive educational campaign

No.	Item	Subjects answered true		*P* value
		Before intervention, *n* = 110	After intervention, *n* = 109	
1	Increased diastolic blood pressure also indicates increased blood pressure	65 (59.1)	81 (74.3)	< 0.001
2	High diastolic or systolic blood pressure indicates increased blood pressure	71 (64.5)	84 (77.1)	< 0.001
3	Drugs for increased blood pressure must be taken every day	76 (69.1)	99 (90.8)	< 0.001
4	Individuals with increased blood pressure must take their medication only when they feel ill	44 (40.0)	77 (70.6)	< 0.001
5	Individuals with increased blood pressure must take their medication throughout their life	43 (39.1)	75 (68.8)	< 0.001
6	Individuals with increased blood pressure must take their medication in a manner that makes them feel good	83 (75.5)	89 (81.6)	0.042
7	If the medication for increased blood pressure can control blood pressure, there is no need to change lifestyles	99 (90.0)	103 (94.5)	0.120
8	Increased blood pressure is the result of aging, so treatment is unnecessary	96 (87.3)	103 (94.5)	0.042
9	If individuals with increased blood pressure change their lifestyles, there is no need for treatment	17 (15.5)	59 (54.1)	< 0.001
10	Individuals with increased blood pressure can eat salty foods as long as they take their drugs regularly	78 (70.9)	96 (88.1)	< 0.001
11	Individuals with increased blood pressure can drink alcoholic beverages	107 (97.3)	107 (98.2)	0.420
12	Individuals with increased blood pressure must not smoke	103 (93.6)	105 (96.3)	0.270
13	Individuals with increased blood pressure must eat fruits and vegetables frequently	108 (98.2)	108 (99.1)	0.440
14	For individuals with increased blood pressure, the best cooking method is frying	107 (97.3)	106 (97.2)	0.490
15	For individuals with increased blood pressure, the best cooking method is boiling or grilling	98 (89.1)	101 (92.7)	0.120
16	The best type of meat for individuals with increased blood pressure is white meat	31 (28.2)	99 (80.7)	< 0.001
17	The best type of meat for individuals with increased blood pressure is red meat	103 (93.6)	105 (96.3)	0.270
18	Increased blood pressure can cause premature death if left untreated	46 (41.8)	91 (83.5)	< 0.001
19	Increased blood pressure can cause heart diseases, such as heart attack, if left untreated	87 (79.1)	108 (99.1)	< 0.001
20	Increased blood pressure can cause strokes, if left untreated	61 (55.5)	106 (97.2)	< 0.001
21	Increased blood pressure can cause kidney failure, if left untreated	57 (51.8)	91 (83.5)	< 0.001
22	Increased blood pressure can cause visual disturbances, if left untreated	39 (35.5)	59 (54.1)	< 0.001

Data are presented as *n* (%). Comparative study used paired sample *t*-test and Wilcoxon signed rank test.

test re-test reliability, and discriminative validity procedures. The final scale had 22 items with six sub-dimensions. The 22-item HK-LS scale was applied to all participants, before and 2 mo after the intervention ended. Following the Virtual Anti-Hypertensive Educational Campaign implementation, there was a significant improvement in the knowledge aspects ($P < 0.001$) in the intervention group[22].



DOI: 10.4330/wjc.v14.i12.626

Figure 1 Flow chart diagram of this study.

Attitude

For each question that focused on attitude, the distribution of responses from participants is presented in (Table 4). We used the adapted 28-Likert items instrument of TAQPH instrument, to measure adherence to pharmacological and non-pharmacological treatment (lifestyle), in patients with primary hypertension, before and after the intervention. The adapted TAQPH version had modifications without affecting the instrument's original structure to maintain the semantic equivalence, a fact validated by its author. An average of a 4-point Likert-type scale were being used to determine the attitude of the subject participants (1 = strongly disagree; 2 = disagree; 3 = agree; 4 = strongly agree). Following the Virtual Anti-Hypertensive Educational Campaign implementation, there was a significant improvement in the knowledge aspects ($P < 0.001$) in the intervention group.

Practice

For each question of practice, the distribution of responses from participants is presented in (Table 5). Medication adherence was tested using the Bahasa version of the validated MMAS-8. The MMAS-8 is a structured self-report measure of medication-taking behavior that has been widely used in various cultures. Following the virtual anti-hypertensive educational health campaign, no significant change had been observed in the overall practice parameters ($P = 0.131$).

DISCUSSION

This study was conducted and aimed at measuring the baseline level of knowledge, attitude, and practice of hypertension management and perceptions regarding the disease among Indonesian people. The findings reveal the effects of planning virtual health education programs for non-communicable diseases and regarding the change of knowledge, attitude, and practice of hypertension management. Since the outbreak of the COVID-19 pandemic in Surabaya City which started in March 2020, this pandemic led to substantial socioeconomic damages in the whole town. Vigorous measurements have been enforced and implemented including lockdown of Surabaya City and a community quarantine by Surabaya local governments since the outbreak to mitigate the disease effectively. In addition, public health education has been recognized as an effective measure to prevent and control non-communicable

Table 4 Results of the attitude section evaluated with principal components of the items of the questionnaire to measure adherence in patients with primary hypertension

No.	Likert item	Average Likert scale		*P* value
		Before intervention, *n* = 110	After intervention, *n* = 109	
1	Have you taken the medications according to the frequency indicated in the formula provided by the physician?	38 (34.5)	61 (55.9)	< 0.001
2	Have you taken the medications according to the dosage indicated by the physician?	82 (74.5)	87 (79.8)	0.035
3	Have you taken the medications according to the schedule indicated by the physician?	45 (40.9)	64 (58.7)	< 0.001
4	Have you taken the medications for a long period without interruptions, according to indications provided by the physician?	32 (29.1)	35 (32.1)	0.032
5	Have you taken the medications according to indications by the physician, without increasing or diminishing the dosage?	82 (74.5)	87 (79.8)	0.035
6	Have you continued taking the medications even if you don't have symptoms of hypertension?	38 (34.5)	61 (55.9)	< 0.001
7	Have you forgotten to take your medications?	72 (65.5)	49 (44.9)	< 0.001
8	Have you suspended the medications when you have felt that symptoms have improved?	73 (66.4)	59 (54.1)	< 0.001
9	Have kept using the medications in spite of feeling that the symptoms have worsened?	37 (33.6)	60 (55.0)	< 0.001
10	Have you complied with a low-salt diet?	32 (29.1)	81 (74.3)	< 0.001
11	Have you complied with a low-fat diet? Reducing consumption of fried preparations, sauces, dressings, sausages (cold cuts - Mortadella - fast foods in general)	28 (25.5)	67 (61.5)	< 0.001
12	Have you complied with a low-cholesterol diet? Reducing consumption of red meats, chicken skin, eggs, sauces (mayonnaise - tomato sauce - industrial vinaigrettes), oil, lard and butter)	45 (40.9)	71 (65.1)	< 0.001
13	Have you diminished consumption of sugar and sweets?	18 (16.4)	31 (28.4)	< 0.001
14	Have you increased consumption of fiber? Such as papaya, pineapple, soursop, peaches, pears, and apples; also cereals, like oats, quinoa and bran	29 (26.4)	47 (43.1)	< 0.001
15	Have you increased consumption of fresh vegetables?	71 (64.5)	89 (81.6)	0.006
16	Have you increased consumption of fresh fruits?	36 (32.7)	70 (64.2)	< 0.001
17	Have you increased consumption of grains? Including beans, chickpeas, lentils, peas. Besides dry nuts, like peanuts and almonds?	28 (25.5)	47 (43.1)	< 0.001
18	Have you increased consumption of low-fat dairy products?	28 (25.5)	67 (61.5)	< 0.001
19	Have you diminished the consumption of coffee?	63 (57.3)	70 (64.2)	0.028
20	Have you limited consumption of alcoholic beverages?	106 (96.4)	107 (98.2)	0.440
21	Have you stopped smoking?	13 (11.8)	28 (25.7)	< 0.001
22	Have you performed physical exercise at least five times per week?	17 (15.5)	32 (29.4)	< 0.001
23	When performing physical exercise, have you dedicated at least 30 min to it?	12 (10.9)	25 (22.9)	< 0.001
24	Have you been able to control the amount of food you consume?	63 (57.3)	68 (62.4)	0.032
25	Have you maintained your body weight under control?	59 (53.6)	61 (55.9)	0.280
26	Have you set aside daily time for relaxation for yourself?	14 (12.7)	26 (23.8)	< 0.001
27	Have you recurred to some forms to relieve stress or tension?	17 (15.5)	18 (16.5)	0.240
28	Have you controlled yourself emotionally in light of sudden events?	51 (46.4)	59 (54.1)	0.012

Data are presented as *n* (%).

diseases.

In managing non-communicable diseases such as hypertension and cardiovascular diseases, there are no better ways than prevention[25]. However, traditional diet campaign may not be the optimal educational strategy during this situation. In our study, the virtual anti-hypertensive educational

Table 5 Item structure of the 8-item Morisky Medication Adherence Scale rotation of the initial factor extraction using the principal component method

No.	Items	Subjects answered "yes"		*P* value
		Before intervention, *n* = 110	After intervention, *n* = 109	
1	Do you sometimes forget to take your hypertensive pills?	47 (42.7)	39 (35.8)	0.160
2	People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your hypertensive medicine?	70 (63.6)	65 (59.6)	0.310
3	Have you ever cut back or stopped taking your hypertensive medication without telling your doctor, because you felt worse when you took it?	23 (20.9)	19 (17.4)	0.180
4	When you travel or leave home, do you sometimes forget to bring along your hypertensive medication?	49 (44.5)	47 (43.1)	0.380
5	Did you take your hypertensive medicine yesterday?	96 (87.3)	97 (89.0)	0.430
6	When you feel like your hypertension is under control, do you sometimes stop taking your medicine?	81 (73.6)	65 (59.6)	< 0.001
7	Taking medication every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your hypertensive treatment plan?	51 (46.4)	49 (44.9)	0.390
8	How often do you have difficulty remembering to take all your medications? (likert scale: 1 = never; 2 = seldom; 3 = sometime; 4 = frequently)	3.1 ± 0.8	2.3 ± 0.6	< 0.001

Data are presented as *n* (%). Response choices are "yes" or "no" for items, except Likert scale for item number 8.

campaign and various educational interventions augments the health literacy of individuals and found to moderately improve knowledge and attitude towards hypertension, medication and healthy lifestyle. While individuals with hypertension benefited from practical interventions, there is no beneficial effect on practical aspects with the virtual anti-hypertensive educational campaigns. Different from knowledge and attitude aspects, practice of our subjects did not change significantly. Therefore, an effective strategy to improve the practical aspects in hypertension management and to achieve blood pressure goal is mandatory.

Virtual anti-hypertensive educational campaigns alone are unable to increase the individual's practice towards healthy diets and lifestyles, and therefore there may be no tangible benefit to blood pressure reduction. Despite finding heterogeneity in the population of this study, there are a few reasons why practical aspects did not improve significantly following serial interventions. Firstly, conducting only one education session every week may diminish the importance in lifestyle changing. Secondly, in virtual education, subjects are more engaged in the home environment and healthcare professionals find it difficult to accurately assess each individuals lifestyle changes and get immediate feedback. Thirdly, conducting an education session virtually has greater physical and psychological barriers compared with face-to-face education. However, in the pandemic era, online education modalities should be encouraged as improvement was seen in the knowledge and attitude aspects in hypertensive patients who received the virtual anti-hypertensive educational campaigns where barriers to face-to-face education were assessed and addressed.

Dealing with hypertension is a behavior change process which demands serious learning efforts from patients, families and caregivers. Strong organized efforts by multiple stakeholders, including governments, non-government organizations, public and private partnership, and medical workers at all levels, will be key not only to improve health literacy, but also to achieve sustainable strengthening of health systems for a healthier future and well-being for all[26]. While the outbreak is ongoing, staying at home is safe. In many ways, social media and webinar platforms have transformed the practice of cardiovascular preventionists and have opened up new avenues for communicating food and nutrition information. Social media and webinar have also been an effective tool for virtual nutrition counselling, patient education, peer-to-peer support, and public health campaigns[27]. Virtual health education activities should enhance the overall goal of the health promotion and disease prevention program[28].

In a previous study by Oliveira-Filho *et al*[29], the diagnosis of non-adherent behavior through the use of the new MMAS-8 in patients treated with antihypertensive drugs was a risk factor of elevated systolic and diastolic blood pressure[29]. Considering that non-adherence is a major cause of uncontrolled blood pressure, the use of self-report scales related to BP is a simple and inexpensive measure to assist the clinical treatment of patients with hypertension.

Strength and limitation

The strengths of the present study include that our population is a crossover experimental study and that the study used strict quality control methods. Also, we have developed an interactive session of virtual education with the aid of a webinar-based platform. Several instructors were involved in observing participants' focus and concentration. Each session had a 2 h duration, with serial evaluation given at the end of each session. However, some limitations should be acknowledged. First, the nature of our data precludes establishing causal associations between education and CV health. Therefore, we may only discern association. Second, since our virtual anti-hypertensive educational campaign consisted of online self-assessment questionnaires and online education, we cannot guarantee that our population is characterized as real-practice patients, because subjects may not be sincere and may even over-evaluate their own performance. Compared with face-to-face interviews, a virtual self-report has limitations including multiple biases. Third, the study sample was drawn from one district in Surabaya; thus, the findings cannot be generalized to all subjects across the country. Fourth, virtual assessment from population surveys invariably poses the problem of social desirability, whereby study participants are reluctant to admit socially poor acceptable knowledge, attitude, and practice to avoid giving a negative impression.

Despite several limitations, our data clearly indicates a significant improvement of knowledge and attitude, but no significant change in the practice and blood pressure status in the setting of hypertensive patients. In our opinion, these data have important implications for policy making. The general recommendation would be to focus on creating the most effective way to transfer practice and health benefits throughout the virtual education series. Such a strategy should ensure that subjects with hypertension are not disadvantaged with respect to educational background or access to the internet or other opportunities. Accordingly, a virtual healthy educational campaign clearly has to be considered in the strategies of hypertension control and global cardiovascular risk reduction.

CONCLUSION

The COVID-19 pandemic has created many challenges for healthcare providers to deliver health education to the society, even during the new normal era. Remote and virtual options that align with the WHO's social distancing guidelines are essential for the continuation of health education. Creating a virtual health education program takes time and does not happen overnight. It requires sources, funding and precise guidelines. It is similar to telemedicine applied to society. The different background of subjects in the society poses a unique challenge to the maintenance of quality of information transmitted to the subjects in these pandemics. It should be remembered that conducting virtual health education programs may be better than doing nothing during this pandemic. This study relied on online questionnaires, suggesting that virtual anti-hypertensive educational campaigns may be effective in transforming knowledge and attitude, yet may not be effective to improve practice of hypertension management in the society. It is concluded that multiple experts from different fields are needed to work together addressing this issue and put their suggestions into practice.

ARTICLE HIGHLIGHTS

Research background

In the unprecedented times of the coronavirus disease 2019 (COVID-19) pandemic, many offices were shut down all across the world. Onsite classes and events were postponed. As a result, the educational health campaign has changed dramatically, with the distinctive rise of e-learning, whereby the health campaign is undertaken remotely by digital platforms. With this sudden shift away from the conventional campaign, in many parts of the globe, some are wondering whether the adoption of virtual learning will continue to persist post-pandemic, and how such a shift would impact the perception and transfer of knowledge towards hypertensive patients. To keep the community safe, but still well-informed about the dangers of hypertension and how to build a healthy lifestyle, we decided to create a Virtual Anti-Hypertensive Educational Campaign.

Research motivation

The importance of this paper is to evaluate the impact of the Virtual Anti-Hypertensive Educational Campaign towards knowledge, attitude, and the practice of hypertension management in the primary care setting during the COVID-19 pandemic.

Research objectives

Our teams designed a virtual anti-hypertensive educational campaign curriculum for community health care advocates in the community health care of the Mojo District, Surabaya, Indonesia to identify and

prevent health risks of hypertension. The first goal is to conduct research on the risks of hypertension and identify an educational model for community health advocates. The second goal is to educate people to improve health literacy in the field of hypertensive healthy plans. The virtual anti-hypertensive educational campaign aimed to help dispel misinformation while promoting healthy lifestyle recommendations and medical guidelines set by the Ministry of Health of the Indonesian Government and Indonesian Cardiologist Association. Therefore, the purpose of this paper is to highlight the impact of the virtual anti-hypertensive educational campaign towards knowledge, attitude, and the practice of hypertension management during the COVID-19 pandemic.

Research methods

The trial was a randomized double-blind, placebo controlled, crossover design. The study was completed over 6 mo duration (1 October 2020-30 April 2021) of the virtual anti-hypertensive educational campaign with randomization (1 mo); treatment period one (2 mo); washout (1 mo); and finally, treatment period two (2 mo). Subjects were randomly assigned among patients with established hypertension using a pre-test post-test-controlled group design. This study was conducted in October-December 2020 in the Mojo District of Surabaya City. We conducted an online survey from October to December 2020. The survey involved an online questionnaire that was distributed virtually, by email or by WhatsApp and social media, to more than 500 hypertensive patients in the Mojo district of Surabaya, Indonesia, to which 110 participants actively replied. The questionnaire was self-administered without intervention by the authors or any specific person, and it did not contain any identifying data of the participants to ensure confidentiality. Questionnaires with incomplete information or missing data were excluded from the analysis. Completed paper questionnaires were collected anonymously to ensure confidentiality and to prevent any response bias. Unreturned or uncompleted questionnaires were recorded as missing. Participants were not aware of the study aim or outcomes to reduce the risk of any possible bias. The survey included only hypertensive patients who were living in the Mojo district of Surabaya city.

Research results

A total of 110 participants were included in the analysis, 55 in the intervention group and 55 in the control group. Following the Virtual Anti-Hypertensive Educational Campaign implementation, the only parameter that showed significant improvement were knowledge and attitude ($P < 0.001$). There is no significant change in the practice parameters ($P = 0.131$).

Research conclusions

The COVID-19 pandemic has created many challenges for healthcare providers to deliver health education to the society, even during the new normal era. Remote and virtual options that align with the WHO's social distancing guidelines are essential for the continuation of health education. Creating a virtual health education program takes time and does not happen overnight. It requires sources, funding, and precise guidelines. It is like telemedicine applied to society. The different background of subjects in the society poses a unique challenge to the maintenance of quality of information transmitted to the subjects in these pandemics. It should be remembered that conducting virtual health education programs may be better than doing nothing during this pandemic. This study relied on online questionnaires, suggesting that virtual anti-hypertensive educational campaigns may be effective in transforming knowledge and attitude, yet may not be effective to improve the practice of hypertension management in the society. It is concluded that multiple experts from different fields are needed to work together addressing this issue and put their suggestions into practice.

Research perspectives

The Department of Cardiology and Vascular Medicine created a virtual education series about healthy lifestyle and dietary guidelines that refers to Dietary Approaches to Stop Hypertension by adapting the local wisdom of the Surabaya community. We aimed to evaluate the impact of the Virtual Anti-Hypertensive Educational Campaign towards knowledge, attitude, and the practice of hypertension management in the primary care setting during the COVID-19 pandemic.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the assistance of Mrs. Fita Triastuti, Mr. Kurniadi Doni and Mrs. Sri Redjeki for the excellent administrative support of the survey. The authors would also like to acknowledge Dr. I Gde Rurus Suryawan and Mrs. Anudya Kartika Ratri for their assistance in verifying the statistical approach used in our study and proof editing. The authors would like to dedicate this manuscript to honor the effort of brave health-care workers who sacrificed their lives to fight against COVID-19.

FOOTNOTES

Author contributions: Andrianto A is the principal investigator, conceived the ideas and supervised the project; Ardiana M helped project administration, validation and funding; Nugraha RA initially wrote the manuscript and interpreted the data; Yutha A, Khrisna BPD and Nugraha RA highlighted the potential use of virtual health education for society during the coronavirus disease 2019 pandemic and drafted the manuscript; Putra TS and Shahab AR provided the materials and access to crucial research components; Andrianto H, Kikuko IH, Puspitasari AN and Hajjrin MR participated in the design of the study and the visualization of the software; All authors read and approved the final manuscript.

Institutional review board statement: In order to conduct the study, approval was obtained on July 1st, 2020, with a decision of the Bioethics Committee at the Faculty of Medicine Universitas Airlangga (Ref. number 532/UN3/2020) under the name of Andrianto as principal investigator.

Informed consent statement: All participants provided virtual informed consent prior to participating in the study, without identifiable data. The schedule of enrolment, intervention and measurements according to Standard Protocol Items: Recommendations for Intervention Trials (SPIRIT) requirements. The study's data were collected in accordance with the Helsinki Declaration. The consent form documented the aims, nature, and procedure of the study. Anonymity and confidentially were strictly maintained.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: The authors confirm that the data supporting the findings of this study are available within the article.

CONSORT 2010 statement: CONSORT 2010 checklist of information to include when reporting a randomized trial.

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S-Editor: Gong ZM
L-Editor: Filipodia
P-Editor: Gong ZM

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World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2022 December 26; 14(12): 640-656

DOI: 10.4330/wjc.v14.i12.640

ISSN 1949-8462 (online)

SYSTEMATIC REVIEWS

Telemonitoring in heart failure patients: Systematic review and meta-analysis of randomized controlled trials

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Specialty type: Cardiac and cardiovascular systems

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Lakusic N, Croatia; Su Q, China; Yang YQ, China

Received: August 28, 2022
Peer-review started: August 28, 2022
First decision: October 24, 2022
Revised: November 2, 2022
Accepted: November 30, 2022
Article in press: November 30, 2022
Published online: December 26, 2022

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Abstract

BACKGROUND

Home telemonitoring has been used as a modality to prevent readmission and improve outcomes for patients with heart failure. However, studies have produced conflicting outcomes over the years.

AIM

To determine the aggregate effect of telemonitoring on all-cause mortality, heart failure-related mortality, all-cause hospitalization, and heart failure-related hospitalization in heart failure patients.

METHODS

We conducted a systematic review and meta-analysis of 38 home telemonitoring randomized controlled trials involving 14993 patients. We also conducted a sensitivity analysis to examine the effect of telemonitoring duration, recent heart failure hospitalization, and age on telemonitoring outcomes.

RESULTS

Our study demonstrated that home telemonitoring in heart failure patients was associated with reduced all-cause [relative risk (RR) = 0.83, 95% confidence interval (CI): 0.75-0.92, $P = 0.001$] and cardiovascular mortality (RR = 0.66, 95%CI: 0.54-0.81, $P < 0.001$). Additionally, telemonitoring decreased the all-cause hospitalization (RR = 0.87, 95%CI: 0.80-0.94, $P = 0.002$) but did not decrease heart failure-related hospitalization (RR = 0.88, 95%CI: 0.77-1.01, $P = 0.066$). However,

prolonged home telemonitoring (12 mo or more) was associated with both decreased all-cause and heart failure hospitalization, unlike shorter duration (6 mo or less) telemonitoring.

CONCLUSION
Home telemonitoring using digital/broadband/satellite/wireless or blue-tooth transmission of physiological data reduces all-cause and cardiovascular mortality in heart failure patients. In addition, prolonged telemonitoring (≥ 12 mo) reduces all-cause and heart failure-related hospitalization. The implication for practice is that hospitals considering telemonitoring to reduce heart failure readmission rates may need to plan for prolonged telemonitoring to see the effect they are looking for.

Key Words: Telemonitoring; Heart failure; Telehealth; Home monitoring; Remote monitoring

Core Tip: Home telemonitoring has been used as a modality to prevent readmission and improve outcomes for patients with heart failure. However, studies have produced conflicting outcomes over the years. This meta-analysis aims to determine the aggregate effect of telemonitoring on all-cause mortality, heart failure-related mortality, all-cause hospitalization, and heart failure-related hospitalization in heart failure patients. This study found that home telemonitoring using digital/broadband/satellite/wireless or blue-tooth transmission of physiological data reduces all-cause and cardiovascular mortality in heart failure patients. Additionally, prolonged home telemonitoring (12 mo or more) led to both decreased all-cause and heart failure hospitalization, unlike shorter duration (6 mo or less) telemonitoring. The implication for practice is that hospitals considering telemonitoring to reduce heart failure readmission rates may need to plan for prolonged telemonitoring to see the effect they are looking for.

Citation: Umeh CA, Torbela A, Saigal S, Kaur H, Kazourra S, Gupta R, Shah S. Telemonitoring in heart failure patients: Systematic review and meta-analysis of randomized controlled trials. *World J Cardiol* 2022; 14(12): 640-656
URL: https://www.wjgnet.com/1949-8462/full/v14/i12/640.htm
DOI: https://dx.doi.org/10.4330/wjc.v14.i12.640

INTRODUCTION

Heart failure is a clinical syndrome in which patients develop signs and symptoms, including dyspnea, fatigue, and/or fluid retention due to cardiac dysfunction or abnormality in cardiac structure[1]. Heart failure is classified as heart failure with reduced ejection fraction (EF) (< 40%), heart failure with mildly reduced EF (41% to 49%), or heart failure with preserved EF (> 50%)[1]. Heart failure has become the primary cause of hospitalization in the United States in the elderly[2,3]. The prevalence increases with increasing age, and affected individuals significantly consume healthcare resources. It has significant public health implications, with an estimated cost of about $30.7 billion in the United States in 2012, with the projected total rise in cost up to $69.7 billion by 2030[2,4]. Additionally, heart failure is associated with high morbidity and mortality, with a readmission rate during six months following discharge as high as 50%[5]. Heart failure is not just a problem in the United States but a global disease, with its prevalence increasing across the globe[1,2].

As the survival of patients with acute myocardial infarction improves and with a population that continues to age, we will continually see a rise in patients with heart failure and, thus, more rehospitalizations. Various modalities have been in the works to improve outcomes for patients with heart failure to prevent readmission. One of these modalities, termed home telemonitoring, involves tracking patients' health status using electronic devices at home[6-10]. Healthcare providers can obtain patients' vital signs, weight, and other parameters recorded and transmitted through communication technology and contact the patients if abnormalities are noted. In this way, deteriorations in patients' conditions are detected early, resulting in early interventions. A review of randomized controlled trials of noninvasive home telemonitoring compared to standard practice for people with heart failure has shown a reduced risk of all-cause mortality, heart failure-related hospitalizations, and improvement in quality of life and heart failure knowledge and self-care behaviors in some studies[6].

Though using home telemonitoring to monitor patients remotely has been going on for a while, further evaluation is needed as studies have reported inconsistent results over the years. While telemonitoring was beneficial in reducing hospital admission, all-cause mortality, and emergency room visits in some studies, others did not show such benefits[7-10]. These differences in outcomes from multiple

studies suggest that careful analysis of study outcomes is needed to determine its aggregate benefit to heart failure patients. This meta-analysis aims to determine the aggregate effect of telemonitoring on all-cause mortality, heart failure-related mortality, all-cause hospitalization, and heart failure-related hospitalization in heart failure patients. We also conducted sensitivity analysis to examine the effect of telemonitoring duration, recent heart failure hospitalization, and age on telemonitoring outcome.

MATERIALS AND METHODS

Study design

Our systematic review and meta-analysis was designed according to the guidelines included in the PRISMA statement[11].

Outcomes

Our primary outcomes were all-cause and heart failure-related mortality and all-cause and heart failure-related hospitalizations.

Eligibility criteria

We included only randomized controlled trials of home telemonitoring in heart failure patients that reported mortality or readmissions as the outcome measure. We defined home telemonitoring as patients self-measuring their vital signs (such as pulse, weight, blood pressure) at home and using a digital/broadband/satellite/wireless or blue-tooth device to transmit the data to healthcare professionals. The healthcare professionals reviewed the transmitted data and instructed the patient on the next steps if the values were abnormal, including medication adjustment. We excluded studies not written in English. Two authors independently reviewed the abstracts after our literature search to assess if they met the inclusion and exclusion criteria to be included in the study.

Literature search

Articles were obtained by searching the PubMed, Embase, Google scholar, Reference Citation Analysis and Cochrane databases with the term heart failure, combined with the following terms: "telemonitoring", "telehealth", "home monitoring", and "remote monitoring". In PubMed and Embase, we used a filter to limit our search to randomized controlled trials conducted between January 1, 2000, and September 2021. In the Google scholar search, we restricted the search to the article titles that contain the search terms.

Data extraction of primary studies

Information on study participants, methods, interventions, and outcomes, including hospitalization and death, was extracted onto a data-sheet in Excel (Microsoft Corporation, 2018). We reported only the result of the heart failure patients for articles that included heart failure patients and patients with other illnesses but reported separate results.

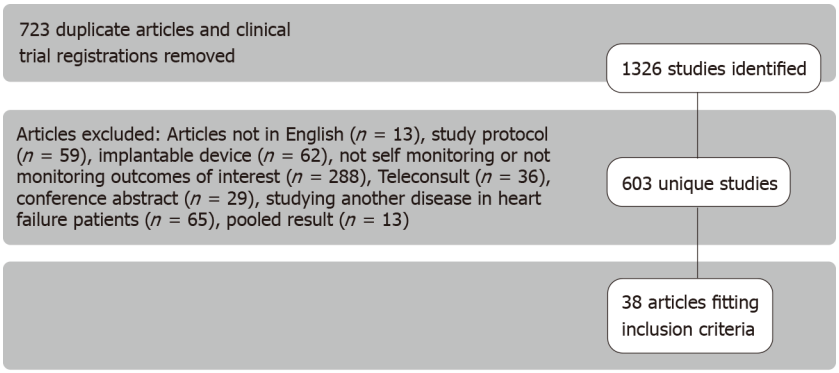
Methods for assessing the risk of bias

We assessed the risk of bias using the methods presented in the Cochrane handbook[12]. First, the risk of bias was evaluated independently by two authors. In case of disagreement between the two authors, the matter was discussed and decided by consensus. The presence of publication bias for each outcome was assessed using funnel plots.

Quantitative data synthesis

The study's primary endpoints are the effect of telemonitoring on all-cause mortality, heart failure-related mortality, all-cause hospitalization, and heart failure-related hospitalization in heart failure patients. We calculated the relative risk (RR) and 95% confidence interval (CI) for each outcome in each study. We used the random effect model and tested the null hypothesis using Z-score. A P value of < 0.05 was interpreted as statistically significant. We tested heterogeneity in study outcomes using the χ^2 test and the I^2 statistic.

To assess the outcomes in different sub-groups, we performed a series of subgroup analyses: (1) Comparison of cumulative outcomes in the telemonitoring and usual care approach, according to the duration of follow-up (≤ 6 mo and ≥ 12 mo). The median and modal duration of follow-up in the studies was six months, and most of the studies that extended beyond six months lasted for at least 12 mo. Thus, we decided to compare studies with a duration of ≤ 6 mo with those ≥ 12 mo; (2) Comparison of cumulative outcomes in the telemonitoring and usual care approach, in studies of patients with recent heart failure hospitalization, which we defined as heart failure hospitalization within six weeks before the study, and those that did not; and (3) Comparison of cumulative outcomes in the telemonitoring and usual care approach, in studies that recruited patients ≥ 65 years. The analysis was done using Comprehensive Meta-Analysis Version 3.



DOI: 10.4330/wjc.v14.i12.640

Figure 1 The literature search result.

RESULTS

Identification of relevant studies

Our search produced 1326 articles, of which 603 were unique articles after removing duplicate publications and clinical trial registrations. Two researchers independently reviewed the 603 abstracts to assess if they met the inclusion and exclusion criteria in the review. We excluded papers not in English (n = 13), papers that used implantable devices such as pacemakers (n = 62), papers on telemonitoring study protocol (n = 59), papers on teleconsulting (n = 36), conference abstracts (n = 29), papers that did not measure heart failure patients' hospitalization or mortality or did not include self-monitoring (n = 288), papers studying another disease in heart failure patients (n = 65), and papers that joined the results of patients with heart failure and patients with other illnesses (n = 13) (Figure 1).

Our study included 38 randomized controlled trials on telemonitoring in heart failure patients between January 1, 2000, and October 3, 2021[7-10,13-46] (Table 1). Fourteen thousand nine hundred and ninety-three patients were recruited in the 38 studies, with a mean of 394 and a range of 48 to 1653. The mean duration of the studies was 9.4 mo and a range of 1 to 32 mo in Table 1. Forty-seven percent of the studies were done in North America (the United States of America and Canada), and the majority of the remaining were done in Europe. All the studies involved patients measuring their vital signs and weight and using digital/broadband/satellite/wireless or blue-tooth to transmit the data to the healthcare providers. The patients transmitted their data daily in 92% of the studies and weekly in 8% of studies (Table 1). The nurses were the primary healthcare professionals that monitored the patients' data and informed the physicians of abnormal values in 79% of the studies. They also contacted the patient if there were abnormal values with instructions on what to do next. Physicians led the process in 6 studies (16%), where the physicians reviewed the transmitted patients' data and contacted them if values were abnormal with instructions on what to do next. A case manager led the process in one of the studies, and a non-clinician led one study (Table 1).

Risk of bias assessment

There was a low risk of bias in the randomization process, measurement of outcome data, or missing outcome data in the studies included in the meta-analysis. However, the intervention was not blinded in any of the primary studies because of the nature of the studies. Additionally, many of the studies did not provide information on whether outcome assessors were aware of the intervention received by study participants. Thus, it is unclear how these affected the study outcomes. Furthermore, many studies did not indicate if the data was analyzed per a pre-specified plan that was finalized before unblinded outcome data were available for analysis. Thus, we did not have information to assess the risk of bias in selecting the reported result. Table 2 shows the bias assessment in each of the primary studies. The heterogeneity within the studies ranged from low (for cardiovascular mortality, I^2 = 0%) to substantial (for all-cause hospitalizations, I^2 = 69%). The funnel plots did not show any major publication bias in the primary outcomes assessed (Supplementary Figures 1-3).

All-cause mortality

The pooled estimate of the effect of telemonitoring on all-cause death in comparison with standard care in 28 studies with 13188 patients showed that telemonitoring was associated with reduced all-cause mortality in heart failure patients (RR = 0.83, 95%CI: 0.75-0.92, P = 0.001) (Figure 2A). Our sensitivity analysis showed that the duration of telemonitoring did not influence all-cause mortality in heart failure patients. Analysis of 15 studies of six months or less duration showed reduced all-cause mortality (RR = 0.78, 95%CI: 0.65-0.94, P = 0.009). Similarly, analysis of 12 studies of 12 mo or more months duration also showed reduced all-cause mortality (RR = 0.86, 95%CI: 0.74-0.99, P = 0.032) (Table 3).

Table 1 Summary of studies included in the meta-analysis

Ref.	Number of patients	Duration of follow-up (mo)	Country	Person responsible for monitoring telemedicine data	Frequency of measuring and transmitting vital signs	Frequency of clinicians reviewing data	Included telemonitoring patients' education	Included control group patient education	Recruited patients ≥ 65 yr	Recruited recently discharged patients	Recruited frequently hospitalized patients
Nouryan *et al* [15], 2019	89	6	United States	Nurse	Daily	Daily	Yes	Yes	Yes	No	No
Seto *et al*[16], 2012	100	6	Canada	Physician	Daily	Daily	No	No	No	No	No
Weintraub *et al* [17], 2010	188	3	United States	Nurse	Daily	Daily	Yes	Yes	No	Yes	No
Blum and Gottlieb[18], 2014	156	27	United States	Nurse	Daily	Daily	No	No	No	No	No
Dansky *et al* [19], 2008	284	4	United States	Nurse	Daily	Daily	No	No	No	No	No
Kashem *et al* [20], 2008	48	12	United States	Nurse	Daily	Daily	No	No	No	No	No
Benatar *et al* [21], 2003	216	12	United States	Nurse	Daily	Daily	No	Yes	No	Yes	No
Pedone *et al* [22], 2015	96	6	Italy	Physician	Daily	Daily	No	No	Yes	No	No
Wade *et al*[23], 2011	316	6	United States	Case manager	Daily	Daily	Yes	Yes	Yes	No	No
Comín-Colet *et al*[24], 2016	178	6	Spain	Nurse	Daily	Daily	No	No	No	Yes	No
Olivari *et al* [25], 2018	339	12	Italy	Non-clinician	Daily	Daily	No	No	Yes	No	No
Lyngå *et al*[26], 2012	319	12	Sweden	Nurse	Daily	3 d a week	No	No	No	No	No
Scherr *et al*[27], 2009	120	6	Austria	Physician	Daily	Daily	No	No	No	Yes	No
Antonicelli *et al* [28], 2008	57	12	Italy	Nurse	Weekly	Weekly	Yes	No	Yes	No	No
Giordano *et al* [29], 2009	460	12	Italy	Nurse	Daily	Daily	Yes	No	No	No	No

Ong *et al*[30], 2016	1437	6	United States	Nurse	Daily	Daily	Yes	No	No	Yes	No
Kalter-Leibovici *et al*[10], 2017	1360	32	Isreal	Nurse	Daily	Daily	Yes	No	No	No	No
Mortara *et al* [31], 2009	461	12	United Kingdom, Poland, and Italy	Nurse	Weekly	Weekly	No	No	No	No	No
Dar *et al*[32], 2009	182	6	United Kingdom	Nurse	Daily	Daily	No	No	No	Yes	No
Vuorinen *et al* [33], 2014	94	6	Finland	Nurse	Weekly	Weekly	No	No	No	No	No
Goldberg *et al* [34], 2003	280	6	United States	Nurse	Daily	Daily	No	No	No	No	No
Soran *et al*[35], 2008	315	6	United States	Nurse	Daily	Daily	No	No	Yes	No	No
Chaudhry *et al* [36], 2010	1653	6	United States	Physician	Daily	Daily	No	No	No	Yes	No
Koehler *et al* [13], 2018	1571	12	Germany	Physician	Daily	Daily	Yes	No	No	No	No
Cleland *et al* [14], 2005	418	8	Germany, Netherlands, and United Kingdom	Nurse	Daily	Daily	Yes	No	No	Yes	No
Koehler *et al*[7], 2011	710	26	Germany	Physician	Daily	Daily	No	No	No	No	No
Kotooka *et al* [8], 2018	181	15	Japan	Nurse	Daily	Daily	No	No	No	Yes	No
Pekmezaris *et al* [9], 2019	104	3	United States	Nurse	Daily	Daily	Yes	No	No	Yes	No
Villani *et al*[37], 2014	80	12	Italy	Nurse	Daily	Daily	No	No	Yes	Yes	Yes
Dendale *et al* [38], 2012	160	6	Belgium	Nurse	Daily	Daily	No	No	No	Yes	No
Woodend *et al* [39], 2007	121	3	Canada	Nurse	Daily	Daily	Yes	No	No	Yes	No
Galinier *et al* [40], 2020	937	18	France	Nurse	Daily	Daily	Yes	No	No	No	No
Capomolla *et al* [41], 2004	133	12	Italy	Nurse	Daily	Daily	Yes	No	No	No	No

Kulshreshtha *et al*[42], 2010	150	6	United States	Nurse	Daily	Daily	No	No	No	Yes	Yes
Kenealy *et al* [43], 2015	98	6	New Zealand	Nurse	Daily	Daily	No	No	No	No	No
Dawson *et al* [44], 2021	1380	1	United States	Nurse	Daily	Daily	No	No	No	Yes	Yes
Delaney *et al* [45], 2013	100	3	United States	Nurse	Daily	Daily	No	No	No	No	No
Schwarz *et al* [46], 2008	102	3	United States	Nurse	Daily	Daily	No	No	Yes	Yes	No

Furthermore, our sensitivity analysis showed that being recently hospitalized for heart failure, which we defined as heart failure hospitalization within six weeks before the study, did not affect the telemonitoring outcome. The analysis of 12 studies that recruited patients recently hospitalized for heart failure showed reduced all-cause mortality in telemonitoring patients (RR = 0.83, 95%CI: 0.71-0.97, P = 0.021). Similarly, an analysis of 16 studies that recruited patients who were not recently hospitalized showed reduced all-cause mortality in telemonitoring patients (RR = 0.81, 95%CI: 0.69-0.95, P = 0.01) (Table 3). Analysis of seven studies that recruited only patients 65 years or more showed that telemonitoring reduced all-cause mortality in this age group (RR = 0.66, 95%CI: 0.50-0.87, P = 0.004).

Cardiovascular mortality

The pooled estimate of the effect of telemonitoring on cardiovascular death in comparison with standard care in nine studies with 4043 patients showed that telemonitoring was associated with reduced cardiovascular mortality in heart failure patients (RR = 0.66, 95%CI: 0.54-0.81, P < 0.001) (Figure 2B). Two studies were excluded from the analysis because they reported no cardiovascular deaths in the telemonitoring and usual care groups.

Our sensitivity analysis showed that the duration of telemonitoring did not influence cardiovascular mortality in heart failure patients. Analysis of 3 studies of 6 mo or less duration showed reduced cardiovascular mortality in telemonitoring patients (RR = 0.47, 95%CI: 0.28-0.79, P = 0.005). Similarly, our analysis of 5 studies of 12 mo or more duration showed reduced cardiovascular mortality in telemonitoring patients (RR = 0.71, 95%CI: 0.56-0.90, P = 0.005) (Table 3).

Furthermore, our sensitivity analysis showed that being recently hospitalized for heart failure, which we defined as heart failure hospitalization within six weeks before the study, did not affect the telemonitoring outcome. Analysis of 3 studies that recruited patients with recent hospitalization showed reduced cardiovascular mortality in telemonitoring patients (RR = 0.57, 95%CI: 0.35-0.94, P = 0.026). Similarly, our analysis of 6 studies that recruited patients with no recent hospitalization showed reduced cardiovascular mortality in telemonitoring patients (RR = 0.68, 95%CI: 0.54-0.85, P = 0.001) (Table 3).

All-cause hospitalization

The pooled estimate of the effect of telemonitoring on all-cause hospitalization in comparison with

Table 2 Showing the bias assessment of the primary studies

Ref.	The allocation sequence was random	The allocation sequence was adequately concealed	Participants aware of their assigned intervention	Interventions implementors were aware of participants' assigned groups	Outcome data were available for all, or nearly all, participants randomized	Outcome measurement could have differed between groups	Outcome assessors were aware of the intervention received by participants	Data analysis plan was finalized before data were available for analysis
Nouryan *et al* [15], 2019	Yes	Probably yes	Yes	Yes	Yes	No	No information	No information
Seto *et al*[16], 2012	Yes	Yes	Yes	Yes	Yes	No	No information	No information
Weintraub *et al* [17], 2010	Probably yes	No information	Yes	Yes	Yes	No	No	Yes
Blum and Gottlieb[18], 2014	Probably yes	No information	Yes	Yes	Yes	No	No information	No information
Dansky *et al* [19], 2008	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Kashem *et al* [20], 2008	Yes	Yes	Yes	Yes	Yes	No	No information	No information
Benatar *et al* [21], 2003	Probably yes	No information	Yes	Yes	Probably yes	No	No information	No information
Pedone *et al*[22], 2015	Probably yes	No information	Yes	Yes	Yes	No	No information	No information
Wade *et al*[23], 2011	Yes	No information	Yes	Yes	No	No	No information	No information
Comín-Colet *et al*[24], 2016	Yes	Yes	Yes	Yes	Yes	No	No	No information
Olivari *et al*[25], 2018	Yes	Yes	Yes	Yes	Yes	No	No information	Yes
Lyngå *et al*[26], 2012	Probably yes	No information	Yes	Yes	Yes	No	No information	No information
Scherr *et al*[27], 2009	Probably yes	No information	Yes	Yes	No	No	No information	No information
Antonicelli *et al* [28], 2008	Probably yes	No information	Yes	Yes	Probably yes	No	No information	No information
Giordano *et al* [29], 2009	Yes	Yes	Yes	Yes	Yes	No	No information	No information

Ong *et al*[30], 2016	Yes	Yes	Yes	Yes	Probably yes	No	No	Yes
Kalter-Leibovici *et al*[10], 2017	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Mortara *et al* [31], 2009	Yes	Yes	Yes	Yes	Yes	No	No information	No information
Dar *et al*[32], 2009	Yes	Yes	Yes	Yes	Yes	No	No information	No information
Vuorinen *et al* [33], 2014	Yes	No information	Yes	Yes	Yes	No	No information	No information
Goldberg *et al* [34], 2003	Yes	No information	Yes	Yes	No	No	No information	No information
Soran *et al*[35], 2008	Yes	No information	Yes	Yes	Yes	No	No information	No information
Chaudhry *et al* [36], 2010	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Koehler *et al* [13], 2018	Yes	Yes	Yes	Yes	Yes	No	No information	Yes
Cleland *et al* [14], 2005	Yes	Yes	Yes	Yes	Yes	No	No information	Yes
Koehler *et al*[7], 2011	Yes	Yes	Yes	Yes	Yes	No	No information	Yes
Kotooka *et al*[8], 2018	Yes	Yes	Yes	Yes	No	No	No	Yes
Pekmezaris *et al* [9], 2019	Yes	No information	Yes	Yes	Yes	No	No information	No information
Villani *et al*[37], 2014	Yes	Yes	Yes	Yes	Yes	No	No information	No information
Dendale *et al* [38], 2012	Yes	Yes	Yes	Yes	Yes	No	No	No information
Woodend *et al* [39], 2007	Yes	No information	Yes	Yes	Yes	No	No information	No information
Galinier *et al* [40], 2020	Yes	Yes	Yes	Yes	Yes	No	No information	No information
Capomolla *et al* [41], 2004	Yes	No information	Yes	Yes	No	No	No information	No information
Kulshreshtha *et*	Yes	No	Yes	Yes	No	No	No information	No information

al[42], 2010								
Kenealy *et al* [43], 2015	Yes	Yes	Yes	Yes	Yes	No	No	No information
Dawson *et al* [44], 2021	Yes	Yes	Yes	Yes	No	No	No information	No information
Delaney *et al* [45], 2013	Yes	Yes	Yes	Yes	Yes	No	No information	No information
Schwarz *et al* [46], 2008	Yes	No information	Yes	Yes	Yes	No	No information	No information

Table 3 Result of sensitivity analysis

	All-cause mortality			Cardiovascular mortality			All-cause hospitalization			Heart failure hospitalization		
	No of studies	Number of patients	Effect	No of studies	Number of patients	Effect	No of studies	Number of patients	Effect	No of studies	Number of patients	Effect
Follow up ≤ 6 mo	15	6781	Reduced	3	773	Reduced	19	7442	No effect	8	2774	No effect
Follow up ≥ 12 mo	12	6159	Reduced	5	3022	Reduced	13	5360	Reduced	6	2962	Reduced
Recent hospitalization	12	5865	Reduced	3	607	Reduced	13	6057	Reduced	6	2486	No effect
No recent hospitalization	16	7417	Reduced	6	3436	Reduced	20	6993	Reduced	8	3250	Reduced
Patients ≥ 65 yr	7	1522	Reduced	-	-	-	8	1611	No effect	-	-	-

standard care in 33 studies with 13050 patients showed that telemonitoring was associated with reduced all-cause hospitalization in heart failure patients (RR = 0.87, 95%CI: 0.80-0.94, P = 0.002) (Figure 2C).

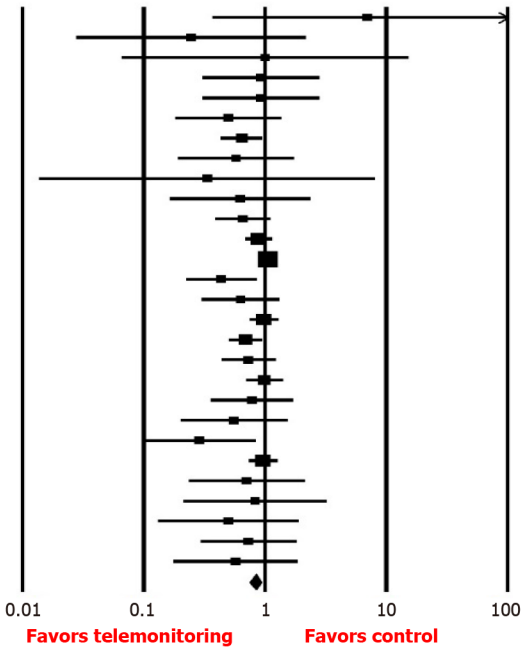
Our sensitivity analysis showed that the duration of telemonitoring influenced all-cause hospitalization in heart failure patients. Analysis of 19 studies with six months or less duration showed no effect of telemonitoring on all-cause hospitalization (RR = 0.93, 95%CI: 0.83-1.04, P = 0.21). Conversely, our analysis of 13 studies with 12 mo or more duration showed that telemonitoring reduced all-cause hospitalization (RR = 0.79, 95%CI: 0.68-0.92, P = 0.002) (Table 3).

Furthermore, our sensitivity analysis showed that being recently hospitalized for heart failure did not affect the all-cause hospitalization. Analysis of 13 studies that recruited recently hospitalized heart failure patients showed that telemonitoring reduced all-cause hospitalization (RR = 0.85, 95%CI: 0.74-0.98, P = 0.03). Similarly, our analysis of 20 studies that recruited patients that were not recently hospitalized showed that telemonitoring also reduced all-cause hospitalization in this group (RR = 0.88, 95%CI: 0.78-0.98, P = 0.03) (Table 3). Analysis of eight studies that recruited only patients 65 years or older showed that telemonitoring did not affect all-cause hospitalization in this age group (RR = 0.77, 95%CI: 0.58-1.02, P = 0.071).

A

Effect of home telemonitoring on all-cause mortality in heart failure patients

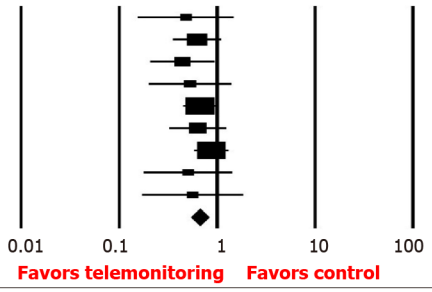
Study name	Risk ratio	Lower limit	Upper limit	*P* value
Seto *et al*[16], 2012	7.000	0.371	132.101	0.194
Weintraub *et al*[17], 2010	0.245	0.028	2.149	0.204
Kashem *et al*[20], 2008	1.000	0.066	15.081	1.000
Pedone *et al*[22], 2015	0.927	0.305	2.812	0.893
Wade *et al*[23], 2011	0.927	0.305	2.812	0.893
Comín-Colet *et al*[24], 2016	0.499	0.183	1.357	0.173
Olivari *et al*[25], 2018	0.643	0 .437	0.947	0.025
Lyngå *et al*[26], 2012	0.567	0.193	1.723	0.324
Scherr *et al*[27], 2009	0.333	0.014	8.005	0.498
Antonicelli *et al*[28], 2008	0.621	0.164	2.359	0.485
Giordano *et al*[29], 2009	0.656	0.390	1.103	0.112
Ong *et al*[30], 2016	0.886	0.691	1.135	0.337
Kalter-Leibovici *et al*[10], 2017	1.058	0.909	1.231	0.465
Goldberg *et al*[34], 2003	0.435	0.224	0.846	0.014
Soran *et al*[35], 2008	0.627	0.303	1.295	0.207
Chaudhry *et al*[36], 2010	0.980	0.747	1.285	0.883
Koehler *et al*[13], 2018	0.693	0.508	0.944	0.020
Cleland *et al*[14], 2005	0.730	0.438	1.216	0.227
Koehler *et al*[7], 2011	0.987	0.699	1.395	0.942
Kotooka *et al*[8], 2018	0.778	0.360	1.682	0.523
Villani *et al*[37], 2014	0.556	0.204	1.512	0.250
Dendale *et al*[38], 2012	0.286	0.098	0.831	0.021
Galinier *et al*[40], 2020	0.965	0.742	1.255	0.791
Capomolla *et al*[41], 2004	0.704	0.235	2.106	0.530
Kulshreshtha *et al*[42], 2010	0.829	0.215	3.193	0.785
Kenealy *et al*[43], 2015	0.500	0.132	1.887	0.306
Dawson *et al*[44], 2021	0.727	0.294	1.797	0.490
Schwarz *et al*[46], 2008	0.571	0.178	1.833	0.347
	0.829	0.745	0.923	0.001



B

Effect of home telemonitoring on cardiovascular mortality in heart failure patients

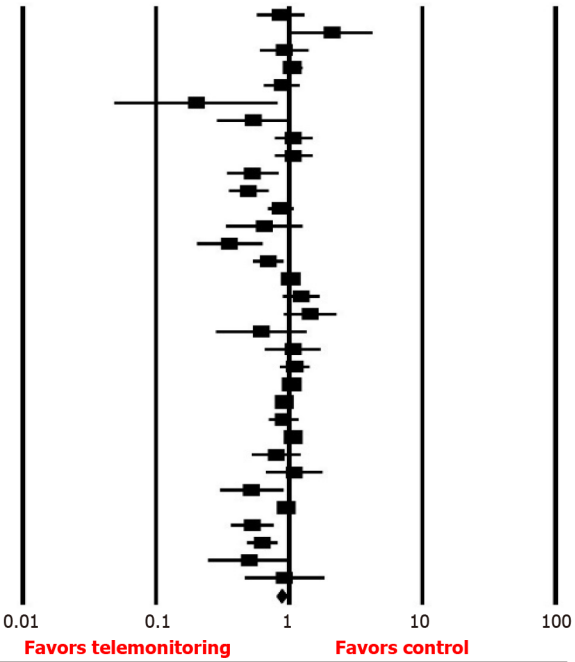
Study name	Risk ratio	Lower limit	Upper limit	*P* value
Comín-Colet *et al*[24], 2016	0.479	0.156	1.470	0.198
Giordano *et al*[29], 2009	0.621	0.355	1.086	0.094
Goldberg *et al*[34], 2003	0.441	0.209	0.929	0.031
Soran *et al*[35], 2008	0.528	0.200	1.394	0.197
Koehler *et al*[13], 2018	0.668	0.451	0.988	0.044
Cleland *et al*[14], 2005	0.633	0.328	1.221	0.173
Koehler *et al*[7], 2011	0.874	0.588	1.301	0.508
Kotooka *et al*[8], 2018	0.506	0.180	1.421	0.196
Capomolla *et al*[41], 2004	0.563	0.173	1.833	0.340
	0.660	0.537	0.810	0.000

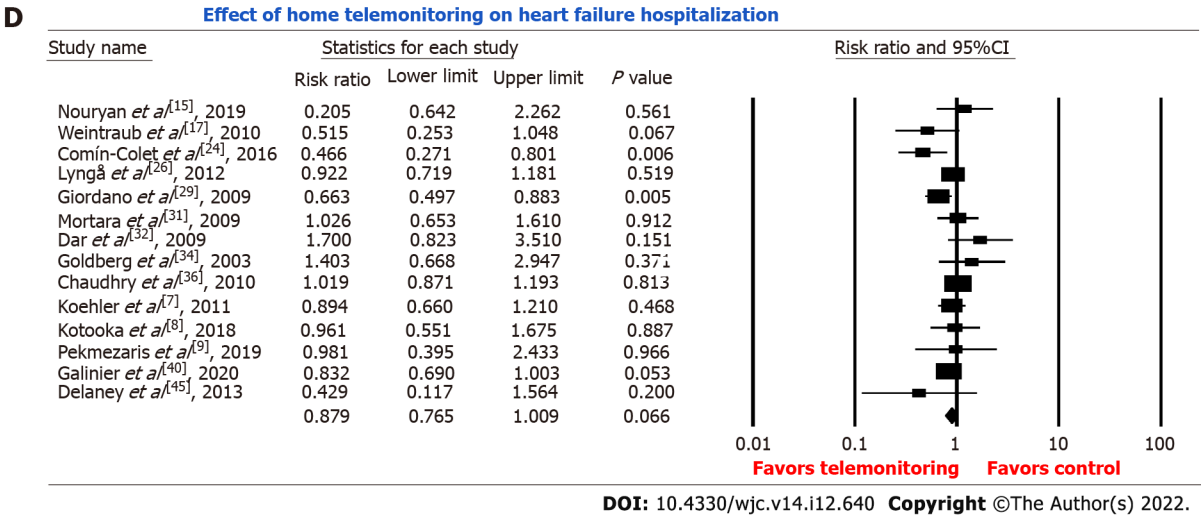


C

Effect of home telemonitoring on all-cause hospitalization in heart failure patients

Study name	Risk ratio	Lower limit	Upper limit	*P* value
Nouryan *et al*[15], 2019	0.861	0.572	1.295	0.472
Seto *et al*[16], 2012	2.111	1.059	4.207	0.034
Weintraub *et al*[17], 2010	0.916	0.603	1.391	0.680
Blum and Gottlieb[18], 2014	1.060	0.904	1.243	0.471
Dansky *et al*[19], 2008	0.883	0.652	1.195	0.419
Kashem *et al*[20], 2008	0.200	0.049	0.818	0.025
Benatar *et al*[21], 2003	0.542	0.291	1.007	0.053
Pedone *et al*[22], 2015	1.078	0.790	1.472	0.636
Wade *et al*[23], 2011	1.078	0.790	1.472	0.636
Comín-Colet *et al*[24], 2016	0.532	0.344	0.823	0.005
Olivari *et al*[25], 2018	0.496	0.355	0.692	0.000
Lyngå *et al*[26], 2012	0.867	0.699	1.074	0.192
Scherr *et al*[27], 2009	0.647	0.335	1.249	0.195
Antonicelli *et al*[28], 2008	0.359	0.206	0.623	0.000
Giordano *et al*[29], 2009	0.689	0.542	0.899	0.005
Ong *et al*[30], 2016	1.033	0.931	1.145	0.544
Mortara *et al*[31], 2009	1.231	0.904	1.676	0.188
Dar *et al*[32], 2009	1.435	0.918	2.241	0.113
Vuorinen *et al*[33], 2014	0.615	0.281	1.346	0.224
Goldberg *et al*[34], 2003	1.067	0.664	1.714	0.788
Soran *et al*[35], 2008	1.101	0.861	1.408	0.444
Chaudhry *et al*[36], 2010	1.040	0.941	1.149	0.446
Koehler *et al*[13], 2018	0.923	0.706	1.165	0.445
Cleland *et al*[14], 2005	0.803	0.531	1.213	0.297
Koehler *et al*[7], 2011	1.089	0.676	1.754	0.726
Kotooka *et al*[8], 2018	0.803	0.531	1.213	0.297
Pekmezaris *et al*[9], 2019	1.089	0.676	1.754	0.726
Villani *et al*[37], 2014	0.522	0.303	0.898	0.019
Galinier *et al*[40], 2020	0.948	0.837	1.073	0.398
Capomolla *et al*[41], 2004	0.525	0.366	0.753	0.000
Dawson *et al*[44], 2021	0.628	0.486	0.812	0.000
Delaney *et al*[45], 2013	0.500	0.249	1.004	0.051
Schwarz *et al*[46], 2008	0.923	0.467	1.825	0.818
	0.869	0.796	0.949	0.002





DOI: 10.4330/wjc.v14.i12.640

Figure 2 Forest plot showing the effect of home telemonitoring. A: On all-cause mortality; B: On cardiovascular mortality; C: On all-cause hospitalization; D: On heart failure hospitalization. CI: Confidence interval.

Heart failure hospitalization

The pooled estimate of the effect of telemonitoring on heart failure hospitalization compared to standard care in 14 studies with 5736 patients showed that telemonitoring had no effect on heart failure hospitalization (RR = 0.88, 95%CI: 0.77-1.01, *P* = 0.066) (Figure 2D). Our sensitivity analysis showed that the duration of telemonitoring influenced heart failure hospitalization. Analysis of 8 studies of six months or less duration showed no effect of telemonitoring on heart failure hospitalization (RR = 0.90, 95%CI: 0.65-1.23, *P* = 0.50). Conversely, our analysis of 6 studies of 12 mo or more duration showed that telemonitoring reduced heart failure hospitalization (RR = 0.85, 95%CI: 0.75-0.95, *P* = 0.004) (Table 3).

Sensitivity analysis showed that telemonitoring had no effect on heart failure hospitalization in patients recently discharged from the hospital. Analysis of 6 studies showed no effect on heart failure hospitalization (RR = 0.85, 95%CI: 0.61-1.21, *P* = 0.37). Conversely, our analysis of 8 studies that recruited patients that were not recently hospitalized showed that telemonitoring reduced heart failure hospitalization (RR = 0.86, 95%CI: 0.76-0.98, *P* = 0.02) (Table 3).

DISCUSSION

Our study demonstrated that home telemonitoring in heart failure patients was associated with reduced all-cause and cardiovascular mortality. These findings are consistent with previous meta-analyses of heart failure patients but inconsistent with some others[6,47-49]. Our sensitivity analysis showed that all-cause and cardiovascular mortality reduction was seen with short (six months or less) and longer (one year or more) telemonitoring. The decrease in mortality was also seen in studies that recruited recently hospitalized heart failure patients, which we defined as heart failure hospitalization within six weeks before the study, and those that did not. The decrease in mortality seen in-home telemonitoring could be due to early detection of clinical deterioration and early intervention.

Our study found that telemonitoring marginally decreased the all-cause hospitalization but did not decrease heart failure-related hospitalization. Some prior meta-analysis did not show reduced all-cause hospitalization[49-52] or heart failure-related hospitalization[52] with telemonitoring in heart failure patients. It is reasonable to expect that telemonitoring and early intervention will reduce hospitalization by detecting clinical deterioration early and early intervention. Conversely, telemonitoring could lead to more frequent hospitalization. This is because telemonitoring patients have more frequent contact with the healthcare system, and severe episodes of decompensation requiring hospitalization will be detected early. In this case, it will be expected that such patients will come to the hospital at the early stage of severe decompensation and that duration of hospitalization will be shorter. Unfortunately, length of hospital stay was inconsistently reported in the studies, preventing meta-analysis of telemonitoring on this outcome. However, our sensitivity analysis showed that while short-duration telemonitoring (6 mo or less) did not affect both all-cause hospitalization and heart failure hospitalization, long-duration telemonitoring (12 mo or more) showed a reduction in both all-cause and heart failure hospitalization. This may explain why some earlier meta-analyses with fewer studies showed a decrease in heart failure hospitalization with telemonitoring[49,53]. In the long run, telemonitoring may lead to early detection of clinical deterioration and early interventions that reduce hospitalization.

Some studies included scheduled nurse-led patient interaction or education as part of the intervention in addition to measuring and transmitting vital signs. The scheduled patient-nurse interactions included counseling if there is an acute change in health status, providing patient self-care education, adjusting medications using designated protocols, monitoring disease signs and symptoms, monitoring medication adherence, and addressing technical and social issues[10,13,14]. Three studies had the scheduled patient-nurse education and interaction in both the control and telemonitoring groups, while seven had the education and interaction in only the telemonitoring group. Thus, we thought that the additional intervention might partially explain the decrease in all-cause mortality with telemonitoring in those studies. However, our sensitivity analysis in the seven studies that received further intervention showed that telemonitoring with additional patient education did not affect heart failure hospitalization or mortality. This points that telemonitoring and not the additional interventions were likely responsible for the improved mortality seen in these studies.

Additionally, we had thought that home telemonitoring might be more helpful in reducing hospitalization and death in recently hospitalized or newly diagnosed heart failure patients who need support and education. However, our sensitivity analysis showed that home telemonitoring reduced all-cause and cardiovascular mortality in both studies that recruited patients recently hospitalized for heart failure and those that did not. Similarly, telemonitoring reduced all-cause hospitalization in both studies that recruited patients who were recently hospitalized for heart failure and those who had not. However, contrary to our expectation, home telemonitoring did not affect heart failure hospitalization in studies that recruited patients recently hospitalized for heart failure. However, this might reflect the small number of trials and participants rather than an actual lack of effect.

Limitations of the study

There are certain limitations to this study. First, home telemonitoring organizations sponsored some of the studies included in this review. This may have introduced a conflict of interest and bias in the results that were published. Secondly, many of the studies had incomplete reporting of their study methodology, making it difficult to classify them as high or low bias studies. Thus, the risk of bias in some of the studies was unclear. Thirdly, some of the sensitivity analyses involved a combination of a few small-sized studies. The small number of studies and participants may make it difficult to detect an effect, even if one exists.

Implications of the results for practice, policy, and future research

Prolonged home telemonitoring (12 mo or more) was associated with both decreased all-cause and heart failure hospitalization, unlike shorter duration (6 mo or less) telemonitoring. The implication for practice is that hospitals considering telemonitoring to reduce heart failure readmission rates may need to plan for prolonged telemonitoring to see the effect they are looking for. In addition, these hospitals or organizations will need to consider the cost of prolonged telemonitoring *viz-a-viz* the cost of rehospitalization. The opportunities for future research include a cost-benefit analysis of home telemonitoring in heart failure patients. There is also a need for more studies on the effect of telemonitoring on frequently hospitalized heart failure patients.

CONCLUSION

The results of this meta-analysis support the benefit of home telemonitoring using digital/broadband/satellite/wireless or blue-tooth transmission of physiological data in reducing all-cause and cardiovascular mortality in heart failure patients. In addition, this analysis also shows the benefit of prolonged telemonitoring (≥ 12 mo) in reducing all-cause and heart failure-related hospitalization.

ARTICLE HIGHLIGHTS

Research background

Home telemonitoring has been used as a modality to prevent readmission and improve outcomes for patients with heart failure.

Research motivation

However, while telemonitoring was beneficial in reducing hospital admission, all-cause mortality, and emergency room visits in some studies, others did not show such benefits. These differences in outcomes from multiple studies suggest that a careful analysis of study outcomes is needed to determine its aggregate benefit to heart failure patients.

Research objectives

This meta-analysis aims to determine the aggregate effect of telemonitoring on all-cause mortality, heart failure-related mortality, all-cause hospitalization, and heart failure-related hospitalization in heart failure patients.

Research methods

We conducted a systematic review and meta-analysis of 38 home telemonitoring randomized controlled trials involving 14993 patients.

Research results

Home telemonitoring in heart failure patients was associated with reduced cardiovascular [relative risk (RR) = 0.66, 95% confidence interval (CI): 0.54-0.81, $P < 0.001$] and all-cause mortality (RR = 0.83, 95%CI: 0.75-0.92, $P = 0.001$). Furthermore, telemonitoring was associated with decreased all-cause hospitalization (RR = 0.87, 95%CI: 0.80-0.94, $P = 0.002$) but not heart failure-related hospitalization (RR = 0.88, 95%CI: 0.77-1.01, $P = 0.066$). Interestingly, prolonged home telemonitoring (12 mo or more) was associated with both decreased all-cause and heart failure hospitalization, unlike shorter duration (6 mo or less) telemonitoring.

Research conclusions

Home telemonitoring reduces all-cause and cardiovascular mortality in heart failure patients. This study found that prolonged home telemonitoring (12 mo or more) led to both decreased all-cause and heart failure hospitalization, unlike shorter duration (6 mo or less) telemonitoring. The implication for practice is that hospitals considering telemonitoring to reduce heart failure readmission rates may need to plan for prolonged telemonitoring to see the effect they are looking for.

Research perspectives

The opportunities for future research include a cost-benefit analysis of home telemonitoring in heart failure patients. There is also a need for more studies on the effect of telemonitoring on frequently hospitalized heart failure patients.

ACKNOWLEDGEMENTS

We will like to thank Dr. Hycienth Ahaneku for reviewing the data analysis and methods section.

FOOTNOTES

Author contributions: Umeh CA, Torbela A, Saigal S, Kaur H, Kazourra S, Gupta R, and Shah S conceptualized and revised the study design; Umeh CA, Torbela A, Saigal S, Kaur H, and Kazourra S extracted the data; Umeh CA analyzed the data; Umeh CA, Torbela A, Saigal S, Kaur H, and Kazourra S wrote the first draft of the paper; Gupta R and Shah S reviewed and revised the paper; and all authors have read and approved the final manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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S-Editor: Wang JJ
L-Editor: A
P-Editor: Wang JJ

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World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2022 December 26; 14(12): 657-664

DOI: 10.4330/wjc.v14.i12.657

ISSN 1949-8462 (online)

CASE REPORT

Early and aggressive presentation of wild-type transthyretin amyloid cardiomyopathy: A case report

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Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Teragawa H, Japan; Wixner J, Sweden

Received: September 8, 2022
Peer-review started: September 8, 2022
First decision: October 13, 2022
Revised: November 3, 2022
Accepted: November 22, 2022
Article in press: November 22, 2022
Published online: December 26, 2022

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Abstract

BACKGROUND

Wild-type transthyretin amyloidosis (ATTRwt) is the most common form of transthyretin amyloid cardiomyopathy, occurring mostly over age of 60 years (mean age of 80 years). Mean survival without treatment is 3.6 years, making early detection imperative. We report an unusual case of a 58-year-old patient with ATTRwt cardiomyopathy requiring heart transplantation.

CASE SUMMARY

A 58-year-old male presented with progressive fatigue, shortness of breath, weight gain, leg swelling, orthopnoea, and paroxysmal nocturnal dyspnoea for several months. Approximately ten months before this clinical presentation, the patient had first received a diagnosis of heart failure with reduced ejection fraction (EF) of 15% to 20%. The patient was started on appropriate guideline-directed medical therapy with only mild improvement in his EF. Upon further investigation, echocardiogram, technetium pyrophosphate scan (Tc PYP), and cardiac magnetic resonance imaging (cMRI) suggested a diagnosis of amyloidosis, and ATTRwt was subsequently confirmed with native heart tissue biopsy, congo red staining, liquid chromatography-tandem mass spectrometry, and genetic testing. The patient was successfully treated with heart transplantation and is doing well post-transplant.

CONCLUSION

Wild-type ATTR amyloidosis should be kept on differentials in all patients (even less than 60 years old) with non-ischemic cardiomyopathy, especially in the setting of increased ventricular wall thickness and other classic echocardiogram,

cMRI, and Tc PYP findings. Early diagnosis and management can be consequential in improving patient outcomes.

Key Words: Wild-type; Transthyretin; Amyloidosis; Young; Heart failure; Heart transplant; Case report

Core Tip: Wild-type transthyretin amyloidosis (ATTRwt) continues to be an underdiagnosed condition. Although rare in patients under 60 years of age, physicians should include the condition in their differential as early diagnosis and early management can impact patient outcomes. Physicians should be aware of the findings on non-invasive testing that supports ATTRwt. Classically on echocardiogram, cardiac amyloidosis can present as thickened ventricular walls, small lehigh valley chamber, biatrial enlargement, apical sparing on longitudinal strain and signs of elevated filling pressures and restrictive diastolic physiology (increased E/A ratio, E/e' and reduced mitral annular tissue velocities). Cardiac magnetic resonance imaging classically shows late gadolinium enhancement. A technetium pyrophosphate study shows an increased heart-to-contralateral ratio and increased Perugini visual grade.

Citation: Boda I, Farhoud H, Dalia T, Goyal A, Shah Z, Vidic A. Early and aggressive presentation of wild-type transthyretin amyloid cardiomyopathy: A case report. *World J Cardiol* 2022; 14(12): 657-664
URL: https://www.wjgnet.com/1949-8462/full/v14/i12/657.htm
DOI: https://dx.doi.org/10.4330/wjc.v14.i12.657

INTRODUCTION

Amyloid deposition is commonly found in aging populations. Transthyretin amyloid cardiomyopathy (ATTR-CM) is an infiltrative, progressive, and potentially fatal cardiomyopathy that is caused by extracellular deposition of misfolded transthyretin-derived insoluble amyloid fibrils in the myocardium [1]. Wild-type transthyretin amyloidosis (ATTRwt) is the most common type of ATTR-CM[2]. ATTRwt has increasingly been identified in patients greater than the age of 60-65 with an average age of diagnosis of 80 years old[2,3]. A retrospective review of 360 patients diagnosed with ATTRwt showed that 93% of the patients with an antemortem diagnosis were Caucasian males greater than 70 years old [4]. Another retrospective review showed only a handful of patients that were diagnosed with ATTRwt in their forties[2]. A recent case of ATTRwt was identified in a 34-year-old male in India[5]. Our case report highlights an unusual case of ATTRwt cardiomyopathy presenting in a relatively young, 58-year-old patient with end stage heart failure (HF) symptoms.

CASE PRESENTATION

Chief complaints

Progressive fatigue, shortness of breath, weight gain, leg swelling, orthopnoea, and paroxysmal nocturnal dyspnoea.

History of present illness

A 58-year-old Caucasian man presented to the heart failure clinic with progressive fatigue, shortness of breath, weight gain, leg swelling, orthopnoea, and paroxysmal nocturnal dyspnoea for several months. On review of symptoms, the patient had no palpitations, carpal tunnel symptoms, neuropathy, or back pain.

History of past illness

Approximately ten months before this clinic presentation, the patient had first received a diagnosis of HF with reduced ejection fraction (EF) of 15% to 20%. At that time, he underwent left heart catheterization which showed no obstructive coronary artery disease. The patient was started on appropriate guideline-directed medical therapy (GDMT) with only mild improvement in his EF. The patient was followed in the heart failure clinic and had recurrences of acute on chronic heart failure episodes. Unfortunately, due to borderline hypotension, he was unable to reach maximum doses of GDMT which ultimately had to be stopped.

Personal and family history

His past medical history was significant for non-ischemic cardiomyopathy (EF 15%-20%), left ventricular hypertrophy, implantable cardioverter defibrillator in situ, atrial fibrillation, moderate to severe mitral regurgitation, prior left atrial thrombus, and prior tobacco use disorder. Other than atrial fibrillation, he had no significant history of other arrhythmias. He worked as a construction worker. His family history was notable only for his father who underwent a coronary artery bypass graft at age 59 years.

Physical examination

Physical exam was notable for the patient appearing well-nourished; however, jugular venous distension, a holosystolic murmur consistent with known mitral regurgitation, abdominal distention, and bilateral lower extremity edema were present. Vital signs depicted borderline systolic blood pressure of 95/70 mmHg with a mean of 78 mmHg, normal heart rate, normal respiratory rate and saturation on room air, and normal temperature.

Laboratory examinations

The patient's presentation to the clinic with progressively worsening heart failure symptoms prompted admission to the hospital.

Imaging examinations

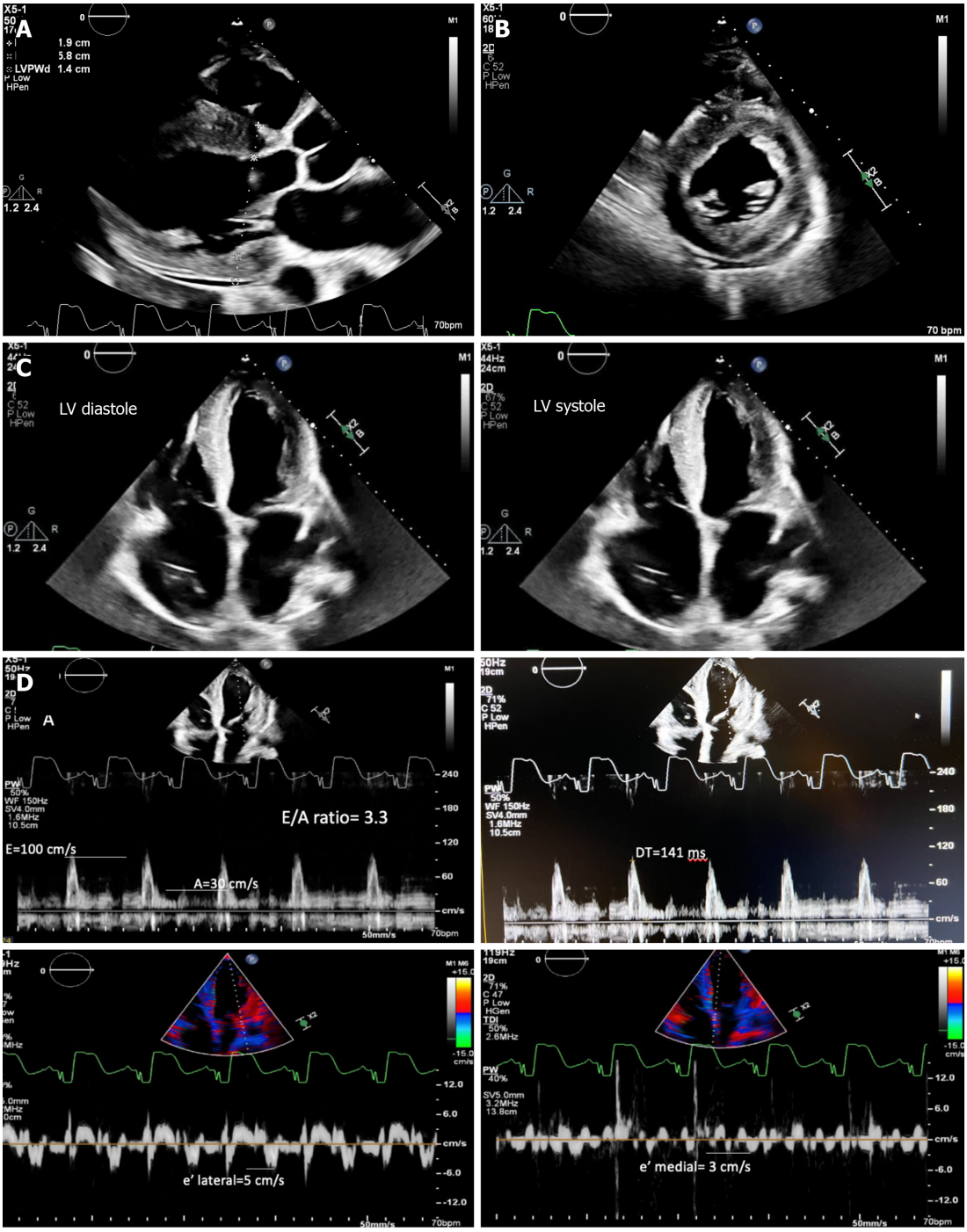
Electrocardiogram showed AV-paced complexes and low voltage in both limb and precordial leads. He underwent right heart catheterization which was consistent with cardiogenic shock with central venous pressure 18 mmHg, polymeraseacidicprotein 43/25 with mean of 32 mmHg, pulmonary capillary wedge pressure 23 mmHg, fick cardiac output of 4.6 L/min, and cardiac index of 2.1 L/min/m^2. Transthoracic echocardiogram demonstrated a reduced EF of 10%, concentric hypertrophy with interventricular septal thickness of 1.9 cm and posterior wall thickness of 1.4 cm, moderately reduced right ventricle (RV) function with a dilated RV, moderate mitral regurgitation, and trivial pericardial effusion (Figure 1A-C). Diastology additionally showed an E/A ratio of 3.3, severely reduced mitral annular tissue velocities (e' medial of 3 cm/s and e' lateral of 5 cm/s), E/e' of 25, and deceleration time of 141 ms (Figure 1D). The increased myocardial wall thickness on echocardiogram as well as parameters consistent with restrictive pathology led to a detailed amyloidosis workup. A technetium pyrophosphate scan (Tc PYP) showed a heart/contralateral lung ratio of 1.77 and visual grade 3 as per the Perugini scale, highly suggestive of cardiac amyloidosis (Figure 2). Cardiac magnetic resonance imaging (cMRI) showed global myocardial delayed hyperenhancement and failure to null most likely due to cardiac amyloidosis (Figure 3). Amyloid light chain amyloidosis work-up including kappa and lambda light chains levels, serum protein electrophoresis, and urine protein electrophoresis was unremarkable. The native heart tissue pathology showed diffuse amyloid deposits between the myocardial fibrils, confirmed on Congo red staining (Figure 4). Liquid chromatography-tandem mass spectrometry was also performed on peptides extracted from the Congo red-positive areas of tissue and was consistent with ATTR-CM. The spectrometry did not detect an amino acid sequence abnormality in the transthyretin protein, suggesting ATTRwt as the diagnosis. Genetic testing was performed and was unremarkable, showing two variants of unknown significance, c.3262-3C>G in the LAMA4 gene and p.K963E in the RBM20 gene. Screening of the TTR gene was unremarkable ruling out hereditary TTR cardiomyopathy.

FINAL DIAGNOSIS

In conclusion, the history, exam, and workup, including genetic testing, confirmed ATTRwt as the final diagnosis.

TREATMENT

The patient was initially supported with inotropes; however, given the concern for end-stage cardiac amyloidosis and risk for progressive cardiogenic shock in the setting of biventricular failure, orthotopic heart transplant evaluation was initiated. He was deemed a suitable candidate for heart transplantation by our multidisciplinary transplant committee. The patient was maintained on milrinone and epinephrine for inotropic support until he underwent transplantation.



DOI: 10.4330/wjc.v14.i12.657

Figure 1 Transthoracic echocardiography. A: Parasternal long axis of left ventricle shows concentric hypertrophy with an increased interventricular septum and posterior wall thickness and a trivial pericardial effusion; B: Parasternal short axis showing thickened walls of the left ventricular myocardium; C: Four-chamber view showing lehigh valley diastole and systole; D: E/A ratio of 3.3, severely reduced mitral annular tissue velocities (e' medial of 3 cm/s and e' lateral of 5 cm/s), E/e' of 25, and deceleration time time of 141 ms, consistent with restrictive pathology. LV: Lehigh valley.

OUTCOME AND FOLLOW-UP

Unfortunately, a few days following the transplant, the patient had pericardial bleeding with tamponade followed by successful evacuation of blood. He had no other postoperative complications and was discharged home on postoperative day eight. The patient has followed closely in the heart failure clinic and is doing very well post-transplant.

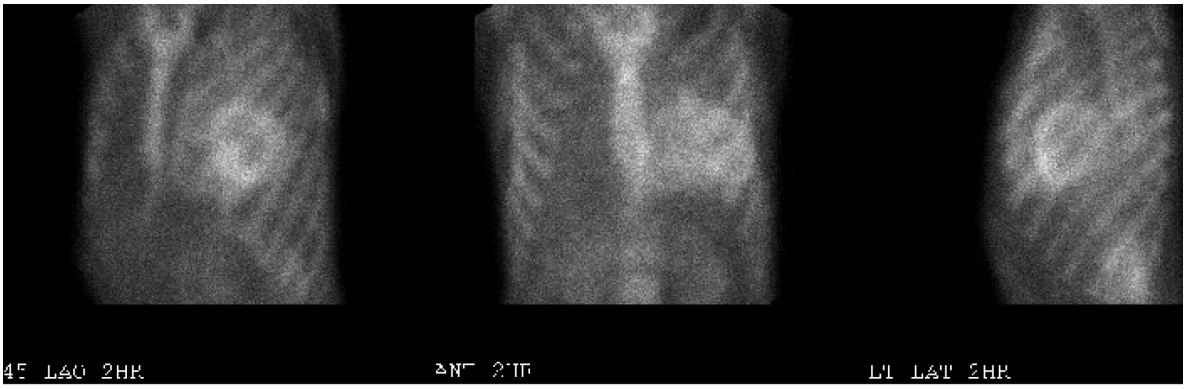


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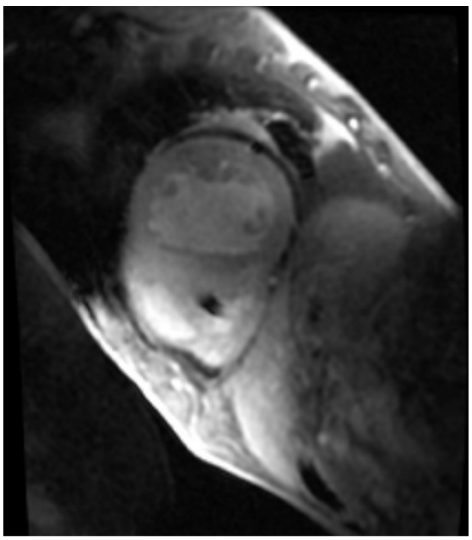
Figure 2 Technetium pyrophosphate scan showing increased myocardial uptake of tracer (visual grade 3) suggestive of transthyretin-mediated cardiac amyloidosis.



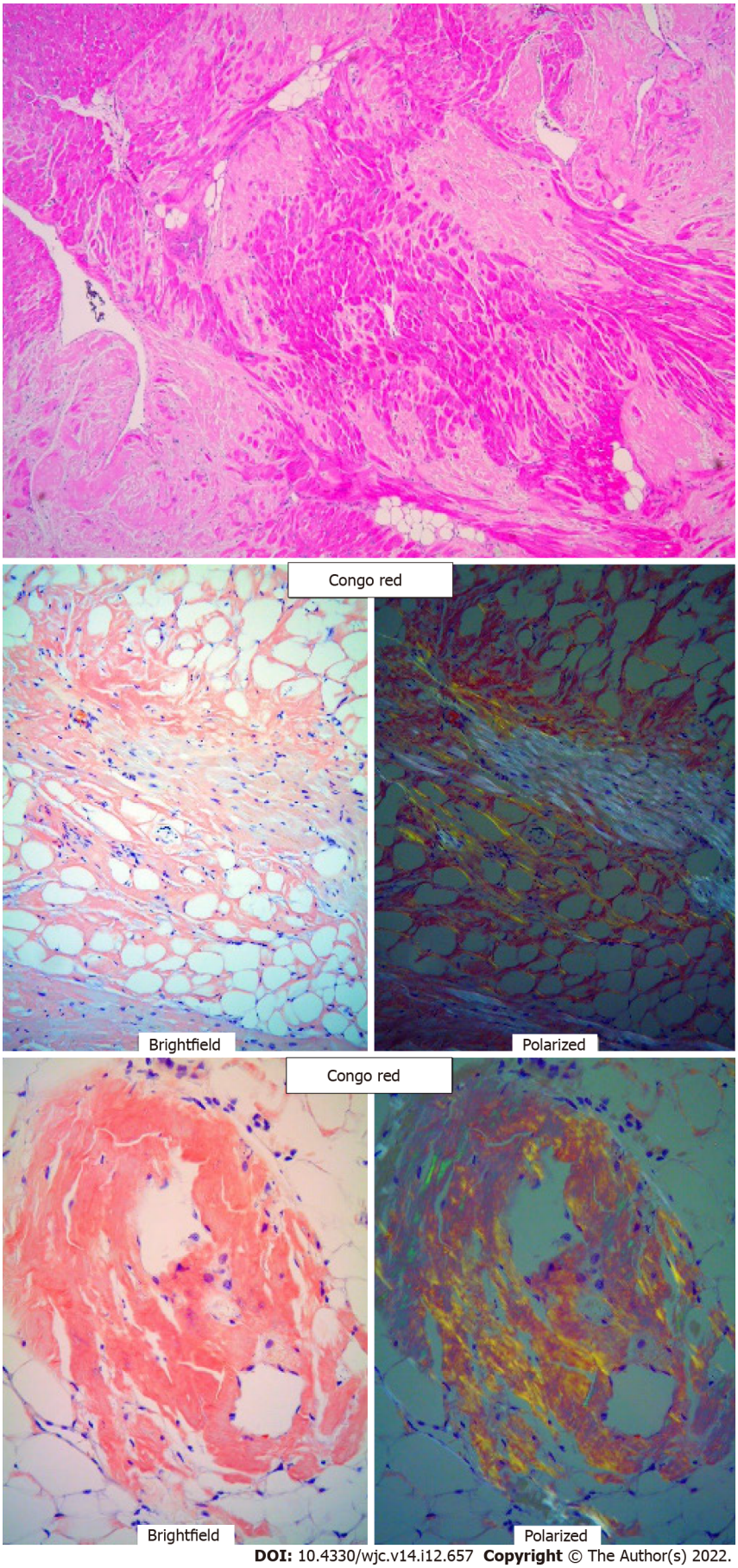
DOI: 10.4330/wjc.v14.i12.657

Figure 3 Cardiac magnetic resonance imaging showing delayed global hyperenhancement and failure to null likely due to cardiac amyloidosis.

DISCUSSION

ATTRwt has increasingly been identified in patients greater than the age of 60-65 with an average age of diagnosis of 80 years old. Although ATTRwt is rare in younger populations, physicians should consider ATTRwt in their differential. Our patient not only developed ATTRwt below the age of 60, but also within 1 year of the patient's HF diagnosis that rapidly progressed to end-stage cardiomyopathy. After review of the literature, it remains uncertain why some individuals may be predisposed to developing ATTRwt at an earlier age. However, early diagnosis can lead to improved management and outcomes as ATTRwt continues to be an underdiagnosed condition.

Classically on echocardiogram, cardiac amyloidosis can present as thickened ventricular walls, small lehigh valley chamber, valve thickening, atrial enlargement, apical sparing on strain and signs of elevated filling pressures, restrictive diastolic physiology (increased E/A ratio, E/e' and reduced mitral annular tissue velocities)[6]. In patients with ATTR-CM amyloidosis, late gadolinium enhancement (LGE) is almost always present on cMRI. Studies have shown with LGE cMRI, an inability to suppress or "null" the myocardial signal or the presence of diffuse subendocardial or transmural enhancement patterns, which suggests amyloidosis with a sensitivity and specificity that approach 85%-90%[7,8]. cMRI also shows elevated native T1 values and increased extracellular volume[7]. Bone scans using Tc PYP scan show increased ^{99m}Tc-PYP uptake in the heart of patients with amyloid infiltration leading to increased heart-to-contralateral ratio and visual grading[3]. The non-biopsy diagnosis of ATTR-CM with TcPYP scan (first described by Gillmore *et al*[9]) is now widely accepted and has replaced the historical endocardial biopsy provided AL amyloidosis is ruled out.



DOI: 10.4330/wjc.v14.i12.657

Figure 4 Native heart tissue pathology on H and E staining showing extracellular amyloid deposits, followed beneath by Congo red

staining showing apple green refringence of amyloid deposits (100× magnification).

In ATTR-CM, several new pharmaceutical therapies that target the disease at various levels have emerged, including TTR stabilizers (example: Tafamidis), and antisense oligonucleotides, RNA interference (example: Patisiran, Vutrisiran and Inotersen). Tafamidis is the only drug approved for ATTR cardiomyopathy so far, although trials with patisiran, vutrisiran, inotersen and eplontersen are underway. All of these are most effective when administered prior to significant cardiac dysfunction[3, 10]. There are rare and isolated case reports of amyloid cardiac deposition recurrence post-transplant [11]. Since there are very few cases of heart transplantation for ATTR-CM reported in the literature given that most patients have a median age of 80, it is unknown how to best prevent the deposition of amyloid again in the transplanted heart. Our patient remains on Tafamidis post-transplant with the hope of stabilizing TTR protein tetramer and preventing amyloid fibrils from depositing in the myocardium.

Hence, it is imperative to diagnose ATTR-CM at earlier stages with available non-invasive testing and FDA approved treatments. Heart transplantation can be considered in select patients with Stage D HF [12]. The current allocation system provides priority as Status 4 to these stage D ATTR-CM patients due to a lack of durable mechanical support options[10].

CONCLUSION

Although ATTRwt is rare in younger populations, physicians should consider ATTRwt in their differential, especially in non-ischemic cardiomyopathy patients with thickened interventricular septum, posterior wall thickness, and arrhythmias especially atrial fibrillation. Early diagnosis of ATTRwt combined with newer therapies can be consequential in increasing patients' quality of life and survival [3].

FOOTNOTES

Author contributions: Boda I contributed to manuscript writing, editing, and data collection; Farhoud H assisted with writing and edits; Dalia T and Goyal A assisted with edits; Shah Z and Vidic A have contributed to conceptualization and supervision; all authors have read and approved the final manuscript.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: All authors declare that they have no conflict of interest to disclose.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: United States

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S-Editor: Wang LL
L-Editor: A
P-Editor: Wang LL

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